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Abstracts

Emotions and the Brain
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Part 1: Abstracts of presentations

1. Linking neurochemistry, emotions, and therapeutics—a feasible project or just a delusion

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Schizophrenia is a disease of the mind as it is diagnosed largely on phenomenological grounds. On the other hand the most empirically sound hypothesis of schizophrenia entails a disorder of dopamine, a chemical change in the brain. Both of these represent two levels of analysis of the same entity. How does one get these different levels of analysis to talk to each other. The presentation will address this challenge. I will first review data from recent neuroimaging studies which posit a central role for dopamine in the psychosis of schizophrenia and the centrality of dopamine blockade in bringing about improvement. This "biology and pharmacology" will then be related to the "psychology" of schizophrenia. In particular, it will be suggested that aberrant and dysregulated dopamine release may lead to an aberrant assignment of salience to ideas and internal perceptual representations, leading to delusions and hallucinations. It will be further suggested that antipsychotics, by blocking the dopamine system, take away propensity to assign aberrant salience. However, the experienced symptoms are now a part of ones episodic-semantic system and it takes a period of "neurochemically assisted unlearning" for the symptoms to resolve. This model of psychosis-in-schizophrenia will then be cast in a more comprehensive model of schizophrenia and the synergism between psychotherapeutic and pharmacotherapeutic approaches will be explored.

2. Motivation and emotion: Attention, affect, and action

Peter Lang
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Emotional reactions are founded on two basic motive systems, appetitive and defensive, that are similar across mammalian species. Neuroscience research with animals has illuminated many of the brain structures and circuits that define these systems, and determine their reflex outputs. While motivated behavior is more complex and varied in humans, it is founded on a parallel neurophysiology. Furthermore, the response patterns mediated by these evolutionarily old brain circuits persist in emotional expression and are modulated in affective perception. Research is presented evaluating human beings watching uniquely human stimuli—primarily picture media (but also words and sounds) that prompt emotional arousal. This work illustrates how the brain's motivational systems may mediate affective reports, organize visceral and somatic responses, prime simple reflexes, and determine processing of affect's symbolic representations in the human cerebral cortex.

3. A theoretical context for adult temperament

Paul Costa
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In this talk I hope to sketch a theory of temperament, its development, and its influence on the individual's adaptation. I will emphasize the role of context in all these issues. Many students of temperament, personality, and development will be surprised by these findings; that is why a new theory is needed.

The theory is based on research on adolescents and adults. Although historically temperament was restricted to infants and children, there are theories of adult temperament by Rusalov, Teplov, Nebylitsyn, Eysenck, and Gray. Contemporary temperament researchers—including Buss and Plomin (1975), Strelau (Strelau, Angleitner, Bantelmann, & Ruch, 1990), and Zuckerman (1979)–have developed instruments to assess aspects of temperament in adults. These scales provide a provisional operational definition of what I mean by temperament. Although the specific temperament variables measured in these systems vary, some common themes emerge clearly when they are factored together. Data presented lead to the surprising conclusion that the domains of adult temperament and personality appear not only overlapping, but essentially isomorphic.

Many longitudinal studies lead to the conclusion that within fairly broad limits, personality traits in adulthood appear almost impervious to environmental influences. Furthermore, analyses of personality scores across cultures with very different recent histories show strikingly similar patterns of age differences, suggesting that personality maturation is relatively uninfluenced by life experience. All of the major features of temperament—its stability, heritability, intrinsic maturation—characterize personality traits equally. It is in a sense an accident of intellectual history that some personality traits are regarded as temperaments whereas others are not. The theory of temperament is therefore neither more nor less than the Five-Factor Theory of personality.

From the perspective of Five-Factor Theory, temperaments are formally similar. They are basic tendencies; when the model is used to describe the personality system of infants and children, temperaments occupy the box that will be filled by personality traits in the adult personality system.

In this talk I will argue for a new theoretical context for interpreting temperament. Empirical parallels with adult personality traits

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are drawn to show that the same biologically based, process-oriented approach that typifies traditional studies of temperament should be applied to the full range of traits. Also offered is a different causal perspective, seeing traits not as products of the environment, nor as dispositions that codevelop in dynamic interaction with it, but as independent forces that follow their own intrinsic course of development. Traits or temperaments and the characteristic adaptations they give rise to provide a crucial context in which human beings adapt and live their lives.

4. Neurophysiology, neuroimaging, and clinical neuropsychology of emotion

Edmond Rolls
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Emotions can be defined as states elicited by rewarding and punishing stimuli, and brain mechanisms that evaluate and learn about which stimuli are rewarding and punishing are therefore closely involved in emotion (Rolls, 1999a). The operation of the orbitofrontal cortex can be understood at least partly in terms of these functions (Rolls, 1999b, 2000).

The orbitofrontal cortex contains the secondary taste cortex, in which the reward value of taste is represented, and these can be combined with information about texture and temperature. It also contains the secondary and tertiary olfactory cortical areas, in which information about the identity and also about the reward value of odours is represented. The orbitofrontal cortex also receives information about the sight of objects from the temporal lobe cortical visual areas, and is involved in learning and in reversing stimulus–reinforcement associations (Rolls & Deco, 2002). The stimulus might be a visual or olfactory stimulus and the primary (unlearned) reinforcer a taste or touch. Indeed, investigations using fMRI in humans show that the orbitofrontal cortex is involved in the representation of the pleasantness and painfulness of touch (Rolls et al., in preparation), the pleasantness of odour (O'Doherty et al., 2000), and in rewards and punishers as abstract as receiving or losing money (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). Damage to the orbitofrontal cortex impairs the learning and reversal of stimulus–reinforcement associations, and thus the correction of behavioural responses when these are no longer appropriate because previous reinforcement contingencies change (see Rolls, 1999a,b). The information which reaches the orbitofrontal cortex for these functions includes information about faces and damage to the orbitofrontal cortex can impair face expression identification. We have recently shown that these effects are also found in patients with discrete surgical lesions of the orbitofrontal cortex (Hornak et al., in preparation). This evidence thus shows that the orbitofrontal cortex is involved in decoding some primary reinforcers such as taste and touch; in learning and reversing associations of visual and other stimuli to these primary reinforcers; and plays an executive function in controlling and correcting reward-related and punishment-related behaviour, and thus in emotion.

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5. Affective style: Neural substrates and behavioral correlates

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The circuitry that underlies two fundamental forms of motivation and emotion-approach and withdrawal-related processes, is described from experiments using brain electrical activity, positron emission tomography and functional magnetic resonance imaging. Data on individual differences in functional activity in certain components of these circuits is next reviewed, with an emphasis on the nomological network of associations surrounding individual differences in asymmetric prefrontal activation and in the activation of the amygdala. Both humans and rhesus monkeys show stable patterns of individual differences in asymmetric prefrontal activation. Individuals with greater relative left-sided prefrontal activation have more positive dispositional mood, greater relative behavioral activation compared with behavioral inhibition, lower levels of cortisol and differences on certain parameters of immune function. Several mechanisms are considered by which individual differences in affective style are produced. One focuses on affective chronometry and specifically on the rapidity of recovery from negative events. This is hypothesized to be instantiated in an inhibitory connection between prefrontal cortex and the amygdala. Individuals with greater relative left-sided prefrontal activation have faster recovery following a negative emotional stimulus and less metabolic activity in the amygdala. Another mechanism focuses on context-dependent modulation of emotional processes and is hypothesized to be hippocampally based. Finally a third mechanism is hypothesized to originate in the anterior cingulate cortex and provides the initial signal for initiating a cascade of changes to regulate or modulate an emotional response which conflicts with contextual expectations. The implications of these findings for models of brain circuitry underlying emotion regulation and affective disorders will be discussed.

6. Neural systems mediating emotional behaviour: Strategies from animal and human studies

Trevor Robbins
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The study of neural mechanisms underlying emotion may profit from analyses of the roles of discrete components of such a system in experimental animals in a way that can be related to studies in humans. This approach is illustrated for limbic-striatal and cortico-striatal systems for behavior with both positive and negative affective valence. Specifically, I consider the neural bases of elementary forms of emotional learning and how these may contribute to more complex forms of human behavior as occurs, for example, in complex decision-making, Bechara, Damasio, and colleagues have argued that for adaptive decision-making, it may be necessary to integrate both somatic and cognitive factors mediated by structures such as the amygdala and orbitofrontal cortex, together with other structures which form components of a common circuitry for affective pro-

cessing such as the nucleus accumbens. From our own studies in the rat, evidence is reviewed that the amygdala appears to mediate two distinct forms of learned influence over emotional behaviour, via Pavlovian and instrumental conditioning, in a symmetrical manner for both aversive and appetitively motivated behavior. More specifically, the central nucleus of the amygdala, via its extensive projections to the hypothalamus, to reflexive systems of the brain stem, and to the origins of the neuromodulatory arousal systems, appears to control both pavlovian learned fear, as measured in terms of defensive responses such as freezing, and also pavlovian approach responses elicited by signals of food reward. The neuromodulatory systems include the mesolimbicocortical dopamine projections which innervate the nucleus accumbens and prefrontal cortex and probably mediate pavlovian conditioned and unconditioned motivational influences (including stress) on the output of these structures. By contrast, the basolateral regions of the amygdala (BLA), while certainly also interacting with the central nucleus, have a greater association with neocortical input and output via the striatum. In parallel with this different neural connectivity, the BLA has been implicated in aspects of instrumental conditioning, including conditioned reinforcement and conditioned punishment. Moreover, this sector of the amygdala appears to interact directly with dopamine-dependent functions of the nucleus accumbens in mediating effects of conditioned reinforcers on goal-directed behavior, as engaged for example in drug-seeking.

Detailed comparison of the behavioral effects of specific lesions of limbic-cortical afferents to the nucleus accumbens, other than those from the BLA, for example from the hippocampus and anterior cingulate cortex, suggest that all of these regions exert dissociable influences on nucleus accumbens function and emotional behavioral output. There is also converging evidence for a role of rat prefrontal cortex in the executive control of nucleus accumbens function and the regulation of effects of reinforcement, which may well be relevant to understanding the role of the human frontal cortex in decision-making cognition, as well as in simpler situations such as reversal learning, when reward contingencies for specific objects have to be re-assigned. I will review neuropsychological, psychopharmacological and functional neuroimaging evidence for possible cortico-striatal mechanisms of decision-making and reversal learning in humans. In one example, using event-related fMRI, I will describe new data suggesting that, in certain circumstances, discrete frontal regions may interact with the nucleus accumbens in a reversal learning task that is particularly sensitive to dopaminergic manipulations.

7. Neuroanatomy of consciousness: Evidence from focal brain lesions

Donald T. Stuss

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The definition of consciousness and the relationship of consciousness to the brain have been contentious issues. Stuss, Picton, and Alexander (2001) suggested that consciousness may be hierarchically organized, with disorders of consciousness being qualitatively different on this hierarchical scaffold. Patients with posterior lesions demonstrate domain specific disorders of consciousness, the domain affected related to the functions associated with that particular brain region. In addition, there are two higher order disorders that are specifically related to the frontal lobes. At one frontal lobe level the disorder of consciousness is related to the executive functions. This is illustrated by patients with Capgras Syndrome. Under specific circumstances, such as confusional states or recovering amnesia, two distinct models of the world may be created. The patient does not have appropriate executive functions to dissociate amongst these models, the consequence is a reduplicative phenomena. In contrast to the lower level (posterior brain regions) disorders of consciousness, at this higher level the knowledge of the problem is intact, but the judgement impaired. At the very highest level, disorder of consciousness exists which takes into account the individuals self and one's relationship to the entire world. Even judgement may be intact, but the ability to use this judgement in a timely manner to make decisions is significantly impaired. This metacognitive ability appears to be related particularly to the right frontal region. Several experimental tasks provide support for these ideas. Individuals with right frontal lobe damage have difficulty appreciating and responding to humorous stimuli, due to impaired ability to make appropriate self-reflective inferences. Individuals with frontal lobe damage also have difficulty on tests of perspective taking and deception, measures which have been considered as excellent indices of theory of mind, or the ability to mentalize. Such deficits cannot be reduced to disturbances in cognitive processes. The ability to take perspective of other's thoughts is less localized within the frontal lobes, although again more related to the right frontal lobe. The ability to detect deception, on the other hand, appears to be more localized in ventral medial frontal lesions, although again with some right frontal pre-eminence. Consciousness can be studied experimentally. The relation of specific processes to distinct anatomical areas does not indicate localization of consciousness, but does suggest which brain regions are particularly important as a basis for consciousness to develop and function. The right frontal lobe, often considered as "silent," appears to play a most important role in these high level human behaviours.

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8. In search of depression circuits

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Converging clinical, post-mortem, and functional neuroimaging evidence suggests that depression is unlikely a disease of a single brain region or neurotransmitter system. Rather, it is best viewed as a multidimensional, systems-level disorder affecting discrete but functionally integrated pathways involving select cortical, subcortical, and limbic sites and their related neurotransmitter, second messenger, and molecular mediators. It is further postulated that depression is not simply the result of dysfunction in one or more components, but also involves failure to maintain homeostatic control in times of increased emotional, cognitive or somatic stress. While mechanisms mediating this "failure" are not yet characterized, they are thought likely to be multifactorial, with genetic vulnerability, affective temperament, developmental insults and environmental stressors all are considered important contributors. Treatments for depression can similarly be viewed in this general framework, with different treatment modes modulating distinct targets resulting in a variety of complementary adaptive and homeostatic effects. Identification of non-invasive neural markers of these physiological, chemical, and molecular changes is one of many goals of functional neuroimaging.

Resting-state abnormalities in regional glucose metabolism and blood flow using PET have been identified in patients with depression,

including changes associated with treatment and clinical recovery. Although the relative contribution of individual regions varies as a function of clinical state, involvement of cortical, paralimbic, and subcortical regions is seen across studies. Cortical deficits normalize with treatment (state effects); paralimbic and subcortical regions show a more complex state-trait pattern. Changes in these same regions are also seen with transient provoked sadness, with differences discriminating controls from depressed patients. Common patterns seen in both unipolar and bipolar patients suggest convergent pathways mediating disturbances in mood across diagnoses including a more generalized vulnerability to emotional stressors across patient groups. Formal testing of disease-specific and state-specific functional interactions among regions in this depression "network" will be discussed, with a perspective aimed at future studies examining mechanisms underlying treatment response, relapse risk, and disease vulnerability.

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9. Apathy: Who cares?

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The syndrome of Apathy has received considerable research interest, particularly over the last 10 years or so. The data available to date suggests that this interest is highly appropriate, as apathy: (i) is common in many neurobehavioural disorders, (ii) is associated with a number of adverse outcomes, (iii) is potentially amenable to pharmacologic intervention, involving dopaminergic agents, amphetamines, acetylcholinesterase inhibitors and atypical antipsychotics, and (iv) can reveal much about the brain and behaviour relationships underlying human motivational behaviour.

The prevalence of apathy has been well studied, particularly in Alzheimer's Disease (AD). Results in AD outpatients using the Neuropsychiatric Inventory (NPI) have provided a point-prevalence rate of 65% in 261 patients. This rate is similar to that found in research using other rating scales, such as the Apathy Evaluation Scale (AES); a rate of 58.5% has been found in 738 subjects. The concordance in rates between instruments suggest that at the group level, at least, these instruments are measuring the same phenomenon. Combining results across instruments gives a point prevalence of 60.3% in 999 AD outpatients. Including other subject sources (e.g., community) gives an overall point prevalence of 55.5% for 1355 subjects in AD. Other disorders have received less attention, however the rates of apathy appear to be high in basal ganglia disorders (40.6%, $N = 589$), in Traumatic Brain Injury (61.4%, $N = 210$) in vascular dementia (33.8%, $N = 145$), post-CVA (34.7%, $N = 190$) and HIV (29.8%, $N = 181$). Apathy has been reported frequently with focal lesions of the thalamus and frontal lobes, and there are reports of apathy in other disorders as well.

Correlations of apathy with adverse outcome include, for example, r's in the range of $-.35$ to $-.5$ for outcomes such as independent functioning and care giver distress. Response to treatment for the disorder appears to be poorer when apathy is present (e.g., $r = .37$ for decreased participation in rehabilitation). Finally apathy predicts outcome of illness (e.g., $r = -.46$ for baseline apathy predicting outcome of depression).

There is preliminary evidence of efficacy for amantadine, bromocriptine and methlphenidate in apathy. Randomized Clinical Trial (RCT) level evidence exists for improved motivational behaviour with acetylcholinesterase inhibitors in Alzheimer's Disease. In schizophrenia, RCT level evidence exists for improved motivational behaviour with atypical antipsychotics such as olanzapine.

In terms of brain and behaviour relationships, neuroimaging has demonstrated decreased activity in subcortical–frontal "loops" involving anterior basal ganglia, thalamus and frontal regions (particularly anterior cingulate and DLPFC). Associated cognitive changes include an inverse relationship with the MMSE (there are also data conflicting with this), and a consistent inverse relationship with frontal system cognitive tasks. A relationship also exists between apathy and depression; apathy appears to be caused by (or associated with) depression in some cases, and shares phenomenologic features with depression (e.g., loss of interest) as well.

Frontal-system cortical–subcortical loops appear to be implicated in apathy. It has been suggested (D. Stuss) that apathy might be considered to be separate states depending on which cortical–subcortical loop is involved.

10. Disorders of clinical case studies

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People engaged in a meaningful relationship often say, "It is not what you said, but how you said it." This lecture will discuss the neuropsychology of emotional communication, including disorders of the comprehension and expression of emotional prosody and faces. Although much of the information about how the brain processes these forms of emotional communication has been obtained from studying patients who have had strokes which altered one or more of these processes, we will also discuss laterality studies performed in normal people and functional imaging.

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Part 2: Abstracts of posters

1. Sex differences in regional cerebral blood flow during the processing of facial emotion

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We were interested in localizing the regionally specific brain responses which underlie emotion processing in men and women. Using positron tomography we measured changes in regional cerebral blood flow during the performance of face detection, identity matching and emotion matching tasks and compared the distribution of rCBF produced by each task. The recognition of facial emotion by men was associated with activation of the right inferior frontal cortex, whereas in women bilateral activation of the frontal cortices was identified. Between-group comparisons of the activations associated with facial emotion processing revealed that women showed greater activation of the left inferior frontal gyrus, left fusiform gyrus and right amygdala and less right sided activation of medial frontal and superior occipital regions than did men. Localization of function to these regions is consistent with other research results identifying greater distribution and less lateralization of cognitive function in women than men.

Report

Discerning emotion in the faces of others plays a vital role in human social communication.

Functional imaging studies have explored the neuroanatomical and functional circuitry underlying this capacity and have identified the involvement of a number of localized cerebral regions including the fusiform, mid-temporal, amygdala, anterior cingulate and inferior frontal cortices. However, for the most part, the results of these studies have been discussed within the general context of emotion processing, without attention to the sex of the study group. It may be quite reasonable to expect sex differences in the functional network engaged by emotion recognition, given evidence from lesion studies identifying more bilateral representation and greater distribution of cognitive functions in females than in males (see for example McGlone, 1980).

The first imaging study to identify sex differences in the processing of emotion was conducted by (George, Ketter, Parekh, Herscovitch, & Post, 1996) and identified greater left frontal activation in women than men during a task that coupled transient self induced sadness with the presentation of sad emotional faces. The study of emotion recognition in an all female group using face stimuli depicting a broad range of emotions has identified bilateral frontal activation George et al., (1993) while the study of an all male group under similar matching demands has identified unilateral right inferior frontal activation (Nakamura et al., 1999). The study of men and women under the same experimental protocol would allow comparisons between groups and identify the circuitry used predominantly by one group or the other. Our study, therefore, was conducted to permit between group comparisons as well as confirm the results of previous studies of visual facial emotion recognition. Based on the work of George et al. (1993) and Nakamura et al. (1999) with individual groups we postulated that the activation pattern for women would be less lateralized and more distributed than that of their male counterparts.

Materials and methods

Eight male (mean age = 21 years, range = 20–23 years) and eight female (mean age = 21 years, range 20–22 years) right-handed adults without history of psychiatric or neurological disorder participated in the study. Regional cerebral blood flow was mapped while participants performed a series of trials in each of three block presentations of three visual tasks; face detection, identity matching and emotion matching. Visual stimuli were presented on a video screen at a distance of 40–50 cm. Responses to the stimuli were made using two hand-held response buttons. A computer program was used to display the activation tasks (MEL Psychology Software Tools, Pittsburgh, PA), and response latency and accuracy data were collected on each trail. Task presentation was block randomized across the participants. The face detection task required that subjects indicate the occurrence of a face in one of two choice locations, left or right. The incorrect choice location was occupied by an oval nonsense pattern. The identity recognition task required that subjects examine two choice stimuli and select the face that matched the identity of a third sample stimulus. The photographs used in the identity task were of neutrally expressive faces photographed in full face and at various angles toward profile. In the emotion matching task subjects selected from two choice stimuli the face depicting the same emotion as that shown in a third sample stimulus. The photographs were selected from a standard battery of facial affect, and the emotions depicted were happiness, sadness, anger, fear, surprise and disgust. Subjects were instructed to match according to emotional content and the individual emotions were not directly labelled for subjects.

Each subject underwent nine PET scans performed on an ECAT 953/31 PET scanner from which the interplane septa had been removed. For each scan, 466 MBq of $H_2{}^{15}O$ in 2 ml of normal saline was injected through intravenous forearm cannula. With a total administration of 4194 MBq of $H_2{}^{15}O$, the participants were exposed to an effective dose of 4.8 millisievert. Experimental trials were begun once the injection was completed and lasted 3 min. Data were acquired over six frames each 30 s in duration. Upon the completion of a block of trials, participants rested quietly for a period of 7–10 min until the next scan. Scan file data were summed across frames 3–5, reconstructed using Hann filter (cut-off frequency of 0.3), corrected for attenuation and assembled into .img format for presentation to the statistical analysis package.

Statistical Parametric Mapping (SPM 99; Wellcome Department of Cognitive Neurology, Queen Square, London, UK) was used to prepare the images and assess significant change between the task conditions. In short, reconstructed images were realigned with reference to the first scan, transformed into standard stereotaxic space and smoothed using a Gaussian kernel of 15 mm (FWHM). Within group analyses were conducted using a multi-subject repeated measures design with the threshold for identifying significant activation set at $P = .001$ (uncorrected).

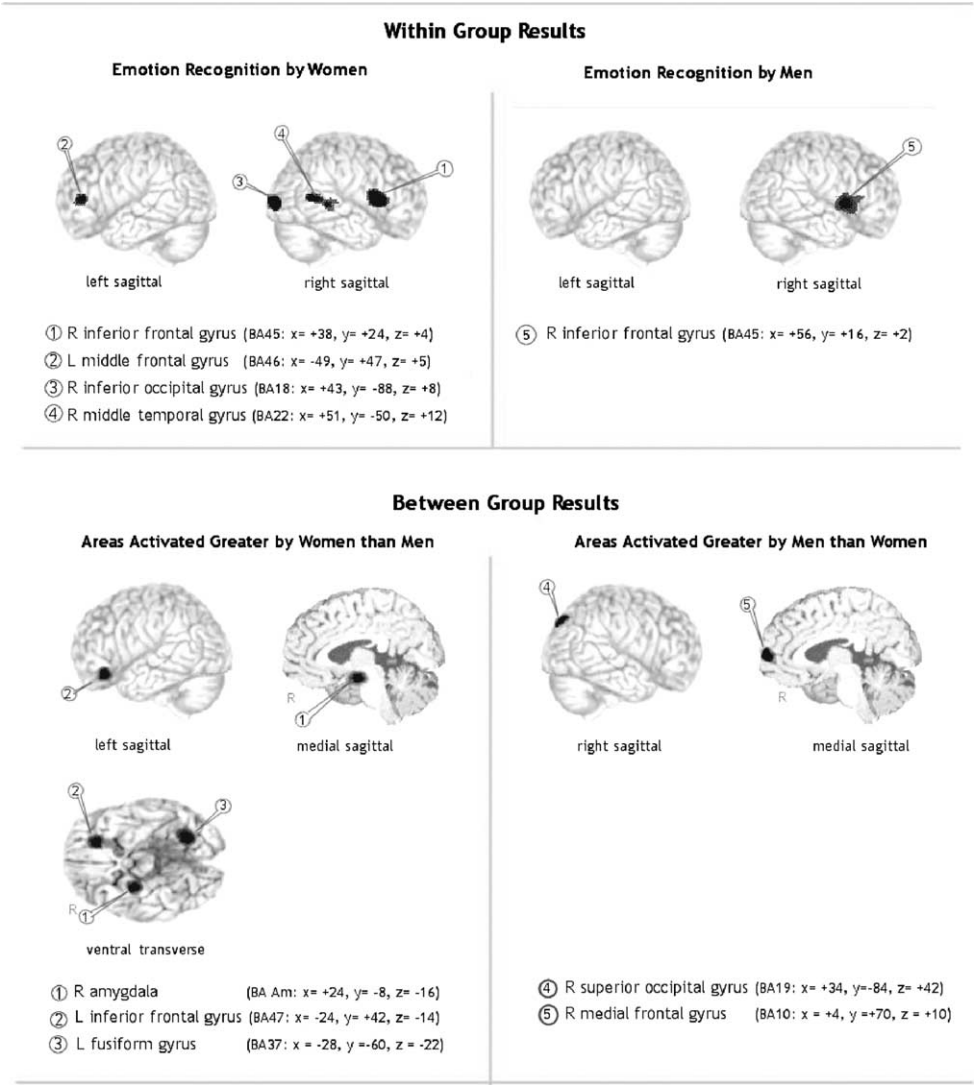

Fig. 1. Regions of activation for emotion matching contrasted with identity matching. Activations are projected onto 3-D brain templates. The coordinates of local maxima are listed along side the label for each region.

Between group comparisons of the emotion data were completed using a random-effects analysis. In this analysis inferences about a group under study are drawn from analyses that treat participant identity as a random effect. Significant activations identified using random-effects analysis relate to areas that have been activated in much the same way in all of the participants of a group and inferences are extended to the population from which subjects have been selected.

Results

Performance

Repeated measures analyses of variance were used to compare the performances of men and women on each of the task conditions. There were no differences in the errors of men and women to the detection task, to the identity task or to the emotion task. In addition there were no differences in the response latencies of men and women to the detection task, the identity task or to the emotion task.

Regional activations

When the rCBF for emotion matching was contrasted with that for the identity matching trials, thus controlling for the extraction of facial information, women activated the right inferior frontal gyrus (BA45: Z-score = 3.2), the left middle frontal gyrus (BA46: Z-score = 3.0), the right inferior occipital gyrus (BA18: Z-score = 3.3), and the right middle temporal gyrus (BA22: Z-score = 3.2). Contrasting the emotion matching with identity matching rCBF for male participants revealed activity in the right inferior frontal gyrus (BA45: Z-score = 4.0).

The between group comparisons identified greater activation for men, in contrast to women, in the right medial frontal gyrus (BA10: Z-score = 3.5), and the right superior occipital gyrus (BA19: Z-score = 3.3). Women showed greater activation than men of the left inferior frontal cortex (BA47: Z-score = 3.4), the right amygdala (BA Am: Z-score = 3.8) and the left fusiform gyrus (BA37: Z-score = 4.3) (Fig. 1).

Discussion

Our results contribute to a growing body of research detailing a functional network of localized regions engaged during the processing

of visual facial emotion and reveal that the relative contribution of these regions to emotion processing is different in men and women. The within group results showed that relative to identity recognition, the processing of facial emotion resulted in common right frontal activation in men and women and left-sided frontal activation solely in women. The inferior frontal cortices are thought to participate in emotion processing by assembling an integrated experience and guiding a subsequent response. These findings are consistent with previous research efforts (George et al., 1993; Nakamura et al., 1999) and support the notion that the processing of facial emotion may be more bilaterally distributed in women than in men. This observation is substantiated by the results of the between group comparisons which showed that visual emotion recognition resulted in greater left frontal activation in women than in men. The medial prefrontal region has been associated with modulation or inhibition of emotional responses (Reiman et al., 1997) and greater activation of this area by men may suggest that they regulated their emotional reaction to stimuli more than women. Whether this reflects a general emotive response in males or an adaptation to the speeded matching task remains a question.

In women, between group results also identified greater left fusiform activation which may be reflective of greater extraction of facial information than men during facial emotion processing or activation that has resulted from reciprocal feedback from the amygdala. In addition, the observation of greater amygdala activation in women, as compared to men, is consistent with the view that women activate a wider portion of the limbic system than men when performing emotion processing tasks (George, Ketter, Parekh, Herscovitch, & Post, 1996). An intriguing suggestion raised by the present findings is the possibility of a modular versus a distributed anatomical network processing affective facial stimuli in male and female brains, respectively.

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2. Gender-related differences in θ bandpower changes of the EEG during the presentation of erotic and child-related stimuli

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Psychophysiological studies using heart rate measures have found gender-related differences in the response to sexual arousing or infant-related stimuli. On the other hand bandpower changes in the θ frequency range of the human EEG are also know to be related to the processing of emotional stimuli. In the present study we analyzed the bandpower changes in individually adjusted θ frequency bands of 17 subjects (9 male 8 female) by means of ERD/ERS with respect to erotic and child-related stimuli. The results show gender-specific responses to erotic stimuli exhibiting a stronger increase in bandpower (activation) for the opposite sex. During the processing of child related stimuli females showed a stronger activation for laughing children while males reacted stronger during the presentation of pictures of crying children.

Report

Different psychophysiological variables, as EDA parameters, heart rate, PET, or fMRI have been used to investigate gender differences during the processing of emotional pictures. In the EEG literature there are several reports addressing emotion and gender differences but none using frequency band specific measure as event-related desynchronization/synchronization (ERD/ERS), especially none reporting the effects in the theta band. The importance of a selective and individually adjusted analysis of the θ rhythm during task-related processing has first been mentioned by Klimesch (for a detailed review 1999). Especially the selective function with respect to memory and the relation to the hippocampal-limbic system, that is also strongly involved in emotional processing, has been outlined.

Aftanas and Golocheikine (2001) analyzed ERD/ERS changes in the theta band during emotional picture processing. The results showed an increase of bandpower in the θ band for all three types of the presented pictures (neutral, negative, and positive) with a maximum at about 300 ms. In more detail the results show that at parietal, parietooccipital, and occipital sites in both hemispheres and anteriotemporal only in the left hemisphere the amount of synchronization increases from neutral stimuli to negative and then to positive.

Using heart rate response (HRR) Furedy et al. (1989) have investigated gender differences with respect to sexual and infant-related stimuli. They compared video sequences showing sexual arousing scenes to those showing crying babies. The major finding was a significant interaction of sex and stimulus indicating higher HRR (increase) for males during the erotic sequences, but lower (decreasing) responses during the baby-cry videos. Female subjects reacted in the opposite direction.

The aim of this study was to investigate effects similar to those reported by Furedy et al. (1989) by using EEG recordings and analyzing ERS% selectively in the theta band. According to the cited studies we expected strong gender related differences in the amount of theta ERS% depending on the type of stimulus.

Material and methods

Subjects

After informed consent 21 healthy right-handed subjects participated voluntarily in this study. Four of these subjects had to be excluded from analysis because of too many artifacts. From the remaining subjects 9 (mean age 25) were male and 8 (mean age 22) were female.

Procedure

EEG recording was performed in a dimly lit and quiet room. On a monitor a series of 276 pictures was presented. These pictures were from six different categories with two different subtypes (23 pictures in each subtype): Erotic (males, females); child (laughing, crying); faces (known,

unknown); landscapes (rough, lovely); buildings (known, unknown); animals (beautiful (lion, cat ...), disgusting (spider, leech ...)). All pictures have been selected out of a larger sample of total 500 pictures according to the average of a rating with respect to the category (more or less erotic, more or less happy, known, unknown, etc.) performed by 32 other subjects (16 male, 16 female). All pictures were presented in a size of approximately 15×15 cm on a black background in a pseudo randomized order for 2.5 s and a warning signal of 250 ms duration was presented 1 s before onset of the picture. The time interval from picture-offset to the next warning signal was 6.5 s.

EEG was recorded with a BEST system (0.1 35 Hz, 128/s) for the following eight positions F3, F4, C3, C4, P3, P4, O1, O2 using a common reference on the nose. Additionally EOG and VEOG have been recorded. EEG raw data have been visually inspected for artifacts. Only the erotic and the child related pictures were analyzed; all other categories were used as distractors to reduce expectancy effects.

Calculation of theta ERS%

Klimesch (1999) pointed out the importance of adjusting the frequency bands to the individual α peak. According to a procedure proposed by Doppelmayr, Klimesch, Pachinger, and Ripper (1998) we adjusted frequency bands as well as the bandwidths individually. In this study θ was defined as that frequency band in the range of 40–60% of the individual alpha peak frequency; applying this method the theta band for a subject with an individual alpha peak frequency of 12 Hz is in the range from 4.8 to 7.2 Hz, while the theta band of a subject with a lower α frequency as for example 10 Hz is in the range from 4 to 6 Hz.

The calculation of ERS% values ($=\mathrm{ERD\%}^{*}-1$) has been performed according to the ERD% formula as described in Klimesch (1999). The reference interval was set from 1500 to 500 ms. before the onset of the warning signal.

First the raw data have been bandpassfiltered. In a second step these data are squared and averaged for each stimulus type. Next the data are averaged over 250 ms. time intervals and at least the percentual increase with respect to the reference interval is computed according the formula $((\mathrm{ref}-\mathrm{test})/(\mathrm{ref}))*100$. This leads to positive values for a power decrease (ERD%). To get positive data for a power increase, which, in the theta range, can be interpreted as activation we transformed ERD% to ERS% as described.

Statistical analysis

Because most ERS effects in the theta band are within the first 500 ms only two time intervals were analyzed. For both (0–250 and 250–500 ms) ERS% values were subjected to a 5 factorial ANOVA. The factors an their levels were: GEN (gender of subject (male/female)), CAT (category (erotic/child)), SUBT (subtype (for erotic pictures (male/females), for the pictures of children (crying/laughing))), LOC (location (frontal, central, parietal and occipital)) and HEM (hemisphere (right/left)). All results are Greenhouse Geisser corrected when necessary.

Results

For time 1 only the 3-factorial interaction TYP $\times$ SUBT $\times$ GEN reached significance ($F(1,15)=8.22$, $p<.05$). As depicted males exhibit stronger ERS% values for erotic female pictures compared to male pictures and stronger ERS% for pictures of laughing children as compared to pictures of crying children. Females reacted in the opposite direction.

Additionally the main factor for TYP ($F(1,15)=4.242$, $p=0.057$) only slightly missed the 5% level and thus indicates a strong tendency for more activation (higher ERS%) for stimuli depicting children.

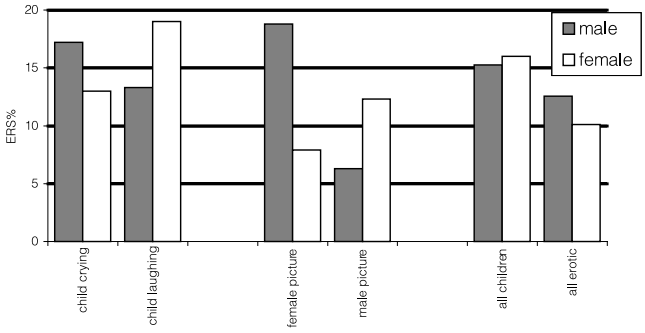

Fig. 1. ERS% of the theta band for different emotional stimuli during 0–250 ms.

For time interval 2 the factor LOC ($F(3,45)=3.16$, $p<0.05$) and the interaction TYP $\times$ LOC ($F(3,45)=3.881$, $p<0.05$) show that generally frontal and central locations exhibit the highest synchronization, followed by the occipital sites; parietal electrode position showed the lowest ERS%. While at frontal and parietal sites ERS% values for pictures of children are similar to those of erotic pictures the former show a stronger synchronization at central, and a weaker synchronization at occipital leads (Fig. 1).

Discussion

Several conclusions can be derived from these results. First we were able to replicate the findings of Furedy et al. with respect to the erotic stimuli indicating a stronger activation for males during the presentation of erotic material; on the other hand we could not replicate their results for child related pictures. While Furedy et al. found a stronger activation in females during the presentation of crying babies we had the opposite effect. It should be noted that Furedy used a longer time interval of 5 s. while we analyzed only the first 500 ms. and that our stimuli were children in the age of about 2–6 years while Furedy presented videos of babies.

Assuming that erotic pictures of the opposite sex are emotional more positive than those of the same sex, our findings are well in line with the cited results of Aftanas et al. who found higher ERS% for emotional compared to neutral stimuli. Furthermore Aftanas and Golocheikine (2001) found a positive correlation between higher theta amplitudes and emotional positive states, a result that can be interpreted in accordance with our finding.

An additional interesting aspect of our study is that there is only a minor difference in the emotional processing of laughing compared to crying children, nevertheless pictures of children exhibited generally a stronger activation than erotic stimuli, except female pictures viewed by male participants.

At last the results show clearly that an ERD/ERS analysis in the theta band is a valuable tool in studying emotions using EEG.

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3. Unattended faces interfere with recognition of facial expressions

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This work investigates if the recognition of a happy versus an angry schematic face is influenced by simultaneous presentation of a happy, angry or neutral face distractor. Measurements of choice manual reaction time (RT) were performed in 40 subjects. The target and distractor were presented for 200 ms in opposite hemifields. When the attended and the unattended faces were the same, reaction times reached the smallest values. When the unattended faces were incongruent but neutral, reaction time was slower, while for the unattended incongruent faces of opposite valences the delay was maximal. These data show that the presence of an unattended face strongly interferes on a choice reaction time task. The emotional incongruence then appears to impart the highest cost to the task.

Report

For adaptive behavior the brain has to select goal-relevant stimuli for privileged processing by mechanisms of attention and additionally detect potentially significant events that may occur unpredictably outside the focus of attention. Stimuli that are unattended are often perceived less accurately and may escape awareness. However, this may not be the case for stimuli with emotional significance (Mack & Rock, 1998). Faces are considered as visual stimuli with relevant biological and social features for the human being. There are evidences that faces are easier detected than other complex visual stimuli even in situations of inattention (Mack & Rock, 1998). Vuilleumier and Schwartz (2001) showed in patients with right parietal stroke that emotional faces capture attention in the unattended neglected side. Furthermore, de Gelder, Pourtois, van Raamsdonk, Vroomen, and Weinskrantz (2001) showed that a subject with extensive lesion of striate cortex presents differential performance in recognition of facial expressions in the intact visual field depending on simultaneous presentation of congruent or incongruent face stimuli in the blind field. Would bilateral presentation of faces, one side attended—the other unattended, elicit similar interference in normal viewers? In the present work we investigate this issue by testing for the interference of unattended emotional faces on the recognition of facial expressions.

Forty right-handed volunteers (20 women) with ages ranging from 17 to 31 years took part of the experiments. Subjects were graduate and undergraduate students, self-reported no neurological or psychiatric disorders and none were taking medication. All of them had normal or corrected vision. The local ethics committee approved the experimental protocol and each of the subjects gave their written consent prior to the study.

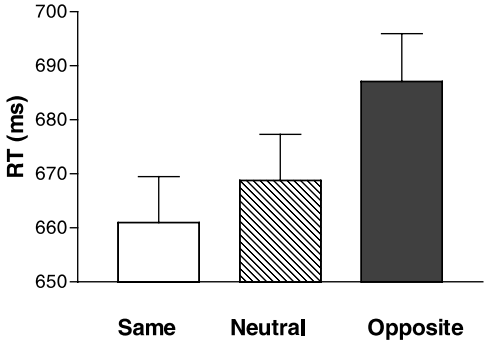

Fig. 1. Mean and standard error of reaction time when the distractor was *same*, *neutral*, or *opposite*.

Schematic faces were used as stimuli. The task consisted on the identification of a happy or an angry expression presented at one visual hemifield. A neutral (N), a happy (H) or an angry (A) distractor face was simultaneously presented at the other hemifield. Target and distractor were displayed each at 6 degrees from a central fixation point. Eye movements were monitored by EOG recordings. Subjects were instructed to press one of two keys, with the right thumb or index finger whenever the happy or the angry face appeared in the attended hemifield. The six combinations of targets and distractors (A/A, A/H, A/N, H/H, H/A, and H/N) were randomized. Each trial began with the presentation of the fixation point for 500ms followed by the presentation of the pair faces for 200 ms. Fixation point and faces were presented in black on a gray screen. A new trial began 1000 ms following subject's response. The experimental sessions (training and test) consisted of four blocks of 90 trials each. They started with two consecutive blocks displaying the target faces at one hemifield, followed by two blocks at the other hemifield. This order was randomized between subjects. The data obtained in the training block was not used for analysis.

Data were analyzed by ANOVA with the reaction times as the dependent variable and three factors as repeated measures: distractor, target (happy versus angry) and hemifield (right versus left). For distractor, there were three levels: same (or congruent), neutral and opposite (or emotionally incongruent). The level of significance adopted was $P < .01$. There was a significant main effect for distractor ($F(2, 78) = 44, 64$; $p < .0001$). The three conditions differ from each other: the *opposite* was the slowest (687 ms) followed by *neutral* (668 ms), the *same* (661 ms) being the fastest condition (Fig. 1). Post hoc analysis (Newman–Keuls) showed that *opposite* was significantly different from *neutral* ($p = .0001$) and *neutral* from *same* condition ($p = .007$).

These data show that the presence of an unattended face strongly interferes on a choice reaction time task consisting on the discrimination of a happy versus an angry face. When the attended and the unattended faces were the same, reaction times reached the smallest values. When the unattended face was incongruent but neutral, reaction time was slower, while for the unattended incongruent face of opposite valence the delay was maximal. The emotional incongruency then appears to impart the highest cost to the task. Interestingly, de Gelder et al. (2001) testing a rather similar paradigm on a blind-sight patient found an equivalent "three-steps" response. The authors also presented a pair of faces. Those were photographs of real faces with angry and fearful (or sad) expressions as targets in the intact field. The same stimuli plus neutral faces were presented at the blindsight field. The "unseen" stimulus (because of a V1 lesion) and the "unattended" stimulus in normal subjects, though, seem to modulate the emotional choice task in a similar way. Such an interference was also reported on a non-emotional choice task by Vuilleumier, Armony, Driver, and Dolan (2001). They showed in normal subjects that fearful as com-

pared to neutral unattended faces renders the attended task slower. The capture of attention by emotional faces seems to be adaptive given the profound social significance of facial expressions. Indeed, as pointed out by Rolls (1999) the sight of a smiling face or an angry face could act as an innate or unlearned reinforcer for primates. The emotion expressed in a face perceived outside the focus of attention can subsequently guide the focus of attention to the location of the face. When a subject is concerned with an attended task, it may be advantageous to automatically monitor the perceptual field for potentially relevant stimuli.

Acknowledgments

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4. Cultural differences in facial emotion recognition

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In light of the recent development of a new set of facial emotion photographs by Matsumoto and Ekman (1988) using Japanese posers, there seems to be a lack of validation studies employing Chinese samples. The speculation that there may be differences in terms of the cultural tendency to suppress overt expression of certain emotions between Asians and Caucasians which may subsequently affect the former's recognition of facial emotion expression based on the photographs developed by Matsumoto and Ekman (1988), serves as the basic rationale for this study. Introductory Psychology students (N=120) were requested to rate 12 selected photographs expressing the six basic emotions. The results indicated that these photographs were reliably judged with their intended emotion, except for those depicting anger and fear.

Report

Facial emotion is probably the most widely investigated form of emotion, relative to other forms of emotion such as prosody, and olfactory emotion. Recently, Matsumoto and Ekman (1988) have developed a new set of facial emotion expression stimuli based on both male and female posers from Japan. These photographs have been validated in many countries, including United States, Sumatra, Vietnam, Poland, Hungary, and Japan. However, acceptable agreement levels (the percentage of people judging each photograph as conveying the intended emotion) across all basic emotions have been obtained in United States only. Specifically, agreement levels obtained for Japanese photographs in a Japanese population were surprisingly low, with the lowest agreement level being 52.3% for a male photograph depicting sadness. This lack of consistent high agreement levels for Japanese photographs across different emotions suggests that there may be a cultural difference in the use of emotion labels for facial emotions. Such differences may also exist for Chinese people's recognition of facial expressions of emotions. In contrast to this speculation, there seems to be a general lack of validation studies for these stimuli within the Chinese population. Hence, the purpose of the present study is to investigate whether these photographs developed by Matsumoto and Ekman (1988) would obtain similar results in a Chinese sample. Evaluation of these photographs is deemed necessary before any investigations of the impact of various neurological pathologies on emotion recognition in Chinese populations could be conducted.

Method

Participants

One hundred and twenty Introductory Psychology students (31 males and 89 females) were recruited for this study. The mean age for males and females was 19.58 ($SD = 1.06$) and 19.38 ($SD = 0.61$) respectively. Informed consent was obtained from all participantsin this study. At the end of the study, a feedback sheet containing some background information about the study was given. One research credit was awarded to all participants for their participation that counted towards their Introductory Psychology course requirement. This study took approximately 20 min to complete.

Materials

Photographs from the Japanese and Caucasian Facial Expressions of Emotion (JACFEE; Matsumoto and Ekman, 1988) were used for this study. However, only 12 pictures of Japanese people from a total of 24 pictures of Japanese people (balanced for males and females) were used. The selection of these photographs was based on their level agreement in terms of their perceived emotion in the latest validation study (Matsumoto & Ekman, 1988). That is, there were two photographs to choose from for each combination of sex and type of emotion displayed. Although validation results for both Japanese and American samples were examined, the former results (from the Japanese sample) took precedence in cases of conflicting results. Photographs with the higher agreement level amongst the two photographs depicting each basic emotion were selected for the purpose of the present study.

Each photograph conveyed one of the six basic emotions (e.g., happy, sad, anger, surprise, disgust, and fear), and is posed by different people. That is, each poser contributes to only one photograph. These photographs were taken together and administered in a randomized order during an identification task. In this identification task, these photographs are presented individually for 10 seconds on a large classroom screen projector. Participants were requested to indicate which of the six basic emotions was conveyed in each photograph by indicating one of the following: 1 = happy, 2 = sad, 3 = anger, 4 = surprise, 5 = disgust, and 6 = fear.

Results

Table 1 contains the agreement levels (in percentages) for each individual photograph. The average agreement level obtained across all male and female photographs from Matsumoto and Ekman (1988) are 81.4% and 78.9%, respectively.

Table 1
Agreement levels (%) for photographs depicting facial emotions

Emotion	Sex of poser	Agreement level
Happy	M	**100.0**
	F	**98.3**
Sad	M	**88.3**
	F	**95.0**
Anger	M	32.5
	F	48.3
Surprise	M	**95.0**
	F	**91.7**
Disgust	M	**87.5**
	F	**89.2**
Fear	M	70.0
	F	65.8

Note. M and F refers to male and female photographs, respectively. Values represent the percentage of participants judging a particular photograph as conveying the intended emotion. Numbers in bold represent values of acceptable agreement level.

Acceptable agreement levels were obtained for both male and female photographs depicting all six basic emotions, with the exception of those depicting anger and fear. For the female photograph depicting anger, 37.5% of the participants judged it as expressing disgust, 13.3% judged it as expressing sadness, and 0.8 judged it as expressing surprise. The female photograph depicting fear lead 31.7% of the participant to judge it as expressing surprise and 2.5% to judge it as expressing disgust. For male photographs, only the one depicting anger was problematic; with 50% of the participants judging it as expressing disgust, while 13.3% judged it as expressing sadness, 3.3% judged it as expressing surprise, and 0.8% judged it as expressing happiness.

Discussion

Photographs depicting basic emotions posed by Japanese posers have obtained acceptable levels of agreement in the present Chinese sample, with the exception of those depicting anger and fear. Specifically, anger and disgust were sometimes confused interchangeably with each other. Fear was mostly confused as surprise, though this was true only for the female photograph. A plausible explanation may be that people in Chinese cultures may not necessarily have the same tendencies in overtly expressing emotion, especially for negative emotions such as anger, disgust, and fear, in accordance with Confusianism. In support of this explanation, Cheung (2000) has obtained similar pattern of results to the present study, based on another set of male photographs developed by Wang (2001). Hence, the low reliability for Matsumoto and Ekman's (1988) photographs depicting anger, fear, and surprise in the present study may not necessarily be stimuli-specific, but rather due to the rater's cultural tendency to suppress overt expression of these emotions. With this in mind, the agreement levels obtained in the present study may in fact reflect acceptable validity of Matsumoto and Ekman's (1988) photographs within Chinese populations. However, this speculation needs to be further investigated by employing emotion stimuli in various channels of input (e.g., auditory and olfactory), as well as people from both Asian and Western cultures.

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5. Perceptual space of six basic emotional expressions of healthy Hong Kong Chinese: A pilot study

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The current report is a pilot study investigating the perceptual pattern of the six basic facial emotional expressions (happy, sadness, anger, fear, surprise, and disgust). We first recruited 28 healthy university undergraduates (Mean age = 20.2, $SD = 1.5$) to rate the dissimilarity of pairs of emotional expressions from a set of 18 photos of basic emotion, then we employed the multidimensional scaling technique to reconstruct the perceptual space of the stimuli. A three-dimensional solution was chosen. The *X*-axis is suggested to be related to the pleasantness of the facial expression, whilst we are not sure about the other two axes. Potential weakness for Hong Kong Chinese in distinguishing fear and surprise, and anger and disgust was observed and discussed, and further study was suggested.

Report

In the literature there exist substantial evidences supporting the universality of several basic emotional expressions (e.g. Biehl et al., 1997). Yet the ability for different cultures to recognize these basic emotions varies. For example, Japanese was noted to be relatively worse in recognizing anger and sadness than some other countries like Americans and Poles; Vietnamese was noted to be bad at identifying disgust (Biehl et al., 1997). These findings suggested that cultural-specific qualities, for example, cultural values and emotional expressiveness, might play a role in affecting the development of the ability to recognize different emotions. In Hong Kong, several pieces of research had been conducted to examine the emotional recognition ability in several clinical groups (for example, Leung & Singh, 1998). With these findings some researchers (see Leung & Singh, 1998) suggested that there might exist cultural influence on the ability to recognize different basic emotional expressions. However, one problem arise with the generalizability of such findings to the general public in Hong Kong as the participants were recruited from the clinical population, or they were teenagers below 15 years old. We did not have data on the healthy, cognitively matured adults' performance to recognize different basic emotional expressions in the Hong Kong population.

With the above reason we initiated this pilot study to investigate the perceptual pattern of six basic emotional expressions of healthy Hong Kong Chinese. Unlike previous research using the forced-choice paradigm to examine the accuracy of emotional recognition, we attempted to address the issue from another perspective. We employed the multidimensional scaling (MDS) technique to examine the perceptual pattern of six basic emotional expressions. With this technique, we were able to estimate the perceptual distances between each emotion, and we were also able to visualize the relative positions of the stimulus in a reconstructed perceptual space. This is indeed an advantage provided by the MDS technique as we could examine how confusing different emotional expressions are when people are asked to judge them.

Method

Participants

Twenty-eight undergraduates from the University of Hong Kong volunteered to participate in the study. All participants were ethnic Chinese (12 male and 16 female) living in Hong Kong. They were healthy young adults (Mean age = 20.2, $SD = 1.5$) without known psychiatric record.

Stimuli

Two sets of photographs portraying the six basic facial emotion expressions (i.e., happy, sad, fear, surprise, anger, and disgust) were used in the study. A set of 12 photographs of six emotional expressions, i.e. two for each expression, were selected from the Japanese male subset of the Japanese and Caucasian Facial Expressions of Emotion (JACFEE, Photo E5, E6, E21, E22, E29, E30, E37, E38, E45, E46, E53, and E54) developed and validated across different cultures by Matsumoto and Ekman (1988). Another set of photographs, developed and validated in Hong Kong by Wang (2001), was also included in this study. This photo set, consisted of six basic facial expressions portrayed by a male professional Chinese actor, was validated in a similar way to that of Matsumoto and Ekman (1988). These two sets of stimuli together provided us a mix of photographs with both cross-cultural and cultural-specific validity, plus an advantage for us to obtain enough data point for possible higher dimensional solutions in the multidimensional scaling processes. We did not include photos of female posers from the JACFEE in this study in order to minimize possible judgment errors caused by different gender of posers.

Several steps were taken to enhance the compatibility of the two stimulus sets. The first step was to convert the full-colour JACFEE digital photos into 256 gray-scale photos with Microsoft Window's Paint Brush program because Wang's set of photo was in 256 gray-scale format. Then the photos from the JACFEE set were edited to a size of 10.8 cm × 11.2 cm, with parts of the photo other than the face of the poser removed. After processing the photos a booklet was printed with each page containing one pair of stimulus. A total number of 153 photo pairs were generated by pairing each photo with the other seventeen photos; the pairs of photos were presented in a randomized order in the booklet.

Procedures

Each participant was tested individually. The stimulus booklet was presented to the participants and they were asked to judge how dissimilar the pairs of facial expressions are. Participants rated the dissimilarity of the photo pairs using a 5-point scale (from zero to four), with the anchor "no difference" placed at zero and the anchor "completely different" placed at four. Participants were instructed to ignore the differences of the actors other than the facial expressions conveyed in each photograph in order to avoid judgments based on attributes other than the poser's emotional expression. Most of the participants finished the whole series of judgments within 20–25 min.

Results

The proximity matrix was analyzed using the ALSCAL algorithm with the SPSS (Windows Version 10.0) program. We generated several solutions starting from one dimensions to six dimensions for consider-

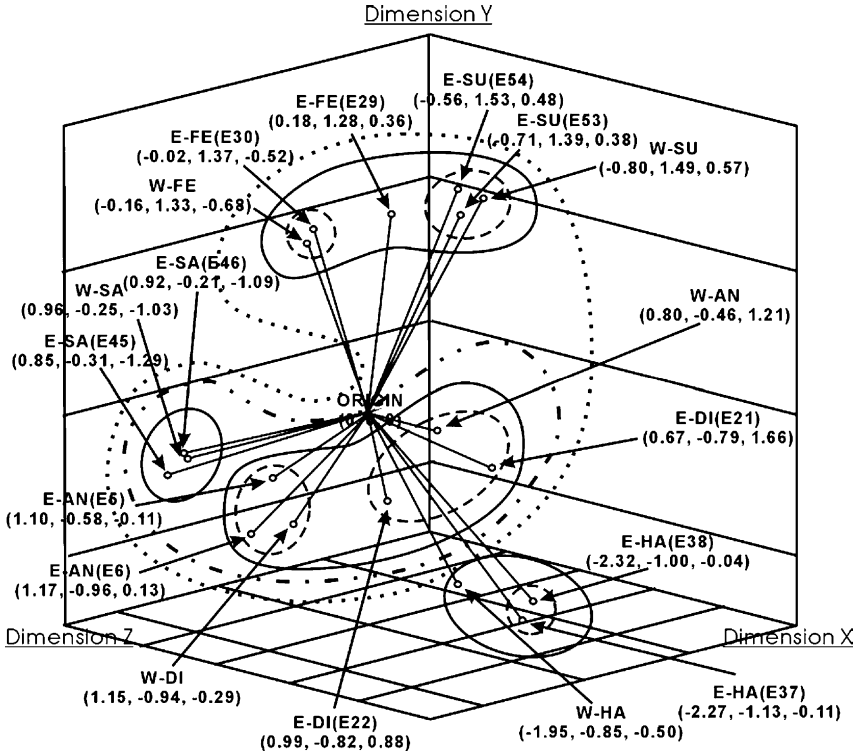

Fig. 1. Plot of the three-dimensional solution. First letter of the label indicates the stimulus set (E = Matsumoto and Ekman; W = Wang). The latter indicate the emotional expression (HA = Happy; SA = Sadness; AN = Anger; DI = Disgust; FE = Fear; and SU = Surprise). Respective JACFEE codes (for Matsumoto & Ekman's photo) and coordinates (X, Y, Z) are shown in brackets.

ation (Stress = .26, .18, .11, .08, .06, .04, and R^2 = .84, .87, .93, .94, .96, and .98, respectively). Choice of dimension was based on the criteria suggested by Kruskal and Wish (1978): goodness-of-fit of data, interpretability of solution, and the number of stimuli used. Despite the relatively smaller stress values and higher R-squares provided by the five- and six-dimensional solutions, they were not considered because the number of stimuli used in this study was inappropriate for solutions higher than four dimensions (the rule-of-thumb is number of stimuli minus one should be at least four times the number of dimensions adopted, Kruskal & Wish, 1978). Plotting the stress values against the number of dimensions, we found that the "elbow" of the curve lay at the three-dimensional solution (Kruskal & Wish, 1978). Thus we adopted a three-dimensional solution with its reasonable interpretability.

In order to aid the interpretation of the MDS solution, we performed a hierarchical cluster analysis on the three-dimensional configuration (using the neighborhood approach as suggested by Kruskal & Wish, 1978). Fig. 1 presented a reconstruction of the perceptual space of the three-dimensional solution, with boundaries indicating the identified clusters. The happy stimuli stood out to be one single cluster, with other emotions formed another big cluster. Then the big cluster was further split into two groups, with one containing sadness, anger and disgust stimuli and the other containing surprise and fear. Examining the subdivision of these two groups, we adopted a four-clusters solution (in concrete lines), with happy stimuli in one cluster, sadness stimuli in another one, and the other two major clusters each consist of two types of basic emotions. One of them consists two minor clusters (in dashed ellipses) of surprise and fear, whilst the other one consists two minor clusters (in dashed ellipses) with a mixture of anger and disgust.

Discussion

With the multidimensional scaling technique and hierarchical cluster analysis, we selected a three-dimensional solution with four major clusters formed. Examining the three different dimensions, we suggested that the *X*-axis reflects the pleasantness of the facial expression, with happy stimuli located on one side ($X = -1.95$ to 2.32) and the other five emotions located on other side ($X = 1.17$ to -0.8) of the *X*-axis. For the other two axes, no clear attributes could be found. They might reflect some subtle attributes that our participants used to distinguish different emotional expressions, e.g., the curling/opening of mouth.

Although no obvious labels were given to the *Y*- and *Z*-axes, from the cluster formation we observed some interesting perceptual patterns of the six basic emotions. In line with previous research (e.g., Biehl et al., 1997), happy and sadness appeared to be most distinctive basic emotions. Among the rest, fear and surprise seemed to fall on the same dimension while disgust and anger fall on another, as indicated by the two clusters formed by the four emotional stimuli. We noticed that there may exist stimuli differences on anger and disgust between Matsumoto and Ekman's and Wang's photo set, yet the two emotions were all lay in the same cluster. In view of our participants' characteristics (i.e., young, well-educated, cognitively and intellectually high functioning), we speculated that our findings indicated a weakness for Hong Kong Chinese to distinguish between anger and disgust, and between fear and surprise. Employing various researchers' argument (Biehl et al., 1997, Leung & Singh, 1998) on the cultural differences on emotional recognition ability, such perceptual pattern of the six basic emotions might be the result of the influence of the Chinese culture in the development of such abilities.

Further research

We did not employ a statistical method to explain the dimensions of the MDS solution in this study but to focus on the perceptual pattern of the stimuli. With regard to this limitation, we suggested that techniques such as property vector fitting could be employed to investigate the property of the dimensions. With further research we not only aim at consolidating our preliminary findings in this study, but also expanding our scope to compare the perceptual patterns of the six basic emotions cross-culturally.

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6. Impaired recognition of negative facial emotions in patients with fronto-temporal dementia

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Frontotemporal dementia (FTD) is often characterized by diminished empathy and impaired social skills. These deficits may reflect in part an inability to recognize facial expressions. We investigated the ability of patients with FTD and 20 normal controls to recognize facial expressions of basic emotions. The patients performed normally in recognizing happy faces, but 7 out of 8 patients were severely impaired in recognizing the other emotions (sad, angry, disgust, surprised, frightened, and neutral). We discuss the implications of these findings in relation to the changes in social behavior exhibited by patients with FTD.

Report

Frontotemporal dementia (FTD) encompasses a heterogeneous group of dementias with varied clinical and pathological presentations. The frontal variant of the disease (fv-FTD) is characterized by changes in personality, impaired social skills, poor decision making, lack of empathy and lack of insight (Rahman et al., 1999). Bilateral dysfunction of the orbitofrontal cortex is thought to contribute to these deficits since patients with orbitofrontal lesions from trauma or stroke show similar deficits to those with fv-FTD (Hornak et al., 1996). Right temporal predominance in FTD can also cause altered emotional responsiveness and inappropriate social behavior (Perry et al., 2001). Bilateral involvement of the anterior temporal regions in FTD causes problems in

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word comprehension and object recognition, leading to the so-called semantic dementia, whereas left fronto-temporal predominance presents as primary progressive aphasia of the non-fluent type.

It is possible that the inability of patients with FTD to behave appropriately in social situations and to show sympathy for other people's feelings stems in part from an inability to recognize facial expressions. Faces convey information about people's feelings, as well as their reaction to the social behavior of others. Thus, impaired recognition of facial expressions would put FTD patients at a disadvantage in social situations, where other cues are frequently ambiguous.

There are neuroanatomical reasons to hypothesize that the evaluation of facial emotion could be impaired in FTD, as many of the brain areas known to participate in the recognition of facial emotion are compromised in FTD. Face-selective neurons exist in the anterior temporal lobe. Neurons in the temporal lobe project heavily to the amygdala, which plays a critical role in the recognition of facial expressions of fear, as both neuropsychological and neuroimaging studies have revealed (Adolphs, Tranel, Damasio, & Damasio, 1994). Right temporal lobe lesions lead to a deficit in facial emotion evaluation (Perry et al., 2001). A recent study reported that two FTD patients with right temporal lobe atrophy were impaired in the naming of facial emotions (Perry et al., 2001). Orbitofrontal cortex, which is frequently abnormal in functional imaging of FTD, appears to be important in the recognition of anger (Blair, Morris, Frith, Perret, & Dolan, 1999).

Methods

Twenty young adults (mean age: 20 years $SD = 2.7$) and eight patients (mean age = 63 years $SD = 8$) with clinical diagnosis of fronto-temporal dementia participated in the study. All patients showed characteristic changes in personality, as assessed by their caregivers who frequently reported the patients to be less caring than they used to be. The patients underwent full neuropsychological assessment including an aphasia battery showing adequate comprehension, as well as SPECT and MRI. They participated in other experimental tasks that will be reported elsewhere (Fernandez-Duque, S. Hodges, and Black, in preparation).

Photographs of neutral faces and the six basic emotions (sad, happy, surprised, angry, disgusted, and frightened) from the Ekman and Friesen series were used. Faces were presented on a laptop computer, one at a time for a maximum of 30 s, or until the subject responded. The emotion labels were displayed on either side of the face and remained there during the whole test. The labels 'sad', 'happy', and 'surprised' appeared on the left side, the labels 'disgusted', 'frightened', and 'angry' appeared on the right side, and the label 'neutral' appeared centered below the face. Subjects reported their responses by touching the screen, which recorded the response. There were seven practice trials (one for each emotion), followed by 56 test trials (7 for each emotion). The photographs were presented in random order.

Results

Young adults were quite accurate in recognizing each of the seven different emotions. For young adults, no emotion was significantly easier or significantly more difficult to recognize than any other. Their overall accuracy was 93%, with a standard deviation of 10%, giving a 5th percentile cutoff of 73%. Seven out of 8 patients scored below this cutoff performance (1.64 standard deviations below the mean).

The deficit exhibited by FTD patients was dependent on the emotion type. Patients were significantly better at recognizing happy faces than at recognizing any other emotion (see Table 1). In fact, the patients' ability to recognize happy faces was as good as normal controls. In contrast, patients were significantly worse than normal subjects at recognizing any other emotion.

Discussion

The current study reveals that patients with frontotemporal dementia are impaired in their ability to recognize facial expressions of emotions. The present data also reveal that the ability to recognize facial expressions of happiness is spared in FTD patients, even when the recognition of any other basic emotions is faulty. This pattern of results might help to explain the lack of empathy frequently exhibited by these patients. How poor recognition of facial expressions relates to the other emotional problems exhibited by FTD patients remains to be explored. For example, future studies need to determine whether the impairment extends to other, non-emotional, facial attributes. It will also be important to explore whether deficits in emotion recognition stem from a conceptual deficit, such as an inability to understand other people's mental states. Pursuing these questions will not only further our understanding of frontotemporal dementia but will also give insight into the interaction of emotion, perception, and cognition in human social behavior.

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Table 1
Percent correct (and standard deviations) for facial expression identification in young normal controls and patients with fronto-temporal dementia

	Happy	Angry	Disgusted	Frightened	Sad	Surprised	Neutral	Average
Young	96 (7.9)	94 (8.5)	89 (19.3)	88 (13.4)	89 (15.4)	98 (4.3)	98 (4.3)	93 (10)
FTD	95 (7.2)	43 (28)	63 (32)	54 (19)	46 (30)	64 (17)	53 (28)	60
Case								
1	86	29[a]	50[a]	50[a]	29[a]	71[a]	57[a]	53[a]
2	100	43[a]	50[a]	17[a]	29[a]	43[a]	14[a]	42[a]
3	100	0[a]	67	50[a]	57[a]	57[a]	100	62[a]
4	100	86	100	50[a]	86	86[a]	86[a]	85
5	86	14[a]	0[a]	83	29[a]	71[a]	43[a]	47[a]
6	100	43[a]	100	67	0[a]	57[a]	29[a]	57[a]
7	86	57[a]	71	50[a]	57[a]	43[a]	57[a]	60[a]
8	100	71[a]	71	67	86	86[a]	43[a]	75[b]

[a] Scores that fall below the 1st percentile of the normal distribution (i.e., $SD < -1.96$).
[b] Scores that fall below the 5th percentile of the normal distribution (i.e., $SD < -1.64$).

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7. Facial emotion expression perception following neurosurgical prefrontal lesions

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The study investigated facial emotional expression in 31 patients with focal neurosurgical prefrontal lesions, comparing their performance to 31 age and IQ matched controls. The participants were given tasks measuring basic facial processing and the ability to detect the emotional expression of faces. The frontal group showed no impairment in basic face processing, but significant impairment in facial emotional expression perception. A task which involved selecting faces following a verbal prompt proved more sensitive to impairment than matching facial expression. Patients with lesions in different regions of the prefrontal cortex showed no difference in the extent of their deficit. It was concluded that the prefrontal cortex is involved in processing facial emotional expression, but the involvement is shown not be limited to one particular region.

Report

Specific brain systems which support the ability to recognise the emotional expression of faces have been postulated. In support of this, patients with selective impairments in this function have been identified (Calder et al., 1996; Hornak, Rolls, & Wade, 1996) and neuroimaging studies have indicated brain correlates of the perception of different types of emotional expressions (e.g., Morris et al., 1998). Such studies have implicated the amygdala, the insula and the prefrontal cortex.

The role of the prefrontal cortex in this function is indicated by the connectivity between orbitofrontal and temporal cortex and evidence that this region is differential active when processing the emotional aspect of faces (e.g., Streit et al., 1999). Preliminary support is also provided by Hornak et al. (1996), who investigated the effects of ventral prefrontal cortical lesions on facial expression recognition, using the Ekman and Friesen (1976) series of faces. In this study, they required the subjects to select the best adjective to label a face from a list of basic emotions and also to describe facial expressions. A significant impairment was found when comparing ventral and non-ventral groups and zthe deficits correlated with observable changes in behaviour. However, the ventral lesion group also had more widespread brain damage than the prefrontal cortex, consequently limiting conclusion to be drawn about the neural basis of facial expression processing.

The aim of study was to investigate facial expression recognition in patients with focal neurosurgical lesions, comparing those with lesions in the orbitofrontal, mesial and dorsolateral cortex. Additionally, the study incorporated control tasks in relation to basic face processing and used different techniques for determining facial expression processing.

Method

Participants

Thirty one patients (mean age = 42.2 years; nart-r iq = 102.2) who had unilateral prefrontal cortical neurosurgery were included in the study (15 right sided; rf; and 16 left sided; lf). Details of the patients with location of brain lesions is given in Rowe et al. (2001). The number of patients involving different sectors of the brain are as follows. Right dorsolateral 9; right medial 9; right orbital 9; left dorsolateral 7; left medial 14; left orbital 15. The exclusion criteria were brain damage other than in the prefrontal cortex, a history psychiatric disorder and physical illness that could affect brain function. They were compared to 31 healthy controls subjects (mean age = 41.6 years; nart-r iq = 104.l). A comprehensive neurpsychological assessment was conducted on both groups and there was no difference in current wais-r intelligence, memory function, including logical memory and visual reproduction. The patients were significantly impaired on tests of executive functioning, including the wcst percent perseverative errors, trail making, stroop test and fas.

Face perception

To test whether impairment in facial emotional expression could be due to underlying impairment in face recognition, two tests were administered, the Benton Face Recognition test and the Warrington Recognition Memory tests. The patients were not impairment on either of these tests.

Experimental tests of facial emotional perception

Two tasks were used to test different aspects of facial expression emotion. In each case the Ekman and Friesen (1976) series of faces was used, with six basic emotions; happy, sad, fear, anger, disgust and surprise. Each task had 12 trials, 2 for each expression.

Perceptual categorisation. A target expression was presented simultaneously with six basic expressions and the subject had to select the matching expression. In this task, the same individual posed the expressions for each trial.

Verbal prompt identification. Displays of photographs of six different emotions were presented and the subject was asked to point to a particular expression following a verbal prompt.

Results

For each task, the LF and RF groups were considered separately and compared to the control participants. A total score, summing across the six expressions was considered and the expressions also considered individually.

Perceptual categorisation. Both the RF and LF groups were impaired on the total score. When considering individual faces, the LF group only were impaired on the fear and surprise faces.

Verbal identification. The RF and LF groups were again impaired on the total score. They were also impaired on sadness, anger, and disgust. With anger, the deficit was significantly greater in the RF group.

Brain region analysis. The patients were further classified according to the prefrontal sectors into which the lesions encroached. Analyses were conducted comparing patients whose lesions in a particular area

with those that did not. This did not reveal any differences between patient groups.

Confusability. Further analysis were conducted determining the types of errors made on the tasks and the confusability matrices between different emotions analysed.

Discussion

The aim of the study was to investigate whether focal prefrontal cortical lesions impair the perception of emotional expression. The results suggest this to be the case and supports the presence of impairment with unilateral lesions. Furthermore, this impairment is not due to difficulties with basic face processing.

The results also showed specificity in relation to different types of emotions, but not consistently between tasks used. Across the main two techniques, the impairments were more widespread when the subjects were required to point to a particular expression, given a verbal prompt. This result may suggest that facial expression matching is a less sensitive measure in these patients. Possibly, the patients were able adopt ameliorative strategies more readily in this condition, for example, matching specific features of faces, without necessary encoding emotions.

The study also found no differences in the severity of impairment when comparing patients with lesions brain lesions in different locations. This either suggests that lesions in the patient groups may not have been sufficiently circumscribed to detect these differences; or alternatively, facial emotional processing incorporates a more widespread functional cortical network involving the prefrontal cortex.

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8. Deficits in facial emotion perception in recently traumatically brain injured adults

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The impaired ability to recognize emotion in faces (for example, an inability to distinguish a fearful face from an angry face) has significant implications for social and occupational functioning. To date, such impairments have been investigated primarily in neurological populations with focal lesions, but not in traumatic brain injury. In the present study, a group of recently traumatically brain-injured adults (**N = 17**) were assessed for deficits in facial emotion perception using the Florida Affect Battery-Revised. The group was significantly impaired on all facial emotion perception tasks relative to a neutral control task, when compared to an age and education matched control group. The present findings have clinical implications; they also provide preliminary evidence for the role of diffuse axonal injury in facial emotion perception.

Report

Deficits in facial emotion perception have been investigated for several decades (see Borod et al., 1998; Heilman & Gilmore, 1998, for reviews). Studies have focused primarily on a narrow range of patient populations, primarily stroke (Borod et al., 1998). These studies have generally implicated right posterior focal lesions (i.e. temporal, parietal, and occipital). Recent studies in this area have also implicated prefrontal lesions (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Hornak, Rolls, & Wade, 1996), though here, only a subset of facial emotion perception tasks were examined (i.e., those requiring verbal labeling of the emotion). Few studies have investigated facial emotion perception in traumatic brain injury (TBI) patients. TBI is ubiquitous, and because patients with TBI are well known for their difficulty in reintegrating into the community following injury, it is reasonable and important to ask whether part of this problem may be attributable to emotion perception deficits. Recent studies have suggested that a network of pathways underpinned by white matter tracts is necessary for the perception of emotion in faces (Adolphs et al., 2000). Thus, diffuse axonal injury, a hallmark of neurological injury in TBI, might therefore leave patients vulnerable to deficits in emotion perception.

In the present study, we asked whether TBI patients display deficits in facial emotion perception. Secondarily, we explored the question of the neurological underpinnings of facial emotion perception by dividing our patient group into those with and those without right posterior focal injury. Since facial emotion perception is compromised by right posterior focal lesions, we would expect that patients *without* such lesions would show lesser facial emotion perception impairment on our tests.

Predictions

1. TBI patients will demonstrate significant impairments on facial emotion perception tasks in comparison to age and education matched controls.
2. TBI patients without right posterior focal lesions will perform better on facial emotion perception tasks than TBI patients with such lesions.

Methods

Participants

Prediction 1: Patients ($N = 17$) were recruited from Toronto Rehab, and matched controls ($N = 17$) were recruited from the community. For the patients and controls, respectively, mean age was 45.0 ($SD = 15.1$) and 42.5 ($SD = 15.1$); mean years of education was 12.7 ($SD = 2.8$) and 14.4 ($SD = 2.4$). Average months post injury for the patients was 2.4 ($SD = 1.4$; range = 1–5). Controls had no history of psychiatric illness, neurological disease or previous brain injury. The two groups did not differ on age ($t = 0.264$, N.S.) or education ($t = -1.69$, N.S.).

Prediction 2: Patients from Analysis 1 above were assigned to one of two groups according to the presence of right posterior focal lesions (RtPL; i.e. temporal, parietal or occipital lesions) or the absence of

such lesions (non-RtPL) as indicated by CT findings. Because we were interested in lateralization of deficits, all patients who were not definitively right handed were excluded from the analysis.

The non-RtPL group ($N = 6$) and RtPL group ($N = 7$) did not differ significantly on mean age (41.7, $SD = 14.9$ and 49.0, $SD = 13.2$, respectively: $t = -0.94$, N.S.) mean years of education (13.3, $SD = 2.2$ and 11.1, $SD = 3.18$, respectively: $t = 1.42$, N.S.) or mean months post-injury (2.33, $SD = 1.51$ and 2.0, $SD = 0.82$: $t = 0.507$, N.S.).

Tasks

The tasks were selected from the facial affect section of the Florida Affect Battery Revised (FAB; Bowers, Blonder, & Heilman, 1991/1998).

Control task: Neutral face discrimination.

- Photographs of two female faces of the same woman or two different women presented.
- Participants decide whether photographs represent the same or different people.

Emotional face labeling.

- Photographs of faces, each expressing one of five different emotions (happiness, sadness, anger, fear or neutrality) shown.
- Participants asked to name the emotion.

Emotional Face Discrimination.

- Pairs of photographs presented displaying two different female faces expressing either same or different emotions.
- Participants decide whether emotions expressed are the same or different.

Emotional Face Matching.

- One face expressing one of five emotions presented on one card. On a second card, five faces presented each displaying a different emotion.
- Participants asked to match emotion on first card with same emotion on second card.

Design

Factorial 2×4 with group (TBI and matched controls) and task (the 4 FAB tasks) as independent variables, and percent correct (on the FAB tasks) as dependent measure.

Results

Prediction 1: *TBI patients will demonstrate significant impairments on facial emotion perception tasks in comparison to matched controls.* A two-way analysis of variance (ANOVA) comparing patients and controls on the FAB tasks yielded a significant main effect of group, $F(1, 32) = 9.12$, $p = .0049$ and task, $F(3, 96) = 17.38$, $p < .001$. Importantly, a significant group-by-task interaction was observed, $F(3, 96) = 4.12$, $p = .0085$. Planned comparisons revealed that while performance in the control task did not differ between the patients and matched controls ($t(32) < 1.0$; N.S.), the patients performed significantly worse than the matched controls on each of the three emotion tasks: labeling ($t(32) = 3.49$, $p = .001$); discrimination ($t(32) = 3.16$, $p = .003$); and, matching ($t(32) = 2.03$, $p = .05$). Moreover, the patient group performed significantly worse on each of the emotion tasks than on the control task: control task vs. emotion-labeling ($t(16) = 7.32$, $p < .001$); vs. emotion-discrimination ($t(16) = 4.17$, $p < .001$); and, vs. emotion-matching ($t(16) = 4.93$, $p < .001$) (see Fig. 1a).

The distribution of the data showed a negative skew, and the sample size was not large enough to compensate for this violation of the normality assumption. Therefore, non-parametric Kruskal–Wallis analyses were conducted to verify the above findings. Patients and matched controls showed significant between-group differences for each of the three emotion-perception tasks (Kruskal–Wallis H values > 6, $p < .01$ for each task), but no significant between-group difference was obtained for the control task ($H = .002$, N.S.).

These converging results on parametric and non-parametric analyses supported Prediction 1.

Prediction 2: *Non-RtPL will perform better on facial emotion perception tasks than RtPL patients.* A two-way ANOVA comparing the Non-RtPL and RtPL groups on all four tasks yielded a significant main-effect of task, $F(3, 33) = 9.00$, $p < .001$. However, no main-effect of group ($F(1, 11) < 1.0$, N.S.) nor group-by-task interaction ($F(3, 33) < 1.0$, N.S.) was obtained, with the means illustrating indicating comparable degrees of impairment between the groups relative to the control task (see Fig. 1b).

In a second ANOVA comparing the two groups on the three emotion-perception tasks *only*, the main effect of task ($F(2, 22) < 1.0$, N.S.) disappeared, and again, there was no main effect of group ($F(1, 11) < 1.0$, N.S.), nor group by task interaction ($F(2, 22) < 1.0$, N.S.). This finding provided further evidence of comparable performances across the experimental tasks, in contradiction of our prediction.

Violation of the normality assumption was addressed by conducting non-parametric analyses to verify the above findings. Between-group comparisons revealed no significant differences for any of the three emotion-perception tasks or the control task (for each, Kruskal–Wallis H values < 1, N.S). Within-groups, Wilcoxin Signed Ranks Tests were conducted to compare performances on the emotion-perception tasks with the control task in the non-RtPL group: emotion-labeling and emotion-matching performances were significantly worse

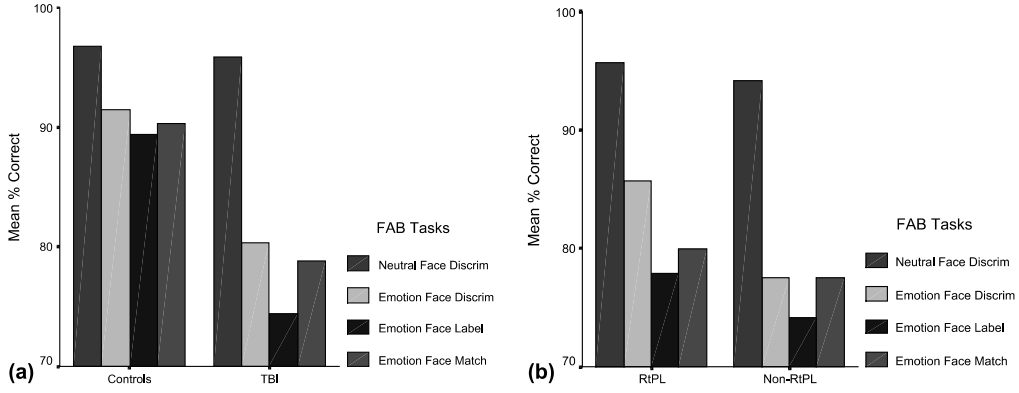

Fig. 1. Mean performance on measures of facial emotion perception. (a) *Prediction 1:* Normal control versus TBI participants ($N = 17$). (b) *Prediction 2*: Performance of right-lateral dominant TBI participants with evidence of right, posterior lesions (RtPL; $N = 6$) and without damage in these regions (non-RtPL; $N = 7$). FAB, Florida Affect Battery-Revised.

than control task performance ($z = -2.21$, $p < .05$; $z = -2.21$, $p < .05$, respectively), but there was no significant difference between the control task and the emotion-discrimination task ($z = -1.47$, $p > .05$) despite equivalent means between the matching and discrimination tasks (mean = 77.5% correct for both). Overall, the findings suggested that performance in the non-RtPL group was compromised, nearly to the level of the RtPL group.

Discussion

Prediction 1: *TBI patients will demonstrate significant impairments on facial emotion perception tasks in comparison to matched controls.* It is clear from Fig. 1a that our patients performed significantly worse on emotion-perception tasks than did matched controls. This discrepancy was found even though both groups performed at similar levels on a neutral control task. Therefore, prediction 1 was supported by these findings. These results, obtained in a sub-acute, but recently brain-injured population undergoing rehabilitation, suggest an important area in which to focus rehabilitation therapies.

Prediction 2: *Non-RtPL will perform better on facial emotion perception tasks than RtPL patients*. This prediction was largely unsupported in that performances between the two patient groups did not significantly differ, and that performances on the emotion-labeling and emotion-matching tasks were significantly impaired relative to the control task in the Non-RtPl group.

There are several possible explanations. The most interesting is that it was the presence of diffuse axonal injury in the non-RtPL group that gave rise to their impaired performances. Such an explanation is compatible with the notion that networks of white matter tracts underlie emotion perception in faces (Adolphs et al., 2000). However, two other explanations must be ruled out. First, the small sample size of the group limited power and thereby limited the ability to detect significant differences between the groups. Secondly, a small number of studies (e.g. Hornak et al., 1996) have demonstrated facial emotion perception deficits in patients with frontal lobe lesions (in facial emotion labeling tasks). Patients with pre-frontal lobe lesions were not excluded from either of our groups; therefore, it is possible that frontal lobe lesions were responsible for the impaired performances.

In conclusion, the present study illustrated that facial emotion perception deficits are a robust feature of a recently traumatically brain injured adult population. The study has also provided some evidence of a role for diffuse axonal injury in the perception of emotions in faces. We are currently undertaking to (a) replicate these findings with a larger sample size and (b) examine a non-TBI, focal pre-frontal group employing the same test battery.

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9. Reduced facial muscle movements in Autism: Evidence for dysfunction in the neuromuscular pathway?

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The present study examined facial muscle movements during the expression of emotion in young children with autism. The main question of interest was whether the lack of facial expressiveness that has been documented in children with autism might reflect some deviation in the neuromuscular pathway of the face. This question was addressed by conducting a microanalysis of facial muscle movements (Izard, 1979) from videotapes taken during a semi-structured play situation. Relative to both language-delayed and normally developing children, children with autism were found to exhibit reduced and weak muscle movements in the eye and mouth regions, but not the brow region of the face. The findings are discussed with reference to the possibility of injury to the motor nuclei of cranial nerves from the brain stem.

Report

A lack of facial expressiveness is well documented in young children with autism (e.g., Yirmiya, Kasari, Sigman, & Mundy, 1989). Findings consistently indicate that children with autism express less positive affect and more neutral or "flat" affect compared to normally-developing and mentally-impaired children. The facial expressions of children with autism have also been described as "mechanical" and not resembling any of the discrete expressions observed in others (Loveland et al., 1994). Such atypicalities have generally been viewed as communicative at root, although an alternate possibility is provided by the recent neuroembryological theory of autism.

Rodier, Ingram, Tisdale, Nelson, and Romano (1996) have proposed that the critical period for susceptibility to autism occurs in the embryo during closure of the neural tube, thus resulting in an early injury to the brain stem. Evidence for this comes from a population study of individuals exposed to thalidomide during closure of the neural tube and in whom autism was identified in 33% of cases. The period of neural tube closure coincides with the production of the first neurons that eventually form the motor nuclei of the cranial nerves. Evidence from the thalidomide cases with autism implicates an injury to the motor nuclei of cranial nerve VII (facial nerve). This begs the question of whether faulty innervation of the face might underlie previous reports of flat and ambiguous expressions in autism.

The present study explored this possibility by systematically examining the functional integrity of the individual muscle movements necessary for the expression of facial emotion. Children were videotaped in a play situation designed to elicit spontaneous facial emotion. Using Izard's (1979) coding system, we conducted a detailed analysis of facial muscle movements in three regions of the face ("upper"/brow, "middle"/eye, and "lower"/mouth), with special reference to both duration and intensity. Data from young children with autism were compared to that from normal and language-delayed children.

Method

Participants

These included 15 children with autism (12 males; M age = 70.1 mos; $SD = 16.5$), 14 children with a specific language disorder, none of which showed any signs of autism (11 males; M age = 65.4 mons;

$SD = 20.25$) and 15 normally developing children (12 males; M age = 53.9 mons; $SD = 24.7$). Children in all three groups were individually matched on nonverbal mental age; children with autism were also individually matched to the children with language delay on verbal mental age.

Play situation

Each child was engaged in semi-structured play with the examiner (E; PC) using a variety of toys (e.g., various wind-up animals, jigsaw puzzles). Four interactive acts ("showing," "requesting" toys, "pointing" to posters on the wall, and "reciprocal" games) were introduced randomly, and all sessions were videotaped.

Coding system

Muscle movements were coded during the four interactive acts, each of which was repeated once, for a total of eight segments per child. This was accomplished using Izard's (1979) Maximally Discriminative Facial Coding System (MAX). Muscle movements in three regions of the face–forehead-brows-nasal root ("upper"), eyes-nose-cheeks ("middle"), and mouth-lips-chin ("lower")–were coded independently. Both duration and intensity of each facial muscle movement were coded. Intensity of each code or muscle movement was rated as "strong" or "weak".

Reliability

Prior to coding the data, the E established agreement (>80%) with the MAX master code to the nearest 0.1. Inter-rater reliability, based on 20% of the data per group, was excellent (>80%) for coding of both duration and intensity of movements.

Table 1
Mean (SD) Duration of ANY muscle movements, strong muscle movments, and atypical muscle movements (expressed in %)

Characteristic	Autistic ($n = 15$)	Language delayed ($n = 14$)	Normal ($n = 15$)
Any Movements			
Upper Region/brow			
M	6.43	7.07	8.01
SD	(5.32)	(7.47)	(9.53)
Middle Region/eyes			
M	12.86*	62.98	52.09
SD	(12.39)	(27.53)	(28.97)
Lower Region/mouth			
M	34.21*	77.79	74.51
SD	(12.21)	(12.05)	(20.11)
Strong Movements			
Upper Region/brow			
M	3.36	4.42	3.94
SD	(3.65)	(7.46)	(3.38)
Middle Region/eyes			
M	5.04*	40.89*	25.14*
SD	(5.32)	(21.13)	(17.47)
Lower Region/mouth			
M	23.78*	58.21	58.34
SD	(20.46)	(12.29)	(18.83)
Atypical Movements			
M	6.20**	0.48	0.23
SD	(6.09)	(0.56)	(0.38)

* $p < .015$.
** $p < .01$.

Results

We first computed the percentage of time (in seconds) each child exhibited "any muscle movement" in each of the three facial regions. Both typical movements (i.e., those described in the MAX manual; Izard, 1979), as well as atypical movements were included. These percentage scores were then averaged for each group. Separate one-way ANOVAs on these mean percentages revealed a significant Group effect for facial movements in the "middle", $F(2,41) = 17.63,\ p = .0001$, and "lower" region, $F(2,41) = 37.04, p = .0001$, but not the "upper" region, $F(2,41) = 0.16, p = .85$. Tukey HSD post hoc tests indicated that the children with autism spent significantly less time displaying any movements in both the "middle" and "lower" face than either the language-delayed or the normal children, who did not differ (see Table 1).

Next, the intensity of muscle movements in each of the three facial regions was examined. Analyses focused on the duration of strong muscle movements. Since the duration of movements differed across groups, scores were transformed into proportions for the purpose of analyzing intensity. This was accomplished by dividing the duration of strong movements by the duration of both strong and weak movements.

Separate one-way ANOVAs on these intensity scores revealed that the three groups did not differ in the percentage of time spent displaying strong muscle movements in the "upper" region, $F(2,41) = .16$, $p = .85$. However, a significant Group effect was found for strong movements in both the "middle" region, $F(2,41) = 18.37, p = .0001$, and the "lower" region, $F(2,41) = 18.86, p = .0001$. Post hoc Tukey tests indicated that the children with autism spent significantly less time exhibiting strong movements in the "middle" and "lower" facial region than both comparison groups (see Table 1). Interestingly, normally-developing children were also found to spend significantly less time displaying strong movements in the "middle" face than children with language delay.

Finally, movements in the face not documented in Izard's (1977) MAX manual were categorized as "atypical". These movements included but were not limited to asymmetrical raising of one corner of the mouth, squinting one eye alone, or upper teeth pressing against lower lip. Separate one-way ANOVAs revealed a significant Group effect for the percentage of time spent displaying these atypical movements in an otherwise neutral face, $F(2,41) = 13.23,\ p = .0001$. Tukey HSD post hoc tests indicated that children with autism spent significantly more time displaying atypical expressions than either the language-delayed or the normal children, who did not differ (see Table 1). Signs of ptosis (droopy eyelids) were also evident in 3 of the 15 children with autism.

Discussion

We have identified facial muscle regions that may contribute to the appearance of "neutral" or "flat" affect that has been reported in children with autism (Yirmiya et al., 1989). The lack of facial expressiveness in autism would appear to be related specifically to reduced movement in the muscles around the eye and mouth regions of the face. For example, the degree of squinting of the muscles under the eye during smiling in both normal and language-delayed children was greater than that in children with autism. Similarly, retraction of the corners of the mouth, or smile, was not as wide in children with autism; indeed, it was often barely

visible. We also identified a number of "atypical" movements in both the eye and mouth regions, including signs of ptosis. These movements may directly contribute to the "mechanistic" appearance of children with autism observed by others (Loveland et al., 1994).

The present results are consistent with the possibility that in autism faulty innervation of the face may contribute to the lack of muscle movement, thus making the face look more neutral or "flat." The co-occurrence of autism and Moebius syndrome in the thalidomide cases serves to underscore this possibility (see Rodier et al., 1996). Moebius syndrome is defined by facial paralysis and lack of lateral eye movement associated with injury to cranial nerves VII and VI, respectively (Kumar, 1990). Rodier et al. propose that the injury in each of these two disorders takes place during the same neuroembryological window. In at least some cases with autism, innervation of the face may be atypical or partially dysfunctional, in contrast to the paralysis characteristic of Moebius Syndrome. Some of the children with autism who participated in the present study appeared to have facial weakness, or a doll-like appearance of the face. Wrinkles were rare in the faces of these children and particular facial muscles appeared relatively inactive.

Note further that anecdotal observations suggest that children with autism are more likely to express facial emotion when they are aroused (e.g., when riding on a roller coaster). Consistent with the possibility of some neuromuscular abnormality, increased levels of arousal may serve to activate an otherwise inactive pathway. On this assumption, it is important that early intervention in autism attempt to create conditions that are likely to maximize the utilization of facial muscles during the expression of emotion. To date, early intervention in autism has not focused on the development of affect. In addition to exercising the facial muscles themselves, programs might be developed to educate parents about the importance of being facially expressive with their children and of reinforcing any of the children's attempts to be expressive in turn. Knowledge of the possible neuroanatomical basis for reduced facial emotion in autism might also help parents deal with these issues.

Finally, the present findings may also have implications for identifying autism early in life. It is possible, for example, that a lack of facial expressiveness in infants may be a risk marker for autism. Future attempts to more directly address the possibility of neuromuscular involvement in autism will hopefully clarify these issues further.

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10. Toward a comprehensive neural network for emotion

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Report

Attempts to identify the neuroanatomical regions mediating normal emotion has a rich history, the model proposed by Papez (1937) still holds heuristic significance. His model, which emphasized the role of the hippocampus, hypothalamus, and cingulate gyrus was conceived at a time when the technology necessary to investigate this conception was unavailable. Functional neuroimaging now offers the means to investigate the neural correlates of emotion in vivo and mood induction paradigms have been used by several investigators to produce the emotion of interest in healthy subjects. Although there has been a significant amount of research investigating the neural correlates of emotion, a comprehensive neural network model, one identifying possible emotion specific neural correlates, has yet to be established. A current methodological shortcoming hindering this effort is the tendency for mood induction paradigms to evaluate merely one or two emotions, thus limiting the extent to which neural correlates can be assessed for their degree of emotion specificity within a particular study and subject group. A second methodological issue is the differential neural activation that can be produced simply by use of different mood induction paradigms. For example, Lane, Reiman, Ahern, Schwartz, and Davidson (1997) have demonstrated that, although sadness induction activated the thalamus and medial prefrontal cortex (PFC) independent of the type of induction paradigm used, the type of induction paradigm did account for differential activation of temporal versus insular regions. Thus, we assert that the assessment of a variety of neuroimaging mood induction paradigms is needed in order to assess which neural correlates correspond to the emotion of interest, as opposed to merely reflecting the experimental paradigm. Furthermore, neuro-imaging mood induction paradigms can benefit from evaluation of several emotional states within their particular subject group in order to be able to assess which neural correlates are emotion specific. In order to address these issues, we have utilized the Velten mood induction procedure, a paradigm that has received little use in neuroimaging studies, in the assessment of three distinct emotional states: happiness, anger, and sadness.

Methods

Subjects. We recruited 12 healthy, right-handed females, aged 18–30, from advertisement. Exclusion criteria included history of medical or psychiatric illness, alcohol abuse, use of illicit substances, or current prescription medications.

Mood induction and self-report. The Velten mood induction procedure (VMIP), developed by Emmett Velten in 1968, entails visual presentation of 50 written sentences to be read silently, with instructions to simultaneously imagine a mood congruent scenario. Each sentence was reviewed in this manner for approximately 20 s and subjects were instructed to maintain the target mood for several minutes after reading the sentences; the total time of mood induction spanned approximately 30 min. All subjects underwent neutral mood induction and were also randomly assigned to participate in two of the three possible mood inductions, (happiness, anger, sadness). Each mood induction occurred on separate days and the order of exposure was randomized. Mood was assessed through repeated administration of the visual analog scale (VAS) prior to and during mood induction. Summation of VAS scores from two assessments sampling the 95 min prior to the mood induction

was used to establish a mood baseline and then compared to the VAS score at the midpoint of mood induction.

Image acquisition, processing, and analysis. Image acquisition occurred by means of the CeraSPECT 3000 stationary annular camera, produced by Digital Scintigraphics Incorporated (DSI, Waltham Massachusetts). The camera utilizes a Sodium Iodide crystal and counts are acquired in 120 views, with three projections in each view. The scanner has a resolution of 5.3 mm for cortical neuroanatomy and a resolution of 7.7 mm for the deep nuclei. Radiotracer (Tc-99m ECD) injection occurred 2–3 min after subjects completed reading the VMIP sentences (i.e., approximately at the midpoint of mood induction). At the time of radiotracer injection, subjects were seated in a quiet room, eyes open with background ambient lighting. Subjects were scanned one hour after radiotracer injection. Image processing corrected all brain images for interscan movement and subsequently included transformation of images to the standard Montreal Neurological Institute coordinate system. The data were then rescaled and smoothed with a Gaussian filter of 15 mm in width (full-width half-maximum). Omnibus analysis of SPECT data was conducted following the theory of statistical parametric mapping through use of the SPM99 software package (Wellcome Department of Cognitive Neurology, London UK). The analysis of variance (conducted within each group) considered scan condition as the main effect and subjects as a block effect. Regions containing foci of activation with z-scores >3.09 are reported. A z-score of >3.09 corresponds to a $p < .001$ (one-tailed) uncorrected for multiple comparisons.

Results

As evident from comparison of group mean VAS baseline scores to those at the midpoint of the VMIP, mood induction was successful for all 3 target emotions.

Neuroanatomical regions of activation and deactivation are presented in Table 1. Areas activated during sadness include the orbitofrontal aspect of the left inferior frontal gyrus, Broca's area, the right anterior cingulate, and the right mid-insular region. Areas deactivated during sadness include the left mid-anterior cerebellum, left middle temporal gyrus, the right medial occipital gyrus, the right fusiform gyrus, right anterolateral cerebellum, left superior temporal gyrus, and the left superior temporal gyrus–insular cortex junction.

In regard to elation, our mood induction did not demonstrate any regions of activation, but did identify several regions of deactivation. For the right hemisphere, these include the ventrolateral PFC, anterior cingulate, anterior insula, superior temporal gyrus, precuneus, and the angular gyrus. On the left, we found deactivation of the fusiform gyrus, dorsolateral PFC, Broca's area, inferior parietal lobule, anterior cingulate, anterior insula, middle temporal gyrus, and occipital gyrus. For anger, we encountered several regions of activation, but none of deactivation. In the right hemisphere we found activation of the posterior cingulate and precuneus, and in the left hemisphere, the middle temporal gyrus and the junction of the anterior cingulate and inferomedial aspect of the superior frontal gyrus.

Discussion

Papez's classic conception of the limbic circuitry underlying emotion included projections from the hippocampus through the fornix to the mammillary bodies, with continued projections through the anterior nucleus of the thalamus reaching the cingulate gyrus to then project back to the hippocampus by means of the cingulum. This conception has been refined by several investigators. MacLean's classic paper (1952): Some psychiatric implications of physiologic studies on the frontotemporal

Table 1
Neural correlates of sadness, happiness, and anger

Region	Sadness coordinates (x, y, z)	z-score	Happiness coordinates (x, y, z)	z-score	Anger coordinates (x, y, z)	z-score
R VLPFC			32, 54, −6	−4.72		
L DLPFC			−22, 56, 20	−4.53		
Broca's Area	−60, 0, 20	+3.77	−54, 24, 20	−4.41		
Inferior aspect of L IFG	−38, 34, −18	+3.96				
L SFG* (inferior portion of medial aspect)					−8, 20, 40	+3.61
R Ant Cingulate	10, 12, 36	+3.22	2, 36, 26	−3.77		
L Ant Cingulate			−8, 36, 26	−3.59	−8, 20, 40	+3.61
R Post Cingulate					1,−40, 22	+3.63
R Insula	42, 10, 0	+3.13	36, 8, 10	−3.93		
L Insula	−44, −6, −8	−3.17	−34, 20, 6	−3.52		
R Superior Temporal Gyrus			46, −46, 12	−3.90		
L Middle Temporal Gyrus	−58, −14, −8	−4.05	−50, −40, −26	−3.87	−50, −44, −10	+3.85
L Superior Temporal Gyrus	−48, 12, −18 and	−3.20				
	−44, −6, −8	−3.17				
R fusiform Gyrus	32, −64, −14	−3.52	34, −54, −10	−3.86		
L fusifom Gyrus			−20, −58, −6	−5.05		
L Occipital Gyrus			−26, −96, 12	−3.49		
R Occipital Gyrus	46, −70, 4	−3.94				
R Precuneus			4,−44, 54	−3.64	8,−64, 56	+3.51
R Angular Gyrus			54, −66, 20	−3.42		
L Inferior Parietal			−44, −60, 30	−4.28		
R Anterolateral Cerebellum	24, −42, −24	−3.30				
L mid−anterior Cerebellum	−18, −46, −24	−4.49				

Regions of activation and deactivation have positive and negative z scores, respectively. L: Left; R: Right; DL: Dorsolateral; VL, Ventrolateral; PFC, prefrontal cortex; Ant, Anterior; Post, Posterior; IFG, Inferior Frontal Gyrus; SFG*, Superior Frontal Gyrus, this coordinate lies at the interface of the LSFG and anterior cingulate.

portion of the limbic system (visceral brain), introduced the phrase 'limbic system' by means of a model that synthesized the circuit of Papez with the insights of Yakolev, who described the relevance of the orbitofrontal and insular cortices and the amygdala to emotion. Evolution of the limbic system construct has undergone continued refinement, as more recently exemplified by the model from Alexander et al. (1990), which unified limbic and frontal–subcortical circuits through a common nidus, the anterior cingulate. Limbic circuits underlying emotion and memory thus concretely interact with frontal–subcortical circuits underlying executive function, motivation, and reward; the anterior cingulate potentially serving as a neuroanatomical nidus for resolution of conflict.

Hence, as based on lesion studies, animal studies, and clinical anecdotes, the neural circuitry for emotion can be appreciated as containing core limbic structures with extensive projections to the prefrontal cortex. As a complement to these methods of investigation, functional neuroimaging provides the necessary technology for more direct investigation of the neural correlates of emotion. In this context, our functional neuroimaging findings of greatest a priori interest deserve further discussion.

It is of continued heuristic interest to assess whether the structures historically considered 'limbic' demonstrate neural correlates specific to each of the emotions investigated, or whether investigation of neocortical regions is necessary to identify emotion specific neural correlates. For sadness, our results of greatest a priori interest (as based on similar findings from the mood induction literature), included activation of the left orbitofrontal cortex (OFC), right anterior cingulate, and right midinsular region, and deactivation of the left insular cortex. Our findings have some overlap with the work of Damasio et al. (2000), who also found activations in the left OFC, right anterior cingulate, and right insula. The finding of OFC activation during sadness, observed in Damasio's study and ours, possibly holds neuoranatomical differentiating significance specific to sadness. Damasio et al. (2000) have demonstrated that, in contrast to activation of the OFC for sadness, happiness, anger, and fear all demonstrate deactivation of the OFC, thus possibly identifying OFC activation as an emotion specific valence change.

The most striking finding from our evaluation of elation induction was the absolute lack of any significant regional cerebral activation. This finding has also been demonstrated by George et al. (1995). Our findings suggest that elation may be primarily characterized by the harmonious deactivation of a network of regions including the anterior cingulate, anterior insula and lateral prefrontal cortex.

The finding of greatest a priori interest for anger was activation of both the anterior and posterior cingulate. Damasio et al. (2000) have shown that anger induction uniquely demonstrated both activation and deactivation of the anterior and posterior aspects of the cingulate gyrus. Our study did not demonstrate this unique bivalent coupling, but it is significant that anger was our only mood induction to recruit both the anterior and posterior cingulate. Our lack of a bivalent coupling effect may be due to our use of SPECT, which has limited resolution in comparison to PET.

In summary, each of our mood inductions demonstrated a distinctive limbic neural activation pattern. Thus, convergent evidence from different methods of investigation (techniques spanning animal and human research) supports the central role of the limbic system to emotion. More specifically, as supported by our findings, each distinct emotion may prove to be distinguishable by differential neural activity within even just the limbic system. This issue may be resolved more definitively as emotion induction paradigms undergo continued replication and further methodological refinement.

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11. The influence of neuroticism on limbic-cortical pathways mediating transient sadness

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Blood flow changes with mood induction in High and Low Neurotic (N) healthy subjects were measured with PET. In both groups (and as seen in non-selected controls) there were increases in subgenual cingulate (Cg25) and decreases in prefrontal cortex. High and Low N also showed divergent changes in medial frontal and cingulate regions concordant with differential changes seen with mood induction in depressed patients. High N (like depressed subjects) showed decreases in medial frontal with increases in Cg25; Low N subjects showed increases in these same regions with increases in Cg25. The results highlight the influence of personality on brain activity associated with sadness.

Report

A working model of depression has been proposed based on a series of converging resting-state and mood-challenge positron emission tomography (PET) studies of depressed patients and healthy volunteers (Mayberg, 1997). In this model, alterations in the functional interactions between specific limbic, paralimbic and neocortical regions is seen as critical to the pathological changes in mood regulation that characterize major depressive disorders. Mood induction experiments in unipolar and bipolar patients implicate orbital frontal cortex (BA11), dorsolateral prefrontal cortex (BA9), rostral cingulate (BA24a) and subgenual cingulate (BA25) as sites of dysregulation in patients relative to healthy controls studied under comparable experimental conditions (Liotti et al., 1997). The involvement of Cg25 has been an additional focus of interest since suppression of activity in this region has been independently seen with successful response to antidepressant treatment.

The similar findings with mood induction in remitted and acutely depressed patients suggest that these aberrant regional changes may be an illness trait marker, reflecting an underlying stress diathesis unmasked by the mood challenge paradigm. Unfortunately, these previous data could not distinguish a true trait marker from an adaptive change to illness as all patients had experienced a minimum of one depressive episode at the time of the study.

Parallel studies examining potential trait markers of depression have focused on the relationship between personality traits and vulnerability to major depression—particularly Neuroticism as measured by the Revised NEO-Personality Inventory (NEO PI-R; Costa and McCrae, 1992). Neuroticism is the predisposition to experience psychological stress as manifested by anger, anxiety, depression or other negative affects. Neuroticism scores have been shown to be higher in both bipolar and unipolar depressed patients compared to matched non-depressed healthy controls. Although Neuroticism scores decrease with successful treatment, remitted depressed patients still score well above the norm on this personality dimension, suggesting that a highly neurotic temperament may be a preclinical risk marker for major depression (Santor, Bagby, & Joffe, 1997).

To link these two sets of observations, this study assessed the effects of these personality traits on pathways mediating acute changes in mood state. Two hypotheses were tested: (1) brain changes associated with acute sadness distinguish High Neurotic and Low Neurotic healthy subjects, revealing sites of potential vulnerability for depressive illness in the High Neurotic group; and (2) regions of differential change with mood challenge in High N subjects overlap disease-specific changes previously identified in remitted depressed patients studied under comparable conditions, thus identifying a preclinical risk marker of major depression. To this end, blood flow changes associated with transient changes in mood state were assessed using [^{15}O] water PET scanning in healthy non-depressed subjects selected for presence and absence of High levels of Neuroticism.

Methods

Subject selection

Scanning was performed on 12 subjects (9 female and 3 male) selected on the basis of their NEO-PI-R scores. The High Neuroticism Group (Hi N; $n = 6$) required a minimum T score >60; the Low Neuroticism group (Low N; $n = 6$) required a 45–55 T score. These subjects were further screened using SCID interviews to exclude subjects with any unrecognized psychiatric diagnoses, most critically an affective disorder. Only subjects with normal interviews including absence of a family history of major depression, and no evidence of other neurological and chronic medical illnesses were included. The Beck Depression Inventory (BDI) and the 20-Item Toronto Alexithymia Scale (TAS-20) were additionally administered to screen for the presence of subsyndromal depressive symptoms and ability to verbally express emotion, respectively. Subjects gave informed consent in accordance with the CAMH Ethics Committee.

Imaging protocol

Regional cerebral blood flow (rCBF) was measured using a [^{15}O]water bolus technique, in two mood states—sad and neutral (2 scans each). Prior to scanning, subjects were asked to provide a neutral and a sad autobiographical script, which were used for the mood induction. The scripts were presented on a PC screen suspended over the PET table. Scanning was commenced after the appropriate mood-state was achieved. Past studies have consistently found that depressed subjects, like healthy volunteers can achieve the appropriate state within approximately 7 min using this mood induction paradigm. By timing the preparation of the tracer, scanning was performed once the maximal state was stable for a minimum of 2 min. This was quantified using subject self-report and a 7-point Likert Scale (e.g., 1, not sad, 7, extremely sad). All subjects reported achieving a 6 or 7 during each mood induction session. The 4 scans were spaced approximately 15 min apart to allow for isotope decay (7 half-lives) and to reestablish a baseline euthymic mood state.

Statistical analyses

Common and divergent regional changes associated with acute sadness in Hi N and Low N subjects were assessed using partial least squares (PLS) (McIntosh et al., 1996). In addition, group differences in the functional connectivity of the subgenual cingulate (Cg25)—the area of both maximal change in unselected healthy subjects and apparent non-response in depressed patients in previous mood induction previous experiments—was also assessed using seed PLS. Statistical significance was determined using permutation tests; bootstrap estimation of the standard errors was secondarily used to test the reliability of the resulting regional brain salience values (McIntosh et al., 1996).

Results

Task PLS (rest vs sad; Hi N vs Low N subjects vs unselected controls) identified two latent variables (LV) characterizing common and divergent patterns of regional covariance across Hi N and Low N groups during sad induction. Common to both groups was a pattern (LV1) involving increases in subgenual cingulate (Cg25) and hippocampus (HC) and concurrent decreases in ventral and dorsal prefrontal (BA10/BA9) and dorsal anterior cingulate (BA24b), consistent with past findings in non-selected healthy volunteers using univariate statistical methods (SPM99, CDA). In contrast, the regional covariance pattern (LV2) that distinguished Hi N and Low N subjects involved increases in Cg25, premotor (BA6), and parietal cortex and concurrent decreases in orbital frontal (BA11), medial frontal (BA10), and posterior cingulate (BA31).

Seed PLS performed using a Cg25 region extracted from the preceding task PLS analysis (Talairach coordinate: x8, y22, z−4) identified group-specific patterns of regional covariance with Cg25 that further distinguished Hi N from Low N groups, independent of task (LV1; $p = .008$). With increasing activity in Cg25 in Low N subjects, orbitofrontal (BA 11), medial prefrontal (BA10/BA9), rostral anterior cingulate (BA 24a), posterior cingulate (BA31) increases and insular, dorsolateral prefrontal (BA9/46) and premotor (BA6) decreases were seen. The opposite pattern, decreases in medial frontal (BA11/10, BA32/24) and increases in lateral prefrontal and premotor (BA 9/46, BA6) with increasing Cg25 activity was seen in the Hi N group, most critically during sad induction (see Fig. 1).

Discussion

Mood induction in Hi N and Low N healthy subjects involves several similar regions to those identified in unselected healthy controls using univariate analytic methods: increases in Cg25; decreases in ventral and dorsal prefrontal cortex. There are however additional areas where Hi N and Low N subjects differ not only from one another, but also from non-selected controls–specifically, medial frontal and cingulate regions (OF11, mF10, Cg25, and pCg31); areas concordant with sites of differential change seen with mood induction in depressed subjects. Seed PLS most clearly demonstrates the site of divergence in Hi and Low N subjects and areas of potential overlap between Hi N and depressed subjects. Hi N subjects show decreases in medial frontal with increases in Cg25 comparable to that seen in depressed subjects, specifically with sad induction; Low N subjects show increases in these same regions with increases in Cg25 in both the resting and sad conditions.

The presence of this divergent pattern in the Hi N group with acute mood challenge provides new support for the hypothesis that high neuroticism may be a risk-factor for depression, with mood provocation providing a controlled "environmental stressor" of a

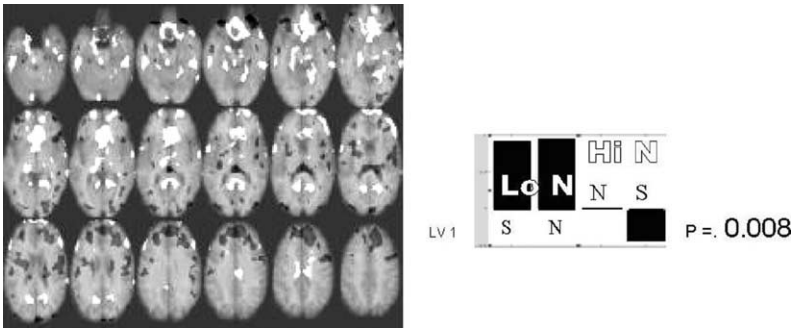

Fig. 1. Seed Cg25 ($x8$, $y22$, z −4).

type often associated with illness onset or relapse in depressed patients. Direct comparisons of Hi N and remitted depressed patients will be needed to further test the hypothesis that mood provocation PET studies can serve as a preclinical depression "stress-test" revealing fundamental disease-specific dysfunctional mood circuits. These findings nonetheless highlight the importance of personality style as a mediating influence on brain activity associated with the phenomenology of emotion, and opens up a new field for future brain mapping endeavours.

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12. The mind and the amygdala: A quantitative fMRI study of amygdala perfusion during cognitive mood induction

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In reviewing the literature on mood induction and brain activity, Reiman (1997) and others have noted that only studies involving external negatively valenced stimuli evoke amygdala activity; purely cognitive mood induction procedures such as recalling emotional memories have not, to date, been found to influence amygdala activity. This seems consistent with the view that the amygdala mediates early, immediate processing of threat, negative and/or ambiguous stimuli, bypassing higher-order cognitive processes and conscious awareness. In the present study, subjects were scanned while imagining the death of a loved one, as well as while resting in a baseline condition, and rated their mood between scans. Degree of increase in rated sadness correlated highly with degree of increase of left amygdala perfusion.

Report

Brain activity associated with sad mood has been studied using functional neuroimaging and a variety of mood induction procedures: listening to sad music, viewing sad faces, recalling sad autobiographical events, and viewing sad film clips. A reasonably consistent answer has emerged, implicating increased activity in orbitofrontal cortex and anterior cingulate cortex, decreased activity in dorsolateral prefrontal cortex and, in some cases, increased amygdala activity.

Without exception, studies demonstrating amygdala activity used stimulus-driven mood induction procedures (see, e.g., Reiman, 1997). When the recall of sad autobiographical events is used as a mood induction procedure by itself, no amygdala activity has been observed in functional neuroimaging studies. This is unlikely to result from the ineffectiveness of the procedure for changing mood. Self-reported mood ratings verify mood change, as do visible signs of sadness such as tears, and such procedures evoke characteristic patterns of brain activity in prefrontal regions. Instead, the engagement of amygdala activity during stimulus-driven but not purely cognitive mood induction seems more likely to reflect intrinsic aspects of amygdala function.

Animal and human studies alike have suggested that the amygdala is important for fast and immediate processing of threat and/or emotionally ambiguous stimuli, independent of higher-order cognitive processes and conscious awareness. For example, the amygdala is crucial for fear conditioning in animals, and receives information about the conditioned stimulus without cortical processing (LeDoux, 1996). It is activated by visual perception of emotional facial expressions, even when that perception is rendered subliminal by the use of brief presentations and masking, that is, when subjects have no conscious awareness of having seen an emotional face (Whalen et al., 1998). In the context of these findings, the insensitivity of the amygdala to purely cognitively induced mood does not seem surprising.

In the present study we re-examined the role of the amygdala in mood states of purely cognitive origin, using perfusion fMRI (Alsop & Detre, 1996), which enables quantitation of absolute rate of blood flow and thus allows degrees of mood change and of activity change to be correlated.

Methods

Five women and four men, all Caucasian, participated. Subjects, aged 19–46 (mean = 28.6) were recruited from the university community, and all but one were right-handed. Before being scanned subjects filled out a Beck Depression Inventory (BDI) in order to exclude dysphoric or depressed individuals. Several weeks after the scan, they were administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IP). The highest BDI score was 5; a structured clinical interview (SCID-IP) revealed three subjects with a history of Major Depressive Disorder (MDD). Of these four subjects, one was diagnosed with a comorbid anxiety disorder. Two subjects with a history of MDD were currently taking a psychotropic medication at the time of the scan. Five subjects met strict criteria for absence of psychopathology. Results will be reported with these subjects alone and with the whole group.

Prior to the scan, subjects were told they would be asked to imagine the death of a loved one, and were encouraged to develop some specific images and thoughts which could be revisited during the scan. They were also told to prepare themselves to repair their sad mood, by focusing on the unreality of the scenario just imagined, and questioning the likelihood that such an event would happen in the foreseeable future. The use of an analog mood rating scale of 0–100 (worst ever felt to best ever felt) was then explained.

Scanning took place on a 1.5 T GE Signa MRI scanner equipped with a prototype fast gradient system for echo-planar imaging, using a standard quadrature radiofrequency (RF) head coil. Sagital and axial T1-weighted images were obtained in every subject. Fluid-attenuation inversion recovery (FLAIR) images were also obtained. For measurements of perfusion, gradient echo-planar images were obtained with a field of view of 24 cm along the frequent-encoding direction and 15 cm for the phase direction and an acquisition matrix of 64×40. Following the structural and FLAIR images, four 6-min perfusion scans were obtained in the following order: Baseline I (rest and let your mind go blank), Dysphoric scan (vividly imagine someone you love dying), Mood Repair scan (question the soundness or validity of your negative thoughts), and Baseline II. Subjects were given as much time as they needed after the first Baseline scan to fully enter a sad mood (3–5 min). (Brain activity during Mood Repair is the subject of a separate abstract.) They were also given time to rest immediately following the Dysphoric scan, before undertaking Mood Repair (3–5 min). Mood ratings were obtained before and after each scan.

Perfusion data were saved as raw echo amplitudes and transferred to a workstation for further processing. Images were corrected for motion, normalized and regions of interest were automatically segmented within the normalized brain.

Results

Analyses focused on the relation between amygdala perfusion and mood rating. In order to minimize the effects of individual differences in baseline mood and perfusion, the measures of interest were changes in mood and perfusion between conditions. In order to minimize the effects of individual differences in baseline mood and perfusion, the measures of interest were changes in mood and in perfusion between conditions. Given the limitations of space, only those analyses most directly relevant to the role of the amygdala in sad mood will be reported.

Rank order correlations were computed for the relation between residualized mood changes and perfusion changes from Baseline I to Dysphoric, for left and right amygdala. The results of each test will be reported three ways: for the full group of 9 subjects, excluding the one individual with a current diagnosis, and using the most stringently selected group of 5 individuals no current or prior psychopathology.

Spearman rank correlations revealed a significant positive relationship between the degree of mood change from Baseline I to Dysphoric and perfusion blood flow in the left amygdala ($n = 9$, $r = .93$, $p < .001$; $n = 8$, $r = .90$, $p < .002$; $n = 5$, $r = 1.00$, $p = .02$). These same comparisons are not significant in the right amygdala ($n = 9$, $r = .18$, N.S.).

Discussion

The present study is, to date, the only neuroimaging study to find an effect of a cognitively induced mood on amygdala activity. We found that the change in activity level of the left amygdala was correlated with change in mood, with worsening mood accompanied by increasing perfusion. No such relationship held for the right amygdala.

Although our full subject group was not screened in advance for current or prior psychopathology, the relationship of interest held when data from only the most stringently selected subjects was considered.

Our findings suggest that the distinction between stimulus-driven and cognitively-induced emotional experience may not be a hard-and-fast one from the point of view of amygdala function. Purely cognitive activity exerts an influence on this evolutionarily old structure, which is specialized for fast, unconscious processing of emotional stimuli. Furthermore, this influence has a quantitative specificity to it, reflecting the degree of cognitively induced and rated mood change and not simply the occurrence of a change.

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13. Prefrontal–amygdala interaction and mood regulation: A perfusion fMRI study

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The hypothesis that prefrontal cortex (PFC) regulates mood by influencing amygdala activity has found support in neuroimaging studies of depression and mood. Activation of PFC and amygdala are reciprocally related, with hypoactive prefrontal regions associated with hyperactive amygdalae in depression and normal sadness. This evidence concerns the relative activation levels of PFC and amygdala before and after mood regulation; even more direct evidence would come from measuring PFC activation, amygdala activation, and mood while people actively attempt to improve a sad mood. This study, using perfusion fMRI, confirmed: (1) The amount of mood improvement is proportional to amount of prefrontal activation during the attempt to improve mood and (2) amount of prefrontal activity during mood improvement is proportional to the decrease in resulting amygdala activation.

Report

Prefrontal cortex (PFC) is implicated in mood regulation by a number of findings. In humans, prefrontal damage can cause emotional lability, an apparent diminution in patients' ability to regulate their emotional responses to attractive, annoying, frightening or frustrating stimuli. In depression, arguably a disorder of mood regulation, prefrontal cortex shows both functional and structural abnormalities in neuroimaging studies. These same studies have also shown hyperactivity in limbic regions including the amygdala, and normalization of most cortical and limbic functional abnormalities in remission and mood recovery (Drevets, 2000; Liotti & Mayberg, 2001).

The hypothesis that PFC serves to normalize downward the activity of a highly activated amygdala, and that this is a mechanism of emotion regulation, fits well with the observations summarized above. More direct evidence for such a regulatory mechanism is to be found not in mood regulation but in fear conditioning experiments with rats. The site of learning underlying fear conditioning is the amygdala. However, the extinction of a conditioned fear response, once the previously conditioned stimulus is no longer paired with a punishment, does not involve the unlearning of the association within the amygdala. Rather, it involves yet further learning, involving the PFC and its connections to the amygdala. Whereas lesions of PFC do not impair the acquisition of fear conditioning, they do eliminate the extinction of such conditioning (LeDoux, 1996). This influence of PFC on the amygdala can be viewed as a form of emotional self-regulation, in that the rat reduces its acquired amygdala response to the feared stimulus through descending inputs from PFC.

What has yet to be demonstrated directly is prefrontal–amygdala interaction in association with mood regulation perse. The animal evidence does not concern mood at all, and the evidence from humans concerns the relative activation levels of PFC and amygdala before and after mood regulation, but not in association with the process of mood regulation perse.

The purpose of the present study was to determine the relationships between PFC activation, amygdala activation, and mood, while people actively attempt to improve a sad mood. If recovery from a sad mood is the result of activity in PFC acting upon the amygdala to decrease activity in the amygdala, then the following two relations should hold among PFC activity, amygdala activity, and mood: (1) The amount of mood improvement should be proportional to the amount of prefrontal activation during the attempt to improve mood. (2) The amount of prefrontal activity during the attempt to improve mood should be proportional to the decrease in amygdala activation resulting from that attempt.

In the current investigation, using perfusion fMRI (Alsop & Detre, 1996), subjects were scanned following a negative mood induction and while engaging in a mood repair activity.

Methods

Five women and four men, all Caucasian, participated. Subjects, aged 19–46 (mean = 28.6) were recruited from the university community, and all but one were right-handed. Before being scanned subjects filled out a Beck Depression Inventory (BDI-II) in order to exclude dysphoric or depressed individuals. Several weeks after the scan they were administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IP). The highest BDI score was 5; a structured clinical interview (SCID-IP) revealed four subjects with a history of Major Depressive Disorder. Of these four subjects, one was diagnosed with a comorbid anxiety disorder. The other two subjects were currently taking antidepressant medication at the time of the scan. Five subjects met strict criteria for absence of psychopathology. Results will be reported with these subjects alone and with the whole group.

Prior to the scan, subjects were told they would be asked to imagine the death of a loved one, and were encouraged to develop some specific images and thoughts that could be revisited during the scan. They were also told to prepare themselves to repair their sad mood, by focusing on the unreality of the scenario just imagined, and questioning the likelihood that such an event would happen in the foreseeable future. The use of an analog mood rating scale of 0–100 (worst ever felt to best ever felt) was then explained.

Scanning took place on a 1.5 T GE Signa MRI scanner equipped with a prototype fast gradient system for echo-planar imaging, using a standard quadrature radiofrequency (RF) head coil. Sagial and axial T1-weighted images were obtained in every subject. Fluid-attenuation inversion recovery (FLAIR) images were also obtained. For measurements of perfusion, gradient echo-planar images were obtained with a field of view of 24 cm along the frequent-encoding direction and 15 cm for the phase direction and an acquisition matrix of 64×40. Following the structural and FLAIR images, four 6-min perfusion scans were obtained in the following order: Baseline I (rest and let your mind go blank), Dysphoric scan (vividly imagine someone you love dying), Mood Repair scan (question the soundness or validity of your negative thoughts), and Baseline II. Subjects were given as much time as they needed after the first Baseline scan to fully enter a sad mood (3–5 min). (Changes in amygdala activity associated with sad mood induction are the subject of a separate abstract.) They were also given time to rest immediately following the Dysphoric scan, before undertaking Mood Repair (3–5 min). Mood ratings were obtained before and after each scan.

Perfusion data were saved as raw echo amplitudes and transferred to a workstation for further processing. Images were corrected for motion, normalized and regions of interest were automatically segmented within the normalized brain.

Given the limitations of space, only those analyses most directly relevant to the role of PFC–amygdala interaction in mood regulation will be reported. Furthermore, given indications of left frontal dominance for mood regulation, and the direct connectivity between orbital frontal cortex and the amygdala, we will report numerical results for the left orbital gyrus of the PFC only here. Other regions of the PFC show variable patterns of significant and nonsignificant correlations across tests.

Two kinds of rank order correlations were computed. To assess the degree to which elevation of PFC activity (relative to baseline) improves mood, we correlated residualized increase in PFC perfusion between Baseline and Mood Repair with residualized increase in mood between Dysphoric and Mood Repair. To assess the degree to which elevation of PFC activity drives down amygdala activation, we correlated the residualized increase in PFC perfusion between Baseline and Mood Repair with the residualized decrease in ispilateral amygdala perfusion between Dysphoric and Baseline II. The results of each test will be reported three ways: for the full group of 9 subjects, excluding the one individual with a current diagnosis, and using the most stringently selected group of 5 individuals no current or prior psychopathology.

Spearman correlations revealed a significant relationship between increased perfusion to the left orbital gyrus during Mood Repair relative to Baseline I and the degree of mood improvement from Dysphoric to Baseline II ($n = 9$, $r = .81$, $p < .01$; $n = 8$, $r = .76$, $p < .03$; $n = 5$, $r = .7$ ns). There was also a significant relationship between increased perfusion to the left orbital gyrus during Mood Repair relative to Baseline I and decreased perfusion of the left amygdala from the Dysphoric scan to Baseline II ($n = 9$, $r = .75$, $p < .03$; $n = 8$, $r = .97$, $p < .0001$; $n = 5$, $r = 1.00$, $p = .02$).

Discussion

PFC has long been associated with mood regulation. In particular, the inhibitory influence of PFC on the amygdala has been considered a

plausible mechanism for recovery from negative mood. The results of the present study support this view of PFC–amygdala interaction in mood regulation. Following a sad mood induction, the degree of PFC activation over the next several minutes predicted how fully people's mood recovered. It also predicted, over the same time course, the reduction of amygdala activity.

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14. Increased event-related θ activity during emotional scene encoding

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Previous research indicates that an increase in event-related power over parieto-occipital areas 100–300 ms post-stimulus reflects the encoding of stimuli into working memory. In the present study, we demonstrate that the topography of power to emotionally arousing scenes is different. Namely, frontal areas reveal a significant increase in activity at 200–300 ms post-stimulus for emotional compared to neutral scenes. This shift presumably reflects the selective recruitment of a frontolimbic network during the initial encoding of emotional stimuli.

Report

EEG analysis in the frequency domain offers the possibility to focus on specific bandwidth components in response to eliciting stimuli. Because there is good evidence that different neural networks operate in different oscillatory frequency domains, this approach may be used to investigate the possible involvement of specific networks.

In this paper we focus on the θ frequency range. Animal studies have provided good evidence that the hippocampal θ rhythm is related to memory processes. A series of recent studies has shown that a similar relationship holds true for the human scalp EEG (e.g., Klimesch, 1999 for a review). The basic finding is that an event-related increase in a narrow frequency band of 2 Hz width (lying 4 Hz below the individually defined α frequency) reflects encoding processes of a complex working memory system. For example, subsequent memory for words is correlated with an event-related increase in θ band power during encoding. In a similar way, during successful retrieval in a word recognition task, correctly recognized words show a significantly larger phasic θ response than correctly identified distractors and false alarms. The interpretation of these and related findings is that the strength of θ power reflects the extent of processing resources tapped by a working memory system (e.g., Klimesch, 1999).

The aim of the present study was to determine whether emotional stimuli, which tend to be better remembered than neutral stimuli, are characterized by enhanced event-related θ activity. For the encoding of neutral pictures or words, occipital recording sites show an early increase in θ activity (from 125 to 375 ms post-stimulus), whereas frontal sites exhibit a late increase (from 750 to 1000 ms) (Klimesch et al., 2001). We investigated whether these effects are modulated by the emotional qualities of the stimuli.

Methods

Subjects

Ten healthy young adults participated after providing informed consent (2 female, 8 male). All subjects were right-handed with a mean age of 19 years (range = 18–21 years). They underwent a brief medical screening to rule out incidence of neurologic or psychiatric illness or current drug use.

Procedure

Subjects viewed 50 negatively-valent emotionally arousing pictures and 50 neutral pictures under incidental encoding conditions. Pictures were obtained from the International Affective Picture System (Center for the Study of Emotion and Attention, Gainesville, FL) supplemented by additional pictures developed independently to equate the stimulus categories for mean luminance, color content, presence of human figures and qualitative complexity of the visual scene. During the experiment, subjects rated each picture on a 3-point arousal scale by manipulating a joystick. Pictures were presented individually and centrally on a computer monitor. Stimulus duration was 3 s, with a 1-s interstimulus interval marked by a fixation cross. No more than 2 items from each stimulus category were presented in a row to prevent the induction of a persistent mood state.

During this task EEG was recorded from 32 scalp locations using electrodes mounted in a custom elastic cap (Electrocap). Electrodes were placed in accordance with the standardized International 10–20 electrode system. Horizontal and vertical EOG were monitored to reject eye movement artifacts. Electrode impedances were kept below 5 kΩ. The right mastoid was used as a reference electrode. EEG (bandpass DC-100 Hz) was continuously digitized at 250 samples per second and stored on hard disk along with stimulus and response codes. All artifact rejection, filtering, averaging and analysis were performed off-line using Neuroscan laboratory software.

Calculation of band power values

Band power values were calculated for four frequency bands and for intervals of 1-s duration beginning with stimulus onset. The raw data were first bandpass-filtered in 4 individually adjusted frequency bands as proposed by Klimesch (1999). The frequency bands obtained by this method are: Theta (IAF(i) −6 to IAF(i) −4); Lower-1 α (IAF(i) −4 to IAF(i) −2); Lower 2 α (IAF(i) −2- to IAF (i)) and Upper α (IAF(i) to IAF(i) + 2). This method of adjusting frequency bands individually before analyzing the band power is important because of two findings: first, α frequency varies as a function of several factors such as age, memory performance and attentional demands. Second, the frequency of the transition region between a task-related increase in band power (as an indicator for the θ band) shows a tendency to vary as a function of α frequency. Data were then averaged into 1-s time bins.

Statistical analysis

For each of the four frequency bands, absolute band power values were subjected to a four-factorial within-subjects ANOVA. The factors and their levels were: EMO, stimulus category (emotional vs neutral);

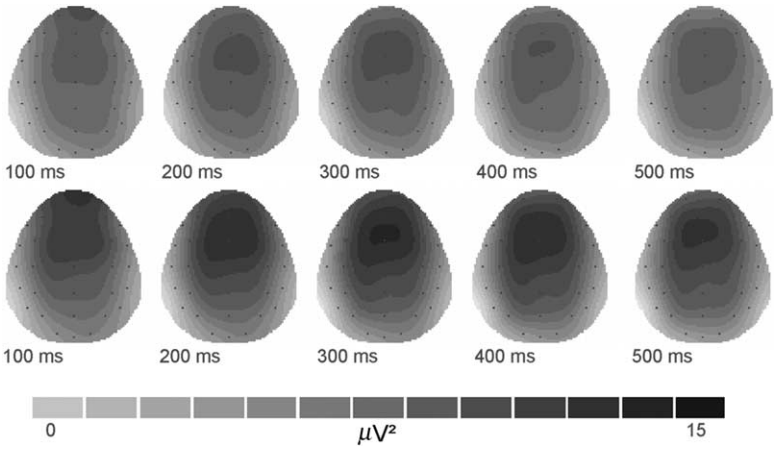

Fig. 1. θ Band power of neutral (upper row) and emotionally-arousing (lower row) pictures. Comparing the power values, differences between these two types of pictures are especially seen at frontal sites at about 200–300 ms.

HEMI, hemisphere (left vs right sides of the scalp); LOC, electrode location [frontal (FP1, FP2, F3, F4), central (FC3, FC4, C3, C4), parietal (CP3, P3, CP4, C4), and occipital (O1, O2)]; and TIME (in ms) [*t*1 (0–200), *t*2 (200–400), *t*3 (400–600), *t*4 (600–800), and *t*5 (800–1000)].

Results

Behavioral data

In contrast to neutral pictures, emotional pictures were rated as more arousing (*t*-test, $t = -5.825$, $df = 9$, $p < .001$). The emotional category was formed by pictures that were rated as medium and high arousing, whereas the neutral group consists of the pictures rated low in arousal. Emotional scenes were better remembered than neutral scenes (89% of the emotional and 68% of the neutral pictures were correctly recognized in a subsequent yes/no recognition memory task).

Results of band power analysis

Only those data will be reported that revealed a significant result with respect to the factor EMO, either as a main factor or as an interaction. The Greenhouse-Geisser correction was used in cases when $df > 2$. In theses cases, the corrected *df*'s and tail probabilities are reported. In the *lower* 1α *band* and the *upper* α *band*, no such significant effects were found. In the θ *band*, the absolute band power is increased for arousing pictures compared to neutral pictures ($F(1/9) = 11.66$, $p < .01$). The interaction between EMO and TIME is significant ($F(1.9/17.5) = 3.8$, $p < .05$), showing the highest power for arousing pictures at t2. The interaction EMO * LOC is also significant ($F(1.5/13.6) = 11.72$, $p < .01$) indicating higher power at frontal and central sites especially for emotional pictures. The 3 factorial interaction EMO * LOC * TIME ($F(2.7/24.2) = 4.3$, $p < .05$) indicates that the emotional pictures exhibit highest power values in frontal areas, at t2, and decreases afterwards. In parietal areas, arousing pictures show more power during t and t3, and at central areas during t2. In occipital areas, the power for arousing pictures is similar to that of neutral pictures, but with more power for neutral pictures. The three-way interaction EMO * LOC * HEMI also shows a significant result ($F(1.9/16.8) = 4.36$, $p < .05$), indicating larger differences between emotional and neutral pictures at central recording sites on the left hemisphere. In the *lower 2* α *band*, the interaction EMO * LOC ($F(1.5/13.6) = 4.72$, $p < .05$) revealed significant results. Here, emotional scenes exhibited lower power values compared to neutral scenes, with the strongest effects at parietal electrode sites.

Discussion

The results show that emotionally arousing scenes elicit significantly more θ power at frontal sites, reaching a maximal value at 200–300 ms. Consistent with previous work, neutral scenes exhibited an occipital topography during their initial encoding. We conclude that this shift in topography implicates a frontolimbic network specialized for memory encoding operations recruited by emotional stimuli. These results complement established findings regarding (1) emotional enhancement of memory processing in the brain (Cahill & McGaugh, 1998) and (2) the role of θ in predicting subsequent memory effects (Klimesch, 1999). Studies using event-related potentials also show an early effect of emotionally arousing pictures at about 200–300 ms post-stimulus (LaBar et al., submitted).

Finally, the results demonstrate a dissociable effect of emotion across frequency bands. The θ band responded with a task-related increase in band power over frontal sites, whereas the lower α band responded with a task-related decrease in band power over parieto-occipital sites. Decrements in the lower α band seem to reflect attentional processes, possibly stemming from a thalamo-cortical network (Klimesch, 1999). These processes might be monitoring processes of the working memory system. Emotional stimuli may engage more attentional monitoring due to their inherent salience and associations in semantic memory (LaBar et al., 2000) (Fig. 1).

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15. Emotional connotations of major and minor musical chords in musically untrained listeners

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Musically untrained listeners were presented with musical major and minor chords in different octaves and with different timbres, with or without simultaneously presented functional magnetic resonance imaging (fMRI) noise, and were asked to judge the chords according to their emotional connotations. Results showed that major chords were judged as happier than minor chords. Moreover, harmonically rich chords were judged as more positive than sine chords, suggesting the relevance of familiarity of the natural harmonic spectrum for evoking positive emotional responses. fMRI scanner noise, presented during the trials, only affected emotional responses to the low pitched chords, which encourages to investigate the neural basis of emotional responses to musical sound elements by means of fMRI.

Report

According to theorists, music is sought by humans for its power to evoke emotions. Biological pre-dispositions of the ability of the human brain to connect music to emotional processes have been suggested by findings of emotional responses to music that are generalized across listeners, and by the existence of certain musical preferences in infants. Consequently, it is a strong hypothesis that emotional processing of music is correlated with consistent neural activation patterns that can be studied with brain imaging tools (cf. Blood, Zatorre, Bermudez, & Evans, 1999). However, in order to investigate the neural correlations of musical emotions, more detailed knowledge about the behavioral responses to musical stimuli is needed.

Behavioral studies have shown that the basic emotions of happiness and sadness are relatively easy to communicate in music. A musical piece can be distinguished as happy or sad on the basis of an excerpt of less than a quarter of a second of music in a group of ''ordinary listeners'' (Peretz, Gagnon, & Bouchard, 1998). The happy/sad judgment is known to vary according to pitch, tempo and mode, in such a way that high pitch, fast tempo and major mode bias the judgment towards happy. The ability to judge the emotional connotation of the major and minor mode of melodies has been observed in adults and children down to 6 years of age (Crowder, 1985). Whereas the study of emotional connotations of the mode of isolated chords has led to contrasting conclusions, the most recent evidence favors a generalized correlation of major and minor chords with happy and sad, respectively (Crowder, 1985).

We investigated the emotional connotation of musical major and minor chords in a group of subjects carefully selected to represent a minimum of musical education. The chords were presented in three different octaves and in three different timbres, to study possible variations of emotional responses as a function of these variables. Furthermore, in order to study how the noisy environment of functional magnetic resonance imaging (fMRI) recordings may affect emotional responses, playback scanner noise was introduced during half of the experimental trials (Fig. 1).

The presence of harmonics has been found to facilitate pitch perception and the ability to discriminate tones (Tervaniemi et al., 2000). We hypothesised that harmonically rich chords, although of short duration, might also be more effective in eliciting emotional responses than chords consisting of sine tones. In order to register small variations in the effects as a function of the variables, subjects were asked to judge happiness/sadness using a graded scale. A post-experimental interview served to

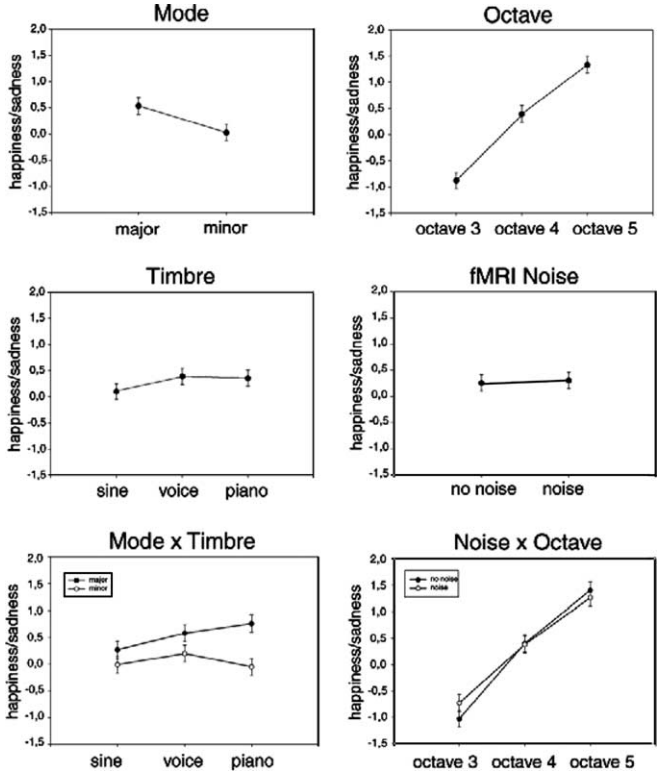

Fig. 1. Effects of Mode, Pitch (Octave), Timbre and fMRI noise on the emotional connotations of musical chords, judged by musically untrained subjects (see text for statistical details). Bars represent the standard error of the means.

assess the subject's musical knowledge and to collect additional information about the strategies employed to perform the behavioral task.

Methods

Subjects were 12 individuals (7 females, average age 25), who had never been trained in music theory or practise, apart from participation in obligatory preschool music classes. One subject was rejected because in the post-experimental interview he showed knowledge of the major/minor musical distinction.

The chord stimuli were 36 major triad and 36 minor triad chords, spanning three octaves from C3 to B5. Each chord was produced in three timbres (sine, piano, and voice). The sine chords were created with a Matlab script and the complex chords with a MIDI A33 Roland keyboard from the Akai sample library, and then edited by the Cool Edit and SoundForge programs to be amplitude normalized and have the same duration (500 ms). The chords were presented binaurally through headphones with the Psyscope program for Macintosh. The interstimulus interval of 7 s was chosen in accordance with the known temporal limits of stimulus interaction effects. The experimental session consisted of 432 trials, divided into 6 blocks (of 72 trials) separated by 1-min breaks. Chords of each timbre were presented during two blocks. In every second block, fMRI noise (16-slice EPI sequence) followed each chord after 75 ms. This time was chosen according to recent routines in auditory fMRI studies. The intensity of the chord stimuli was slightly higher (71 dB) than that of the scanner noise (68 dB).

Subjects evaluated each chord by pressing one of 11 keys, from −5 to +5, where −5 meant "very sad" and +5 meant "very happy." 0 corresponded to "neutral" or "neither happy nor sad."

A four-way repeated measures ANOVA (factors: Octave, Mode, Noise, and Timbre) and Newman–Keuls post hoc tests were performed to statistically analyse the data. Greenhouse–Geisser corrections were applied when needed.

Results

The emotional judgments varied significantly as a function of Octave $[F(2,218) = 204.6;\ p < .0001]$, Mode $[F(1,109) = 66.3;\ p < .0001]$, and Timbre $[F(2,218) = 7.3;\ p < .001]$. Post hoc tests revealed that the major chords were judged as more positive than the minor chords ($p < .0005$). Moreover, the average judgment of piano and voice chords was significantly more positive than the average judgment of sine chords ($p < .005$ for both), but they did not differ from each other. This result corroborated the subjects' answers in the post-experimental questionnaire.

Mode and timbre interacted significantly $[F(2,218) = 10.5;\ p < .0005]$. Major piano and voice chords were judged as significantly happier than sine chords ($p < .0005$ for both), piano and voice chords not differing significantly. Minor sine and piano chords were significantly sadder than the minor voice chords ($p < .005$ for both), and sine and voice chords did not differ significantly.

The fMRI noise did not significantly influence the average judgments, although further analysis of the interaction effect for Octave × Noise $[F(2,218) = 7.5;\ p < .001]$, revealed that fMRI noise significantly influenced the judgements in the 3rd octave ($p < .0005$), manifesting in a less negative average.

Discussion

The first main finding was that the conventional happy/sad emotional connotations of major/minor can be judged even in briefly presented chords by musically untrained listeners. This confirms that explicit knowledge of major and minor tonal structures is not needed in order to produce these emotional responses. The happy/sad distinction simplifies the emotional responses that may be evoked by the sounds, but most subjects found that happy and sad were appropriate descriptive labels. Although lifelong exposure to sad melodies composed in minor and happy melodies in major mode may have been an influential factor, the present result may be explained by the relationship of the chords to the natural harmonic spectrum, the major triad chord being composed of the same tonal relations as those present in natural complex harmonic sounds. The happy response to major mode would then be an example of a phylogenetically developed exposure effect, i.e., familiar stimuli elicit positive affects, often observed in relation to mere exposure on the ontogenetic level. Moreover, the unpleasantness of the larger dissonance produced by less overlapping harmonics in the minor than major chords have also been suggested to account for the overall ability to connect the minor mode to sad and major mode to happy. However, our results did not show a consistent tendency to judge the minor complex chords as significantly sadder than the sine minor chords, despite the presence of harmonics. The existence of happy/sad effects of sine chords may be interpreted as an indication that the emotional connotations of major and minor mode are not exclusively related to phenomena of tonal consonance/dissonance. A functional distinction between the two harmonic dimensions, i.e., major/minor mode versus consonance/dissonance, has been evidenced by distinguishable happy/sad and pleasant/unpleasant judgements in relation to the same major/minor stimuli (Crowder, 1985). Furthermore, one study showed that 6-month-old infants preferred to listen to consonant rather than dissonant sounds, whereas different responses to major and minor could not be traced in the behavioral measures (Crowder, Reznick, & Rosenkranz, 1991).

In accordance with earlier findings, the current results also showed that increasing pitch biased the emotional judgements towards happier. The second main finding that sine chords elicited on average sadder responses than piano and voice chords suggests that harmonic richness plays a role in determining emotional responses, even in relation to briefly presented musical chords. The more positive judgments of the complex chords again favor an interpretation in terms of a mere exposure effect, since those sounds are the most common in our auditory environment.

The third finding was that fMRI noise did not significantly influence the emotional judgments, except in the low octave. A high intensity plateau in the noise energy spectrum, overlapping the frequency range of this octave, may explain the registered interaction. Consequently, the present study indicates that musical stimuli, even as brief and simple as isolated chords, can be employed to study emotional processing with fMRI, without the risk of decreased emotional activations.

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16. Judgments of musical emotion following right-hemisphere damage

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We report judgments of musical emotion for an amateur musician KB, who became amusic following a right-hemisphere stroke. KB and matched controls rated 2-s segments from classical music, or computer-manipulated versions of the segments, on a 10-point scale of happy vs sad. Original segments preserved mode and tempo; manipulated segments reduced variations in mode, tempo, or both mode and tempo to a common standard. KB and controls discriminated happy from sad segments. Unlike controls, KB was unable to use mode as a cue to emotional content and relied instead on other spared cognitive abilities. Functional relations between musical emotion and musical cognition are considered.

Report

We report judgments of musical emotion for KB who became amusic following a right-hemisphere stroke. Relative to matched controls, KB is severely impaired on a variety of musical tasks, including judgments of intervals, scale, and tonality. Pre-stroke, KB had been involved in amateur musical activities and enjoyed a classical record collection; he now reports that music has lost all meaning for him.

It is, however, plausible that KB could succeed at judging the emotional content of music. Recently Peretz and colleagues (e.g., Peretz, 2001; Peretz, Gagnon, & Bouchard, 1998) reported a case where emotional response to music was spared despite the presence of cortical damage affecting cognitive responses to music. Their experimental design was followed in the present research to address questions how neural structures might be differentially involved for musical cognition and musical emotion.

Methods

KB. A detailed description of KB is given in Steinke et al. (2001). He is a 71 years old, right-handed, native English-speaking male with 13 years of formal education, who worked in law enforcement. His music background includes 3 years of playing trumpet and drums and 10 years of amateur singing. At age 64, KB presented with left-sided paralysis and speech production difficulties. His speech problems resolved in a few days, but his paralysis persists. CT scans, taken 6, 8, and 12 months after his stroke, showed focal damage in the frontoparietal area, cerebellum, and the putamen/globus pallidus (i.e., lenticular nucleus) on the right side. In addition, there was evidence of diffuse brain atrophy that was consistent with KB's age.

A standard neuropsychological assessment was conducted 7–10 weeks after KB's stroke. Premorbid estimates of WAIS-R IQ, based on his results on the North American Adult Reading Test, indicated that KB's verbal intellectual functioning was intact post-stroke, while his non-verbal intellectual functioning had declined. KB's Wechsler Memory Quotient was 109, indicating normal memory function for his age. A current (2001) vocabulary score of 109 was obtained with the Kaufman Brief Intelligence Test.

KB was not aphasic, according to the Boston Diagnostic Aphasia Examination (BDAE), and was able to identify musical instruments and non-speech environmental sounds. In sharp contrast, KB revealed both expressive and receptive "amusia." He was impaired at singing and rhythm reproduction (BDAE), at recognizing familiar instrumental melodies, and at recognizing errors in novel melodies. Memory for song melodies was intact, and there was limited sparing of simple pitch and rhythm discrimination.

In addition to his amusia, KB has revealed both expressive and receptive "aprosodia." He was impaired on several linguistic prosody perception tasks in both the auditory and visual modalities. Ongoing work in our laboratory suggests that he is also impaired at perceiving affective (or emotional) prosody.

Controls

Controls. Twelve adults (7 women and 5 men) with a mean age of 70.9 years (range 64–80 years) were recruited. The average KBIT vocabulary subscale score was 113 (range 92–128). All expressed a serious interest in music and listened to classical music on a regular basis. None, however, was a professional musician.

Materials

Two-second segments were extracted from each of 20 musical passages from the classical genre (e.g., Bach, Mozart, Ravel). Ten were in the major mode and had a fast tempo; the other 10 were in the minor mode and had a slow tempo. Mode and tempo have long been considered important determinants of emotional response to music (Peretz et al., 1998; see also Juslin, 1997).

Four experimental conditions were constructed, each with 20 segments. The first condition contained the original segments. The second condition removed the tempo cue by adjusting the original segments to a common tempo (median value 90 beats per minute). The third condition removed the mode cue by presenting all segments in the major mode. The fourth condition removed both the tempo and the mode cue.

The segments, in MIDI format, were realized by a Yamaha S 100 XG piano timbre with the average intensity of each segment constrained to a narrow range (i.e., so that perceived loudness could not be used as a cue to discriminate the segments). They were recorded in random order within each condition onto cassette tape, and presented by a cassette player.

Procedure

KB and half the controls heard the conditions in the following order—original segments, mode cue removed, tempo cue removed, and both cues removed. For the other controls, the order was reversed. Participants rated how happy or sad each segment sounded on a 10-point scale, where 1, very sad; 5, slightly sad; 6, slightly happy, and 10, very happy.

Results and discussion

Table 1 shows the mean ratings and standard deviations for "happy" and "sad" segments (as originally classified) in each condition by con-

Table 1
Means (and standard deviations) of emotion ratings of happy and sad segments by KB and controls across conditions

Condition	Controls		KB	
	Happy	Sad	Happy	Sad
Original segments	7.89 (1.09)	3.96 (1.34)	7.20 (2.10)	4.30 (1.83)
Mode cue removed	7.82 (1.36)	4.79 (1.45)	8.60 (0.84)	3.80 (2.20)
Tempo cue removed	7.42 (1.40)	4.48 (1.52)	7.00 (2.26)	4.80 (2.90)
Tempo and mode cues removed	7.34 (1.61)	5.23 (1.82)	7.70 (1.49)	5.50 (2.46)

trols and KB. Controls were easily able to distinguish between "happy" and "sad" segments in each condition, $F(1,11) = 102.97,\ p < .001$. The distinction decreased as the cues of tempo and mode were removed, $F(3,33) = 18.79,\ p < .001$. KB also easily discriminated between "happy" and "sad" segments with ratings within one standard deviation of controls' mean ratings.

However, the finding that "happy" and "sad" segments were distinguished when both tempo and mode cues were removed, $t(11) = 9.29,\ p < .001$, suggests that emotion was conveyed through variables in addition to tempo and mode. Two such variables emerged through inspection of the data–pitch height, the average fundamental frequency of notes in the segment, and note density, the total number of notes per second. Because the variables were intercorrelated, regression analyses were performed with tempo, mode, pitch height and note density as predictor variables, and the 80 ratings as the dependent variable.

For controls, the regression yielded $R = .85,\ F(4,79) = 46.66,\ p < .001$, with all predictor variables contributing significantly to the equation. Note density was the most important, ($\beta = .486$, $t = 6.68,\ p < .001$), followed by mode ($\beta = .288,\ t = 4.23,\ p < .001$), then pitch height ($\beta = .200,\ t = 3.09,\ p = .003$), and finally tempo ($\beta = .174,\ t = 2.64,\ p = .010$). These results matched those for a younger group (aged 20–35 years) with identical order of predictor variables (Lantz et al., 1999).

For KB, the regression yielded $R = .58,\ F(4,79) = 9.39,\ p < .001$, with a different order of predictor variables. KB relied heavily on note density ($\beta = .268,\ t = 2.33,\ p = .023$), followed by pitch height ($\beta = .235,\ t = 2.29,\ p = .025$). Tempo contributed but marginally to the regression ($\beta = .195,\ t = 1.87,\ p = .066$), and mode failed to reach significance ($\beta = .102,\ t = 0.95,\ p = .346$).

We may conclude that KB responds to the emotional content of music despite the presence of amusia. To do so, it is likely that KB relied on spared cognitive abilities. Limited sparing of pitch and rhythm discrimination may have enabled the processing of pitch height, note density and, perhaps, tempo. From previous work we learned that he is unable to process the mode and tonality of music, and we have learned here that he misses emotional content provided by the major or minor mode. This finding supports Peretz's (2001) proposed two-stage model whereby musical input is first subjected to perceptual organization and then relayed to structures concerned with emotional assessment. When perceptual organization of a given source of musical information is damaged, further emotional processing of that input cannot be engaged.

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17. Neural bases of emotion dysregulation in posttraumatic stress disorder: A functional MRI investigation

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This study investigated the neuronal circuitry of traumatic and non-traumatic emotional memories in posttraumatic stress disorder (PTSD). Ten traumatized subjects with PTSD and ten controls with histories of trauma exposure but no PTSD were studied, using the script-driven symptom provocation paradigm adapted to functional magnetic resonance imaging (fMRI) at 4 T field strength. Four emotional states (neutral, sad, anxious, and traumatic) were investigated with a block design paradigm. Compared to controls, PTSD subjects showed significantly less activation of the thalamus, the anterior cingulate gyrus (BA 32), and the medial frontal gyrus (BA 11) during the traumatic condition. For sad and anxious script-driven memories, the PTSD group again exhibited significantly less activation of the thalamus and the anterior cingulate gyrus (BA 32) compared to control subjects. These findings suggest altered thalamic and anterior cingulate functioning across different emotional states in PTSD. Thalamic and anterior cingulate dysfunction may underlie emotion dysregulation in PTSD.

Report

Individuals with Posttraumatic Stress Disorder (PTSD) often experience a variety of difficulties with emotion regulation, including extremes of reexperiencing and avoiding emotionally distressing memories, and generalized problems with physiological hyperarousal and emotional numbing. The present neuroimaging study was designed to investigate emotion dysregulation in PTSD by examining brain activation during different emotional states (traumatic, sad, and anxious). Our aim was to probe for differential patterns of activation between PTSD and comparison subjects with trauma exposure but no history of PTSD across three negatively valenced emotional rememberances.

Subjects

Ten subjects who had developed PTSD as a result of sexual abuse/assault ($n = 7$) or motor vehicle accidents (MVAs) ($n = 3$) were studied.

Comparison subjects were ten subjects who met criterion A for PTSD [as a result of sexual abuse/assault ($n=6$) or MVAs ($n=4$)] for PTSD but who did not meet DSM-IV criteria. Written consent was obtained from all subjects. Subjects were diagnosed using the Structured Clinical Interview for DSM-IV (SCID) and the Clinician Administered PTSD Scale (CAPS) [PTSD mean 75 (*SD* 15.2); control mean 4.6 (*SD* 2.17)]. Comorbidity in the PTSD group included Major Depression ($n=2$), Dysthymia ($n=4$), and Panic Disorder ($n=3$), lifetime history of drug abuse and dependence ($n=2$), lifetime history of alcohol abuse and dependence ($n=4$), and current nicotine abuse ($n=4$). The comparison subjects were of similar age [35 (*SD* 12.3) for PTSD group and 39 (*SD* 11.03) for comparison group], sex, and race. All subjects were right handed. Patients had undergone a supervised drug washout for at least two weeks prior to scanning. All patients with a history of psychosis, bipolar disorder, and substance use disorder in remission for less than six months were excluded from the study, as were patients with any significant medical conditions, neurological illness or a history of head injury.

fMRI procedures

MR imaging studies were performed on a 4 T whole body Varian/Siemens imaging system with a 90 cm diameter horizontal bore and a whole-body 68 cm diameter gradient set with a maximum strength of 40 mT/m and a slew rate of 120 mT/mins. A whole head hybrid birdcage radio frequency (RF) coil was used for transmission and detection of signal. Prior to imaging, a global shimming procedure, using first and second order shims, was performed to optimize the magnetic field over the imaging volume of interest.

The RF coil was placed around the subject's head. Each functional brain volume was acquired using a navigator echo corrected, interleaved multi-shot (4 shots) echo planar imaging pulse sequence with a 64×64 matrix size and a total volume acquisition time of 5 s [TE = 15 ms, flip angle = 45, FOV = 24.0 cm]. The volume acquired covered the whole brain and consisted of 12 transverse slices, 6 mm thick (voxel size = $1.87 \times 1.87 \times 6$ mm).

SPM99 analysis

Functional maps of the activated pixels were constructed by comparing, on a pixel by pixel basis, the signal intensity in the baseline and task-related images, using Statistical Parametric Mapping (SPM 99, Wellcome Department of Neurology, London, UK, www.fil.ion.ucl.ac.uk/spm). Basis functions representing epochs of interest were entered into SPM. Variability in scans attributed to each basis function relative to SPM99's implicit baseline were revealed using contrasts.

Table 1

Talairach Control > PTSD degrees of freedom = 1648	R/L	Effect lobe	Effect gyrus	Brodmann's area	*p* voxel	*t* voxel
A — TRAUMA						
12, −12, 2	R	Sub-lobar	Thalamus		8.05E-14	8.8207
−4, −8, 6	L	Sub-lobar	Thalamus		4.96E-07	6.6513
−4, −14, 18	L	Sub-lobar	Thalamus		7.31E-07	6.5884
0, 36, −12	R & L	Limbic lobe	Anterior cingulate	BA 32	8.86E-05	5.7497
−6, 7, 25	L	Limbic lobe	Anterior cingulate	BA 24	6.12E-06	6.2316
−8, 64, 6	L	Frontal lobe	Superior frontal gyrus	BA 10	5.20E-04	5.4052
44, 30, −12	R	Frontal lobe	Inferior frontal gyrus	BA 47 & 11	3.55E-06	6.325
−20, 26, −8	L	Frontal lobe	Inferior frontal gyrus	BA 47	7.64E-05	5.7776
24, −84, 42	R	Parietal lobe	Precuneus	BA 19	7.25E-05	5.7875
B — SAD						
12, −8, 10	R	Sub-lobar	Thalamus		9.35E-11	7.8913
−6, −16, 14	L	Sub-lobar	Thalamus		1.86E-07	6.7808
−4, −6, 10	L	Sub-lobar	Thalamus		5.44E-06	6.2228
10, 14, 26	R	Limbic lobe	Anterior cingulate	BA 32, 24	1.00E-03	5.19
−12, 18, 36	L	Limbic lobe	Anterior cingulate	BA 32	2.29E-05	5.9686
−2, −26, 44	L	Limbic lobe	cingulate gyrus	BA 31	2.34E-05	5.9641
20, −30, −2	R	Limbic lobe	Parahippocampal gyrus	BA 27, 30	1.18E-05	6.0875
18, −28, −10	R	Limbic lobe	Parahippocampal gyrus	BA 28	6.29E-04	5.3323
16, −48, −2	R	Limbic lobe	Parahippocampal gyrus	BA 19, 30	4.44E-05	5.8471
−28, −94, 24	L	Occipital lobe	Middle occipital gyrus	BA 19	1.29E-06	6.4669
−14, −94, 22	L	Occipital lobe	Cuneus	BA 19	3.51E-11	8.0233
C — ANXIOUS						
−6, −18, 18	L	Sub-lobar	Thalamus		2.22E-16	10.093
−16, −26, 16	L	Sub-lobar	Thalamus		1.35E-05	6.1105
−8, 32, 4	L	Limbic lobe	Anterior cingulate	BA 24	1.25E-08	7.236
−4, −2, 32	L	Limbic lobe	Anterior cingulate	BA 24	8.04E-07	6.5896
−2, −28, 24	L	Limbic lobe	Cingulate gyrus	BA 23	1.28E-06	6.5134
−20, 32, 30	L	Frontal lobe	Medial frontal gyrus	BA 9	4.70E-12	8.3233
−38, 34, 14	L	Frontal lobe	Inferior frontal gyrus	BA 46	1.79E-14	9.0155
−34, 32, −2	L	Frontal lobe	Inferior frontal gyrus	BA 47	1.10E-06	6.5387
−6, 4, −10	L	Frontal lobe	Subcallosal gyrus	BA 34	9.19E-06	6.1786
16, −100, 18	R	Occipital lobe	Cuneus	BA 18	2.06E-08	7.1614

Fixed-effects analyses were performed by modeling each group's evoked BOLD response using hemodynamically-convolved boxcar basis functions. The regions of interest (ROI) were defined on the basis of T1 weighted images and Talairach coordinates.

Script-driven imagery

The script-driven imagery procedure was adapted to fMRI according to previously published methods (Bremner et al., 1999; Lanius et al., 2001).

Scanning of the neutral, sad (unrelated to the traumatic memory), anxious (unrelated to the traumatic memory), and traumatic memory conditions were repeated three times. A fixed order (neutral scripts followed by sad, anxious, and traumatic scripts) was used for all subjects in order to prevent anxiety elicited by the anxious and traumatic scripts from persisting into the neutral and sad scripts, as previously described by (Bremner et al., 1999). Each scan proceeded as follows: (1) Each subject was instructed to lie still, breathe through his/her nose, and allow himself/herself to begin focusing on the neutral, sad, anxious, or traumatic script as soon as the script was read. Reading of the script lasted 30 s. As soon as the subject heard the script, he/she was encouraged to remember all sensations that were associated with the neutral, sad, anxious, or traumatic event for 60 s. Measurement of heart rate occurred during that time. One hundred and twenty seconds were allowed to pass until the script was repeated. Baseline brain activation was calculated based on average activation patterns 60 s prior to each recollection of the neutral, sad, anxious, or traumatic event. Brain activation during the recall of the neutral, sad, anxious, or the traumatic event was calculated based on average activation patterns during the final 30 s of the recall of the sad, anxious or traumatic event.

Table 1 shows regions of activation during the traumatic, sad or anxious memory recall versus implicit baseline where the comparison group ($n = 10$) shows greater activation than the PTSD group and where the comparison group ($n = 10$) shows less activation than the PTSD group ($n = 10$). For all three of the emotional states (traumatic, sad, and anxious), the comparison group showed greater activation than the PTSD group in the thalamus and the anterior cingulate gyrus.

Our results have shown less activation in the anterior cingulate gyrus and thalamus across traumatic and non-traumatic (sad and anxious) emotional states in patients with PTSD as compared to comparison subjects. Given the role of the anterior cingulate gyrus and thalamus in the awareness and autonomic/arousal regulation aspects of emotion (Reiman et al., 1997), dysfunction of these areas as observed in PTSD may provide a neural basis of emotion dysregulation, including extremes of reexperiencing and avoiding emotionally distressing memories as well as generalized problems with physiological hyperarousal and emotional numbing in this disorder.

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18. Cerebral mechanisms involved in implicit emotional processing in Schizophrenia patients without blunted affect and normal controls: A functional magnetic resonance imaging approach

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Several studies reported impaired emotional processing in schizophrenia. Our aim was comparing the cerebral mechanisms involved in implicit emotional processing in schizophrenia patients without blunted affect and normal controls. The cerebral activity associated with the passive viewing of a video film with emotional content inducing a state of sadness was compared to the viewing of a neutral film using fMRI. Superior frontal activation was prominent in patients (processing an inhibitory function). The medial and inferior frontal gyri were much active in controls (perception of facial expression). The Right and Left superior, and the inferior temporal gyri were active in patients only (attributed to auditory hallucinations) and the medial temporal gyrus was more active in patients than in control (correlation between increased activity and reality distortion).

Report

Since Kraepelin schizophrenia is considered as a neurocognitive disorder, with various signs and symptoms reflecting the downstream effects of a fundamental cognitive deficit. Schizophrenia poses special challenges to the development of cognitive and emotional models because of its breadth and diversity of symptoms. Symptoms include nearly all domains of function, in perception: visual, auditory or tactile hallucinations. In thought: delusions, lack of abstract thinking, persecution. In motor: catatonia, In emotions: affective blunting, apathy, anhedonia. Schizophrenia patients have a central defect in the heteromodal monitoring of emotional-social displays, associated with dysregulation of social behaviors and disruption of interpersonal relations (Poole, Tobias, & Vinogradov, 2000). Affective flattening or blunting is a reduced intensity of emotional expression and response. Unchanged facial expression, monotonous voice, and inappropriate affect during relating emotionally charged material are observed. On the other hand flat affect can clearly foretell the level of social integration patients will experience. Fortunately this symptom is not present in all schizophrenia patients. Liddle (2000), in order to identify the pattern of cerebral activity associated with the occurrence of schizophrenia symptoms, conducted several brain imaging studies (PET and fMRI) of the patterns of activity associated with each of three major clusters of characteristic symptoms of schizophrenia: he found that each of the three groups of characteristic symptoms was associated with a specific, distributed pattern of cerebral activity in association cortex, basal ganglia and thalamus. The pattern of cerebral activity associated with reality distortion (delusions and hallucinations) revealed over-activity in medial temporal lobe, and frontal cortex. According to Liddle's model, patients belonging to the Reality Distortion group do not present flattening of affect. Differentiating between patients with blunted affect and those without is essential to determine the choice of pharmaceutical and behavioral therapy used. Social skills, cognitive and emotional

processing are difficult to separate. Studies on emotion in schizophrenia have not typically taken place in social situations, and the behaviors taken as evidence for deficient emotional expression could also be interpreted as evidence for selective impairment in social communication. In this study we were determined to compare schizophrenia patients without blunted affect to normal controls using measures of emotional perception and emotional experience, and to study the difference in cerebral activity between schizophrenia patients with and normal control.

Methods

Participants

A group of 5 stable and medicated patients with a DSM-IV diagnosis of schizophrenia and 6 controls, were recruited. All the patients belong to the Reality Distorsion group of Schizophrenia according to the scale used by Peter Liddle to characterize psychotic symptoms (SSPI). None of the control subjects had a personal or a family history of psychiatric or neurological disorders. All subjects gave voluntary written consent.

Behavioral experimental procedure

A 16-point scale was developed by Abrams C and Taylor to measure affective blunting in three fields of manifestation: affect itself (absent, limited, invariable, non-relational), behavior (facial expression, lack of social interaction, hygiene, or social skills, lack of emotional response or spontaneity, inappropriate laughter) and thought content (indifference to the fate of family and friends, to his/her own situation, or to his/her future, impoverished thought). This scale was used to evaluate blunted affect symptoms in recruited patients. A score above 17 was considered to be with blunted affect, and below 10 was considered to be without blunted affect. The Positive and Negative Syndrome Scale (PANSS) was used to measure the intensity of positive and negative symptoms, especially concerning emotions and blunted affect.

Neuroimaging experimental procedure and acquisition

Using fMRI we examined the brain activation/regions of schizophrenic patients using a theoretically validated pre-recorded color video to generate two different states of emotions: Either a transient state of sadness. The video depicted, among other things, the tragic death of a father in the presence of his young son. Or a neutral video depicting a carpenter renovating a house. This video was used as a control for any potentially confusing task-related elements that generate emotion in the film. During this task, the videos was presented using a special visor connected to a video system compatible with the magnetic resonance machine. The presentation took the form of a boxcar design in the following sequence: neutral film (shown for 154 s) followed by a rest period of a blank screen (for 32 s) then the emotion-generating film (shown for 154 s).

Echoplanar images (EPI) were acquired on a 1.5 T system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 3 s in an inclined axial plane, aligned with the ACPC axis. These T2* weighted functional images were acquired using an EPI pulse sequence (TR = 0.8 ms, TE = 54 ms, Flip = 90 °, FOV = 215 mm, Matrix = 64 × 64). Following functional scanning, highresolution data were acquired via a Tl-weighted 3D volume acquisition obtained using a gradient echo pulse sequence (TR = 9.7 ms, TE = 4 ms, Flip = 12 °, FOV = 215 mm, Matrix = 256 × 256).

Neuroimaging analyses

Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements and spatially normalized into an MRI stereotactic space (Talairach and Tournoux,). Images were then convolved in space with a three-dimensional isotropic gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

Table 1
Patients and controls anatomical locations and characteristics of clusters (data are presented as sad regions minus neutral regions)

Subjects	Talairach (in mm)			Region name	Brodmann area	Cluster size (in mm^3)	p value corrected
	x	y	z				
Patients Sad—neutral	9	51	36	Right superior frontal gyrus	9	200	0.0001
	18	67	−11	Right superior frontal gyrus	10	189	0.0001
	68	−15	−7	Right medial temporal gyrus	21	161	0.0001
	62	−43	11	Right superior temporal gyrus	22	54	0.0001
	−62	−10	−15	Left inferior temporal gyrus	21	5	0.0001
	−3	64	−11	Left superior frontal gyrus	11	39	0.0001
	−30	19	−26	Left superior temporal gyrus	38	7	0.0001
	3	−13	39	Right anterior cingulat cortex	24	7	0.0001
	33	56	19	Right medial frontal gyrus	10	9	0.0001
Control Sad—neutral	51	43	−17	Right inferior frontal gyrus	47	6	0.0001
	−30	59	8	Left thalamus		7	0.01
	−33	41	−5	Left medial frontal gyrus	47/46	74	0.0001
	3	26	4	Right anterior cingulate cortex	32	73	0.0001
	−45	26	4	Left Inferior frontal gyrus	45	74	0.0001
	−15	−50	50	Left precunus gyrus	7	52	0.0001
	−27	−46	8	Left medial temporal gyrus	21	34	0.0001
	12	45	25	Right superior frontal gyrus	9	14	0.003
	18	−50	−5	Right parahippocampal gyrus	19	6	0.01

Results

Frontal activation was prominent in patients, specially activation of the superior frontal gyrus totaling to 428 clusters while controls activated 14 clusters. On the other hand activation in the medial and inferior frontal gyrii were much higher in control compared to patients (74 versus 9 clusters in medial) and (74 versus 6 in inferior). The Right and Left Superior, and the inferior temporal gyrii were active in patients only and the medial temporal gyrus was more active in patients than in control (161 versus 34). The anterior cingulate was activated in both patients and controls, yet controls activated far more clusters than patients (73 versus 7). Thalamus was activated in patients not in control, while precunus and parahippocampal gyrus were active in controls only (see Table 1).

Discussion

Studies of implicit emotional responses rather than the pervasive characteristic of explicit tasks, portray real life situations that have not been investigated in depth. In this study we were determined to differentiate between schizophrenia subgroups (with and without blunted affect) using 2 psychiatric tests (emotional blunting scale) and (PANSS). This approach is not a usual trend and schizophrenia in general after complying with criteria of DSM is compared to controls. Many studies found that there is a generalized frontal *hypoactivity* during explicit neurocognitive tasks that challenge the frontal cortex (Semkowska, Bédard, & Stip, 2001). The prominent frontal activation in patients found here, specially activation of the superior frontal gyrus during implicit task, is consistent with studies by Catafau (1994). Activity in the left and right superior temporal gyrus, in patients not present in controls, could be attributed to the stimulation of Heschl's gyrus along the superior surface of the superior temporal gyrus, which contains the primary auditory cortex. This area was indicated in many studies to be associated with auditory hallucinations and verbal memory in schizophrenia. The medial temporal gyrus was much more active in patients, which is in accord with Liddle's findings which concluded that there is a correlation between increased activity and reality distortion. Medial and inferior frontal gyri were implicated in some studies to be involved in perception of facial expression and by others in memory of previous sad experience. Activation of these areas is explained by the presence of sad, tearful faces in the film. Yet the marked difference in activation between controls and patients still requires clarification. The inferior temporal gyrus was reported to be involved in auditory association, the detected activity solely in patients suggests the presence of auditory hallucinations (Silbersweig et al., 1995). Increased frontal activity observed in patients proposes that patients may be processing an inhibitory executive function to suppress their subjective emotion, or suppressing hallucinations triggered, facing the stress of an emotional situation. Our conviction that schizophrenia patients do not share the same level of impairment has led our group to extent our investigation to compare schizophrenia patients with blunted affect and without, and further to compare patients with blunted affect with controls, this data will be presented in a later article. Our finding should be interpreted in a sense that refutes the general idea that schizophrenia patients do not experience emotion. There are degrees of impairments where patients do not exactly process emotions as in normal controls, yet they can not be categorized with those with flattening of affect (Fahim et al., 2002). This study opens the door to further examine if a difference is also present between patient with and without blunted affect on the neurocognitive level and social functioning. This study opens the door to further examine if a difference is also present between patient with and without blunted affect on the neurocognitive level and social functioning.

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19. Differential neural responses to emotional stimuli in females and males: A functional magnetic resonance imaging study in humans

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Interest concerning potential gender differences in affective processing is increasing. The present study examined possible differences in neural response to emotionally evocative stimuli. Male and female matched controls underwent fMRI while viewing pictures selected to represent four emotional conditions: disgust/gore, sad, thrilling/sexual, and happy. Analyses revealed extensive regions that differentially activate as a function of gender, a function of the dimension of emotion, and a function of the gender of subjects processing the dimensions of emotion. In conclusion, topographical and neural activation differences between males and females in response to specific dimensions of emotion suggest that gender differences exist in the neurobiological mechanisms involved in emotional processing.

Report

Gender differences have been reported across various domains such as cognitive abilities and strategies. There is an evolving literature elucidating gender differences related to the involvement of neural substrates in emotion and emotional processing. Gender differences are found in skin conductance responses to emotionally evocative film clips (Kring & Gordon, 1998) and, neuroimaging studies have demonstrated limited regional differences in cerebral response to mood induction or discrimination (George et al., 1996; Schneider et al., 2000). For example, despite similar mood self-reports, George et al. (1996) reported greater regional cerebral blood flow in limbic and paralimbic sites in women compared to men. Schneider, Habel, Kessler, Salloum, and Posse (2000) found increased amygdala activation in response to sad facial expressions in males but not in females despite similar subjective ratings of affect. Furthermore, Cahill et al. (2001) found that lateralization of amygdala involvement in emotionally influenced memory was related to gender. In an attempt to better understand possible gender differences in the neural substrates of emotion, this study examined neural regions involved in the processing of four distinct classifications of affective pictures: disgust/gore, sad, thrilling/sexual, and happy in female and male matched controls.

Twelve right-handed, healthy female volunteers and twelve right-handed, healthy male volunteers were matched for age (mean age = 25; range = 18–46 years), education, and smoking status. After providing informed, written consent, volunteers viewed sets of affective pictures while undergoing functional magnetic resonance imaging. Visual stimuli from the International Affective Picture System (IAPS) (?), which contains normative data on the arousal level and valence of each picture, were used. Pictures were selected to represent four distinct emotional conditions: disgust/gore, sad, thrilling/sexual, and happy. The stimuli were presented in a block design with each block comprised of five novel pictures from the same condition. Each picture was displayed for six seconds with no interstimulus interval. Each block of pictures was preceded by five neutral pictures (also 6 s duration with no interstimulus interval) and followed by a 27 s distracting attention task and three seconds of visual fixation. One block from each of the four conditions was presented with the order of the block presentation varied across the four imaging runs. Immediately after the imaging session, volunteers rated the arousal level and valence of each picture using a computerized Self-Assessment Mannequin (SAM) (?).

Contiguous seven millimeter sagittal slices covering the entire brain were collected on a 1.5 T GE Signa scanner with a local gradient coil and birdcage receiving coil using a BOLD gradient-echo, echo-planar pulse sequence (TE = 40 ms; TR = 3000 ms; FOV = 24 cm; 64×64 matrix; 3.75×3.75 mm in-plane resolution). Volume motion correction algorithms were applied to the functional data. Activation associated with each block of pictures was calculated for each voxel relative to the immediately preceding neutral pictures. Percentage BOLD signal change scores were calculated in this manner for each block of pictures in each imaging run. Blocks from the same condition were then averaged over the four runs to return a mean percent change score for each condition. These activation maps were converted to a standard stereotaxic coordinate system and blurred with a 4.2 mm FWHM gaussian kernel. One-sample *t*-tests against the null hypothesis of no change in activation were used to create separate activation maps for males and females for each of the four emotion conditions. These activation maps were thresholded at $p = .05$ and clustered at a contiguous volume of greater than or equal to 150 μl. For each emotional condition, the topography of activation was compared by creating a total mask of activation from the union of the activation maps of each gender. The union mask was thus comprised of clusters that met criterion for males and/or females. Each cluster of activation in the union mask defined a region of interest (ROI) that was used to extract the average percent BOLD activation within that cluster for each volunteer. The average percent BOLD activation within each cluster was then compared across matched volunteers using paired *t*-tests.

Average arousal and valence scores for each of the four classifications of affective pictures were calculated for each volunteer. Results indicated that the volunteers' ratings of the stimuli were in general agreement with normative ratings. Paired *t*-tests comparing subjective ratings across matched male and female volunteers revealed no significant gender differences in valence ratings across all four emotional conditions. Further analyses indicated that males rated sad and thrilling/sexual pictures as more arousing than females ($t = 2.5$; $p < .05$ and $t = 2.3$; $p < .05$, respectively).

A variety of topographical differences between males and females were found for each of the four distinct emotional conditions. Many of the topographical differences were not replicated when the neural activity within these regions was compared across gender. Nonetheless, there were a number of regions whose topography and neural activity were different across males and females. Males demonstrated greater bilateral neural activity and in more regions during the disgust/gore, sad, and thrilling/sexual conditions compared to females. Specifically, males exhibited greater activity in bilateral visual processing areas and females exhibited greater left insular cortical activity while viewing disgusting/gory pictures. During the sad condition, males demonstrated increased bilateral thalamic and caudate activity as well as increased activity in the left pons whereas increased right superior parietal activity was found in females. Males exhibited greater activity bilaterally in thalamic nuclei and in visual processing areas, in the right parahippocampal gyrus, and in the left pons while viewing thrilling/sexual pictures. During the happy condition, increased right dorsolateral prefrontal activity was found in females whereas males demonstrated increased neural activity in the left precuneus and pons.

The present study revealed a variety of topographical and neural activity differences between gender across four distinct emotional conditions. Differential topography and neural activity in males versus females for specific emotion conditions suggest that there are subtle gender differences in the underlying neurobiological mechanisms involved in the induction, experience, and/or expression of emotion. Although speculative, these differences may ultimately provide insight into numerous gender differences in both the expression and incidence of emotional dysregulation symptoms and thereby contribute to pathophysiological rather than phenomenological classification of neuropsychiatric disorders.

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20. The emotional content of material and reality monitoring function in subjects predisposed towards hallucinations

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It has been suggested that the emotional valence of material may influence the externalising bias observed in reality monitoring tasks in subjects with hallucinations. However, studies have inadequately explored this role. One hundred normal subjects were administered a reality monitoring task with emotionally charged material. Subjects were grouped according to their scores on a hallucinations scale. Results revealed an externalising bias of internal information in subjects predisposed towards hallucinations compared to non-predisposed subjects. Furthermore, this pattern was especially marked with emotionally charged material, compared to neutral material. These results suggest a continuity between normal predisposed subjects and patients with hallucinations, in particular, in terms of emotion as an important contributing factor.

Report

Studies have shown that hallucinating subjects show a specific bias towards attributing their thoughts (internal source) to an external source. It has been suggested that this bias may be influenced by the emotional content of material (Bentall, 1990). The only study that attempted to test this hypothesis (Morrison & Haddock, 1997) did not find an effect of emotional valence of material on a reality monitoring task in schizophrenic patients with hallucinations, compared to non-hallucinating patients and normal control subjects.

However, this may be due to methodological weaknesses. Stimuli was inadequately controlled for in terms of emotional valence. Cognitive effort was not controlled for in the study, even though this is an important contributing factor (Bentall, Baker, & Havers, 1991). Also, it is not certain if the control group included in this study also experienced hallucinations. Even though a past psychiatric history was used as exclusion criteria, a number of studies reveal that a large minority of normal subjects without a psychiatric history report having such experiences (Bentall, 1990). An inadequate number of subjects were included in each experimental group ($n = 15$). Failure to find an externalising bias for internal information may be related to the population, in particular, to high levels of depression in this study's patients. The effects of general factors such as IQ were not controlled for, even though recent data suggest that source monitoring errors in schizophrenics with hallucinations are significantly associated with low IQ (Vinogradov et al., 1997). Finally, since all of the hallucinating subjects were receiving neuroleptic treatment at the time of testing, one cannot exclude the influence of neuroleptic medication on cognitive performance.

The present study rectified these limitations. Words were carefully selected in order to control for emotional valence. Words were also controlled for in terms of cognitive effort. Because non-hallucination subjects were selected based on their low scores on a hallucinations scale, we controlled for the non-presence of hallucinations in this group. A large number of subjects were tested, enabling the creation of two large experimental groups ($n = 25$ for each group). Since the population consisted of healthy, active subjects (University students), levels of depression were minimal (at least compared to those levels documented in schizophrenic patients), thus minimising the effects of depression on results. The effect of IQ on results was also minimal as subjects most likely had similar IQ scores within the normal range. Finally, as healthy, normal subjects were tested, one can exclude the influence of neuroleptic medication on cognitive performance.

Methodology

Subjects consisted of 100 normal subjects. To assess predisposition towards hallucinations, subjects were asked to complete the Launay–Slade Hallucinations Scale (LSHS). The reality monitoring task consisted of orally presenting a list of thirty words, 10 of which were positive, 10 negative, and 10 neutral. For each word, subjects were asked to say the first word that came into their mind. For the recognition task, words were randomly presented on a computer screen. These words consisted of those given by the subject, those words presented by the experimenter, and those words never presented. Subjects were first asked to say if the word they saw on the screen was old or new. If the word was considered old, they were asked to identify the source (i.e., whether it was given by the subject or by the experimenter).

Construction of the material consisted of 4 steps. The first step consisted of choosing positive, negative and neutral words from a large data-base of words of which emotional valence was already assessed by subjects. These words were then controlled for in terms of length and frequency. In the second step, a group of normal subjects ($n = 20$) were asked to estimate (on a Likert-type scale from 1 to 7) if the word was agreeable (1) or disagreeable (7). We then selected those words with a score between 6 and 7 (positive), between 1 and 2 (negative), and those between 3 and 5 (neutral). The third step consisted of recording the length of the words, and selecting only those with presentation times between 650 and 900 ms. The fourth step consisted of presenting these words (auditory presentation with the help of a lap-top computer) to another group of normal subjects ($n = 20$), who were asked to give the first word that came to their mind after having heard the word. Reaction times for each word were then recorded. For each valence, those words with the longest and shortest latency times were kept. This resulted in a total of 30 words (i.e., 10 for each valence −5 with long and 5 with short latency times). After this, 30 more words were selected to serve as distracters, which were also controlled for in terms of emotional valence, frequency and length.

Results

Subjects were selected according to their scores on the LSHS. Those scores within the bottom 25th percentile were considered non-predisposed (NONHALL) ($n = 25$), and those scores within the upper 25th percentile were placed in the hallucination group (HALL) ($n = 25$). Scoring of the reality monitoring task followed the procedure introduced by Vinogradov et al. (1997). The first type of error consisted of source discrimination errors, or the difficulty in identifying a specific source of words. The second type of error was the response bias error, or the tendency to misattribute words to a specific source, regardless of the original source.

Results showed that the two groups differed significantly in terms of the number of source discrimination errors when the material was personalised (i.e., where the material was given by the subject, therefore the subject was the source) ($p < .01$). In particular, the HALL group revealed a greater number of discrimination errors compared with the NONHALL group. This difference was not found for non-personalised material (i.e., words presented by the experimenter; $p > .05$). Furthermore, source discrimination errors for personalised material differed significantly between groups when the stimuli was emotionally charged (positive: $p < .05$; negative: $p < .05$). However, this difference was not observed for neutral stimuli ($p > .05$). In terms of attributional bias errors, we observed significant differences between HALL and NONHALL subjects, with a bias towards the experimenter (external) ($p < .05$). However, no significant differences were found in terms of attributional bias errors regarding attribution to the subject ($p > .05$). In terms of attributions towards the experimenter, we observed significant differences between groups when the material was emotionally charged (positive: $p < .01$; negative: $p < .01$), but not when material was neutral ($p > .05$). An effect of emotional valence was not observed for attributional bias errors towards the subject ($p > .05$).

Discussion

The results of the present study reveal greater reality monitoring errors in subjects predisposed towards hallucinations, compared to non-predisposed subjects. This is in line with a number of studies. In addition, these differences were more marked when material was emotionally charged, compared to neutral material. These results clearly show that emotion plays a prominent role in the externalising bias seen in schizophrenic patients with hallucinations and in predisposed subjects. Up to now, this hypothesis had been inadequately tested. According to our knowledge, this is the first study of its kind to explore the role of emotional valence on a reality monitoring task in subjects predisposed towards hallucinations. These findings may be interpreted from a source monitoring framework. In the presence of emotionally eliciting material, it seems that the contextualisation of this information is perturbed.

Binding of contextual information to target information is essential if a source discrimination is to be made. In normal subjects, emotion seems also to perturb this binding process (cf. Larøi et al., 2001). Results from the present study reveal that subjects predisposed towards hallucinations are particularly sensitive to the effects of emotion on the contextualisation of internal information.

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21. Preliminary electrophysiological evidence for modulation of the processing of negative affect by serotonin

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Despite a well-known relationship between serotonergic function and depression, little is known on how modulation of serotonin affects the processing of negative affect. The current study was double-blind-placebo-controlled and investigated the neurophysiological changes in 13 subjects (using steady-state probe topography) that were associated with the processing of negative affect using pictures (from the international affective picture system) and their modulation by citalopram (20 mg). Analysis compared negative images with the neutral images for each treatment condition (placebo and citalopram). Preliminary results suggest that citalopram suppresses the latency reductions displayed in the placebo condition within the frontal, left temporal and right parieto temporal cortices. This study suggests that the processing of negative affect is modulated by acute changes in serotonin.

Report

Emotional processing of negative affect in healthy subjects has been associated with increased brain activity in ventral frontal and decreased activity in dorsal frontal areas in studies using pet and fmri. The pattern of brain activity displayed in these individuals during induced negative affect has been generally consistent with that of patients with major depressive disorder. Studies that have investigated emotional processing in healthy subjects have used many mood induction paradigms, including the international affective picture system (iaps). The iaps has become a popular task for use in neuro-imaging studies to investigate emotional processing and has been considered an effective method for evoking positive or negative affect.

Previous studies using techniques such as pet and fmri have been limited to the investigation of spatial aspects of emotional processing. However, emotion is a transient phenomenon, which may be better tracked through an analysis of the rapid changes occurring in brain electrical activity. Steady-state probe topography (sspt) is a technique that is able to track such changes and has the capacity to reliably measure small variations in ssvep latency, believed to index changes in the information processing speed of neural systems that are participating in a particular task. Our recent sspt study using the iaps found steady state visually evoked potential (ssvep) latency reductions (increased excitatory processes) in the frontal regions during negative relative to neutral images in healthy subjects (Kemp, Eide, Stough, & Silberstein, 2001).

While there is research on the brain regions involved in emotional processing, the role of neurochemicals in modulating such processing remains poorly understood. Clinical studies suggest that antidepressant drugs lead to normalization (or reversal) of pre-treatment brain activity (decreased ventral and increased dorsal frontal activity) in depressed patients (see Brody et al., 2001 for a review). Although the relationship between serotonergic function and depression is well known, little is known on how modulation of 5-ht affects the processing of emotion.

Aim

The aim of the current study therefore, was to use SSPT to investigate the effects of acute SSRI serotonergic manipulation on the neurophysiological changes associated with the processing of negative affect using pictures from the International Affective Picture System (IAPS).

Hypotheses

Emotional processing of negative affect (negative images) relative to neutral affect (neutral images) will be associated with frontal SSVEP latency reductions, whilst increases in serotonin (with citalopram) will reduce the magnitude of these frontal SSVEP latency reductions.

Method

Subjects

Thirteen healthy subjects, consisting of 8 males ($M = 23.90$, $SD = 3.60$) and 6 females ($M = 24.50$, $SD = 4.00$), participated in the current study. Subjects were right-handed, non-smoking, drug-free, and had no history of neurological or psychiatric disorders.

Procedure

The study design was double-blind-placebo-controlled, in which subjects were tested under two conditions (placebo and citalopram 20 mg), each separated by a one-week washout period. Testing was conducted 2 h following drug administration to coincide with the approximate peak plasma levels of citalopram.

A diffuse 13 Hz visual flicker elicited the SSVEP while participants viewed 50 IAPS images, categorized as either neutral or negative. These images were presented in 2 blocks (neutral and negative), which contained 25 images in each block.

IAPS

Image selection was based upon standardized American valence and arousal ratings (Lang, Bradley, & Cuthbert, 1999). Valence ranged between 4.46 and 5.46 (neutral images) and 1.8 and 3.47 (negative images), whilst arousal ranged between 1.55 and 4.27 (neutral images) and 3.52 and 5.5 (negative images).

A one way ANOVA was conducted to assess for any differences in brightness and contrast between neutral and negative picture-categories. No significant differences were found between categories of images for brightness, $F(1,48) = 1.04$, $p = .31$, and contrast, $F(1,48) = 1.26$, $p = .27$.

SSVEP analysis

The SSVEP was produced for all 64 electrodes from the 13 Hz Fourier coefficients evaluated over 10 stimulus cycles at the stimulus frequency of 13 Hz using a cosine window, thus yielding a temporal resolution of 0.77 s. This evaluation period was shifted 1 stimulus cycle and the coefficients recalculated for this overlapping period. This procedure was continued for the entire recording period for both neutral and negative categories.

A target averaging technique was then used to select the SSVEP epochs that corresponded with the presentation of an image and all selected epochs for each category averaged. The SSVEP for each individual were then averaged together to form a group average for both the placebo and citalopram conditions. The SSVEP corresponding to the neutral category was then subtracted from the negative category to yield the activity associated with negative valence for each condition.

To investigate the spatio-temporal processing of valence after administration of placebo and citalopram one time point was selected that corresponded to the most negative deflection in the placebo condition for the negative images relative to the mean of the 6-s image presentation for the neutral images. To aid time-point selection electrodes, Fp1 and Fp2 were chosen as these were regions at which activity was hypothesized. The time series for these electrodes are displayed in Fig. 1.

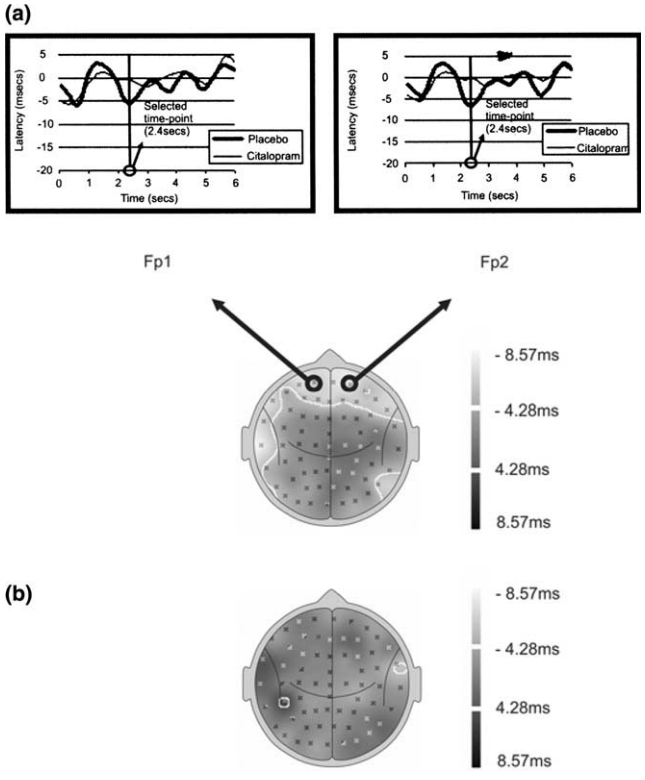

Fig. 1. The latency time-series for electrodes, Fp1 and Fp2 is presented. These display the selected time-point (2.4 s), which is also displayed topographically for both the placebo (a) and the citalopram (b) conditions.

For the purposes of brevity, only the latency results for the negative versus the neutral images will be displayed. Lighter regions in these maps represent reduced latency for the negative images compared to neutral images. Results displayed below are preliminary and general trends are discussed. Statistical analysis was not conducted as the minimum required subject numbers for in-house multiple permutations testing have not, as yet been reached.

Results

Results display the SSVEP latency change at the 2.4 s time point for the negative images after the latency of the neutral images has been subtracted.

Reductions in SSVEP latency predominantly in bilateral frontal but also in the left temporal and right parieto-temporal regions were found in the placebo condition during processing of negative affect (Fig. 1a), whilst the magnitude of this latency change was globally reduced by citalopram (Fig. 1b).

Conclusions

Frontal SSVEP latency reductions were found during the processing of negative affect in the placebo condition. This finding supports previous findings that have shown strong frontal latency reductions during the processing of negative emotional valence in healthy subjects (Kemp et al., 2001).

The latency reductions during the processing of negative affect may be interpreted as an increase in excitatory processes within pyramidal cell networks (Silberstein et al., 2001). In this model, latency reductions in the activation task (negative images) compared to the control task (neutral images) are interpreted as a stronger activation within local networks during the processing of negative affect.

Acute administration of citalopram was associated with reductions in these effects (reduced excitatory processes). A reduction in such processes within pyramidal cell networks following citalopram administration may be explained by increases in extracellular 5-HT in the frontal cortex, left temporal and right parieto-temporal regions leading to inhibition of pyramidal cell activity, either by direct activation of 5-HT_{1A} receptors on layer 5 pyramidal cells or indirectly through activation of GABA interneurons innervating pyramidal cells.

In summary, preliminary findings suggest that emotional processing of negative affect is modulated by acute changes in serotonin particularly within the frontal cortex, as well as regions that have been implicated in physiological arousal (the right parieto-temporal region) and danger recognition (left temporal region). The findings support metabolic blood flow studies that also indicate frontal modulation of brain activity by antidepressants (e.g., Kennedy et al., 2001).

Acknowledgment

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22. Effects of catecholamine depletion on D_2 receptor binding and mood in healthy humans

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The effects of catecholamine depletion, achieved by per-oral administration of 4.5–5.25 g -methyl-*para*-tyrosine (AMPT) over 25–29 h, were studied on measures of dopamine (DA) release and mood in twelve healthy subjects. Neostriatal DA levels in vivo were estimated by comparing the $\mathbf{D_2}$ receptor-binding potential ($\mathbf{D_2}$RBP) before and after catecholamine depletion using [^{11}C]raclopride positron emission tomography. The AMPT treatment increased $\mathbf{D_2}$RBP significantly by $\mathbf{14.7 \pm 5.4}$% and decreased plasma levels of the DA metabolite homovanillic acid by $\mathbf{66 \pm 14}$% and of the norepinephrine metabolite 3-methoxy-4-hydroxyphenethyleneglycol by $\mathbf{64 \pm 11}$%. Catecholamine depletion resulted in decreases in happiness, talkativeness, feeling high, vigor, attentiveness, and openness to feelings, and in increases in drowsiness, sleepiness, sedation, and persistence. These changes were not correlated with the $\mathbf{D_2}$RBP increments.

Report

Neostriatal dopamine (DA) levels have been estimated in humans in vivo by comparing radiotracer binding at baseline and after rapid catecholamine depletion induced by the tyrosine hydroxylase inhibitor α-methyl-*para*-tyrosine (AMPT) using [^{123}I]IBZM single-photon emission computed tomography (Laruelle et al., 1997). We recently developed a protocol to estimate DA levels with [^{11}C]raclopride positron emission tomography (PET) and observed significant AMPT-induced changes in subjective happiness and sleepiness (Verhoeff et al., 2001). However, because of the small sample size in our original study, we believed that an imperative step in establishing the validity of these effects was to test them in a larger subject group.

Materials and methods

Human subjects

The study was approved by the Human-Subjects-Review-Committee of the University of Toronto and has been carried out in accordance with the Declaration of Helsinki (1975). Five men and 7 women, age 27 ± 7 years (all values in this article are expressed as means ± standard deviation) and all right-handed, completed the study. In- and exclusion criteria were the same as for our original study (Verhoeff et al., 2001).

Depletion regimen and mood monitoring

Each subject was scanned twice, at baseline (PET1-day 1) and after DA depletion (PET2-day 3). DA depletion was induced by oral AMPT administration of in total 4500 mg over 25 h (6 subjects) or 5250 mg over 29 h (6 subjects). AMPT was administered in doses of 750 mg each at the following times: at 10 AM, 1.30 PM, 6 PM, and 10 PM on day 2, and at 7 AM, and 11 AM plus 3 PM (6 subjects) on day 3. During AMPT administration, subjects remained under direct observation at the PET Centre during the day and on a psychiatric inpatient unit during the night. To prevent AMPT urine crystal formation, subjects were instructed to drink $\geqslant$4 L/24 h of fluids, starting on day 2. In addition, to alkalinize the urine, which increased AMPT solubility, sodium bicarbonate 1.2 g orally was given at 10 PM on day 1 and at 7 AM on day 2. Urine samples were collected at 3 PM on day 2 and at 7 AM on day 3 to examine the presence of AMPT crystals.

Subjects were evaluated five times using rating scales for mood states pre-AMPT (on day 1 and on day 2) and post-AMPT (cumulative oral doses of 750 mg on day 2, and 3750 and 4500 mg on day 3). The subjects rated 19 subjective feelings on a continuous visual analog scale (VAS) ranging from 0% (''not at all'') to 100% (''most ever''). Subjective feelings were also rated using the ordinal Profile Of Mood States (POMS) developed by McNair et al. In addition, subjects rated depressive symptoms using the Beck Depression Inventory, Short Form (BDI).

Plasma analyses

Plasma homovanillic acid (HVA), 3-methoxy-4-hydroxyphenethyleneglycol (MHPG) and prolactin samples were collected at 10 AM (day 1), at 10 AM (day 2 pre-AMPT), at 3 PM (day 2 post-1500 mg AMPT), at 1 PM (day 3 post-4500 mg AMPT), and at 3 PM (day 3 post-5250 mg AMPT for 6 subjects). Plasma AMPT samples were collected at 3 PM (day 2 post-1500 mg AMPT), at 1 PM (day 3 post-4500 mg AMPT), and at 3 PM (day 3 post-5250 mg AMPT for 6 subjects). HVA, MHPG, and AMPT levels were measured as the methylated then acetylated derivative, as the 4-acetyl-di-trifluoro-acetyl derivative, and as the pentafluorobenzoyl derivative, respectively, using gas chromatography-mass spectrometry with selected ion monitoring. Prolactin levels were measured using microparticle enzyme immunoassay technology (Abbott Laboratories, Abbott Park, Illinois).

[^{11}C]raclopride PET data acquisition

PET images were obtained with a GEMS PC2048-15B camera (General Electric Medical Systems, Milwaukee, Wisconsin) in five 1-min frames followed by twenty 2-min frames and three 5-min frames after [^{11}C]raclopride bolus injection (pre-AMPT: 376 ± 28 MBq, specific activity $45,029 \pm 15,215$ GBq/mmol; post-AMPT: 376 ± 38 MBq, specific activity $43,776 \pm 20,764$ GBq/mmol). There was no significant difference in the pre- and post-AMPT injected radioactivity and specific activity. The images were attenuation corrected via ^{68}Ge trans-

mission and reconstructed using filtered back projection (Hanning filter, 5 mm full-width-at-half-maximum), and fifteen 6.5 mm-thick transaxial slices were obtained.

Image analysis

Regions of interest (ROIs) were manually drawn following contours of neostriata (pre-AMPT: $4269 \pm 472\,mm^3$; post-AMPT: $4255 \pm 439\,mm^3$) and cerebellum (pre-AMPT: $15,360 \pm 459\,mm^3$; post-AMPT: $15,245 \pm 330\,mm^3$) on two adjacent transaxial PET slices. There were no significant differences in the pre- and post-AMPT sizes of the neostriatal and cerebellar ROIs. The neostriatal D_2 receptor-binding potential (D_2RBP), the product of D_2R density and affinity, was calculated using the simplified-3-parameter-reference-tissue-model developed by Lammertsma and Hume. Since DA competes with [^{11}C]raclopride binding, the fractional D_2RBP increase ($D_2RBP_{shift} = (D_2RBP_{depleted} - D_2RBP_{baseline})/D_2RBP_{baseline}$) is linearly proportional to the baseline DA level, provided DA depletion does not change D_2R density and/or affinity (Verhoeff et al., 2001).

Statistical analyses

Data were screened for univariate statistical violation by testing for skewness, curtosis outlyers, and homogeneity of variance. Correlations between PET data, plasma levels, and mood ratings were tested for using Pearson's product-moment correlation coefficient (r) if these criteria were met or Spearman's rank correlation coefficient if these criteria were not met. AMPT effects on plasma levels and mood ratings were assessed by repeated measures ANOVA if these criteria were met or by Friedman's test if these criteria were not met. Similarly, AMPT effects on PET measurements were assessed by paired Student's t-test if these criteria were met or by Wilcoxon's signed ranks test if these criteria were not met. All tests were 2-tailed and probability values of .05 were used as the significance level. No corrections for multiple comparisons were applied. Statistical analyses were performed with SPSS for Windows, release 10.0.0 (SPSS, Chicago, Illinois).

Results

[^{11}C]raclopride PET

The D_2RBP was 3.16 ± 0.32 at baseline and increased significantly to 3.61 ± 0.27 post-AMPT (paired t-test: $t = -10.515,\ df = 11, p < .001$). The D_2RBP_{shift} was 0.147 ± 0.054.

Plasma levels

Treatment with AMPT resulted in significant decreases in plasma levels of HVA by $66 \pm 14\%$ (Friedman's test, $p < .001$) and of MHPG by $64 \pm 11\%$ (repeated measures ANOVA, $p < .001$), and in significant increases in prolactin levels to $358 \pm 148\%$ (Friedman's test, $p < .001$). Increasing oral AMPT administration from 4500 mg/25 h to 5250 mg/

Table 1
Effect of AMPT on subjective mood ratings with the visual analog scale and profile of mood states

	Baseline	AMPT 750 mg	AMPT 3750 mg	AMPT 4500 mg	Significance of change*
VAS Item					
Happy	70 ± 12	60 ± 21	47 ± 23	42 ± 24	<0.001
Talkative	59 ± 18	46 ± 24	41 ± 22	38 ± 24	0.003
Drowsy	41 ± 16	51 ± 27	72 ± 35	58 ± 29	0.006
Hungry	16 ± 17	5 ± 10	22 ± 28	9 ± 15	0.023∧
High	15 ± 19	11 ± 18	7 ± 14	8 ± 16	0.028∧
Sleepy	48 ± 18	59 ± 23	75 ± 34	60 ± 31	0.032
Tired	44 ± 16	53 ± 30	70 ± 35	52 ± 32	0.076
Energetic	51 ± 12	35 ± 24	26 ± 19	36 ± 32	0.081∧
Sad	13 ± 20	13 ± 20	9 ± 17	6 ± 15	0.088∧
Mania	8 ± 15	6 ± 15	4 ± 10	3 ± 7	0.127∧
Calm	74 ± 18	68 ± 18	60 ±18	55 ± 29	0.155
Restless	15 ± 19	10 ± 16	21 ± 28	21 ± 30	0.194∧
Mellow	65 ± 16	62 ± 25	55 ± 29	49 ± 23	0.290
Nervous	17 ± 22	9 ± 16	10 ± 17	16 ± 26	0.340
Angry	7 ± 14	6 ± 15	5 ± 13	4 ± 10	0.392∧
Fearful	7 ± 14	8 ± 20	6 ± 15	6 ± 15	0.417∧
Anxious	19 ± 20	10± 19	13 ± 19	13 ± 18	0.446
Depressed	9 ± 17	9 ± 15	14 ± 22	8 ± 19	0.515∧
Irritable	13 ± 15	11 ± 17	16 ± 21	16 ± 20	0.633
POMS Dimension					
Vigor	12.1 ± 5.0	8.7 ± 5.6	5.8 ± 5.7	6.3 ± 5.6	0.004∧
Fatigue	5.4 ± 3.1	5.7 ± 3.3	7.7 ± 4.7	7.5 ± 3.8	0.177
Tension	3.0 ± 2.7	1.4 ± 1.9	2.7 ± 3.7	3.1 ± 3.8	0.403
Confusion	2.3 ± 2.3	2.7 ± 1.9	3.3 ± 2.5	2.3 ± 2.2	0.454∧
Depression	1.8 ± 3.8	1.7 ± 3.5	2.3 ± 3.4	1.9 ± 3.2	0.727∧
Anger	2.0 ± 3.6	1.3 ± 2.6	1.7 ± 2.7	1.3 ± 2.3	0.928∧

Levels of significance of change in POMS mood ratings over four cumulative oral doses of AMPT: 0 mg (average of two measurements per subject), 750, 3750, and 4500 mg (one measurement each per subject). Values expressed as means ± standard deviation.

* p values from repeated measured ANOVA (if data met criteria for normal distribution) are not marked, whereas p values from Friedman's test (if data did not meet criteria for normal distribution) are marked with ∧.

29 h in 6 subjects did not resulted in any significant changes in HVA, MHPG, AMPT, or prolactin levels.

Mood effects of AMPT

Effects of AMPT on VAS and POMS scores are shown in Table 1. On AMPT, scores for happiness, talkativeness, and feeling high were significantly decreased whereas, scores for drowsiness and sleepiness and were significantly increased. There was a tendency for subjects to feel more tired and less energetic on AMPT whereas scores for hungriness were quite variable at different times without a clear dose dependence on AMPT. Decrease in happiness was significantly correlated to percentage MHPG decrease ($r = 0.601,\ p = .039$) but not to percentage HVA decrease or to D_2RBP_{shift}. Decrease in feeling high was significantly inversely correlated to percentage HVA decrease ($r = -.613,\ p = .034$) but not to percentage MHPG decrease or to D_2RBP_{shift}.

POMS vigor dimension scores decreased significantly on AMPT. Decrease in vigor dimension was neither significantly correlated with D_2RBP_{shift} nor with AMPT-induced changes in plasma levels or in VAS scores. BDI scores were very low and did not change with AMPT treatment.

Discussion

[^{11}C]raclopride PET

AMPT-induced DA depletion resulted in a significant D_2 RBP increase of $14.7 \pm 5.4\%$, consistent our previous findings (Verhoeff et al. (2001).

Plasma levels

The AMPT-induced decreases in plasma HVA and MHPG in our study are compatible with the decreases of $70 \pm 12\%$ and $66 \pm 6\%$, respectively, obtained by Laruelle et al. (1997). The lack of significant change in AMPT, HVA, MHPG, and prolactin levels with increasing oral AMPT administration (from 4500 mg/25 h to 5250 mg/29 h) in 6 subjects suggests that the extent of catecholamine depletion did not increase any further.

Mood effects of AMPT

The significant decreases in happiness and increases in drowsiness and sleepiness VAS scores on AMPT in our study have also been observed by others in healthy subjects (Laruelle et al., 1997; McCann et al., 1993). The fact that decrease in happiness was significantly correlated to MHPG decrease but not HVA decrease or D_2RBP_{shift} suggests a larger role for norepinephrine depletion than for DA depletion. On the other hand, the fact that decrease in feeling high was significantly correlated to HVA decrease but not MHPG decrease suggests a larger role for DA depletion than for norepinephrine depletion. This would be compatible with the finding that amphetamine-induced increases in euphoria scores correlated with D_2RBP decreases in the ventral striatum but not in the dorsal caudate (Drevets et al., 2001). The latter may explain why we did not find a significant correlation between decrease in feeling high and increase in D_2RBP in the whole striatum. An additional explanation may be the complex relationship between feeling less high and decreasing DA levels. Since the HVA decrease was negatively correlated with the decrease in VAS high scores, it may be that with more severe DA depletion a certain numbing takes place, resulting in less awareness and less reporting of a decrease in feeling high than occurs with mild DA depletion.

The decrease in the POMS vigor dimension scores was not significantly correlated with changes in VAS scores, including those for sedation, indicating that this may reflect a change in subjective experience that is relatively independent from sedation or feeling happy.

The lack of AMPT-induced changes in depression scores on VAS, POMS, and BDI is compatible with previous reports that healthy subjects do not experience significant depressive symptoms on AMPT (Laruelle et al., 1997; McCann et al., 1993; Salomon, Miller, Krystal, Heninger, & Charney, 1997).

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23. A psychometric analysis of the Geriatric Depression Scale (GDS) in a clinical sample

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The present study examined the psychometric properties of the Geriatric Depression Scale (GDS; Yesavage et al., 1983), a popular

30-item screening measure of depression in the elderly, utilizing a clinical sample of 608 psychogeriatric depression day-hospital patients. Factor analysis revealed a four-factor structure for the GDS, with composite factors measuring Depression, Anxiety/Emotional Lability, Social Restriction/Depletion, and Cognitive Complaints, and a higher-order factor measuring Geriatric Depression. This model demons-trated internal consistency, and moderate concurrent validity with the Hamilton Rating Scale for Depression. These findings have implications for the assessment and treatment of depressed seniors.

Report

Depression is one of the most common forms of psychopathology in later life. Among the problems associated with geriatric depression are the increased likelihood of malnourish-ment and physical deterioration, cognitive impairment, anxiety disorders, reduced quality of life, increased risk of suicide, and increased mortality. Health care practitioners often have difficulty recognizing depression in the elderly, due, in part, to difficulties in distinguishing depression from adjustment reactions secondary to major loss, anxiety disorders, and cognitive impairment, or to the common misconception that depression is a natural part of the aging process rather than a clinical condition requiring treatment.

Yesavage et al. (1983) developed the Geriatric Depression Scale (GDS) as a quick screening tool for assessing geriatric depression, given the difficulties inherent in diagnosing depression in seniors. The GDS is an attractive scale for use with the elderly as it is relatively brief, follows a simple yes/no rating format, and does not overlap with somatic symptoms common to both depressed and non-depressed seniors. These strengths notwithstanding, research findings have demonstrated a variety of limitations to the GDS, including those related to its factorial structure. While initially treated as a unidimensional measure (Yesavage et al., 1983), research findings have since demonstrated potential multidimensionality for the GDS (Sheikh et al., 1991). The problems inherent in assigning a single score to a multidimensional measure include the increased potential for inaccurate clinical diagnosis and consequent incorrect treatment intervention. The present study was conducted to help clarify the factor structure of the GDS, and to potentially improve the clinical utility of this popular psychogeriatric measure.

Hypotheses of the present study

The present study was conducted in order to explore the factor structure, reliability, and validity of the GDS within a clinical psychogeriatric sample. Specific hypotheses follow:

1. It was hypothesized that a factor analysis of the GDS would reveal multiple factors.
2. It was further hypothesized that these factors might assess depression, anxiety, and cognitive complaints.
3. It was predicted that the hypothesized depression factor would demonstrate a stronger association with depression (measured with the Hamilton Rating Scale for Depression, and with diagnoses of clinical depression) than would total GDS scores.
4. It was predicted that the hypothesized cognitive complaints factor would demonstrate a stronger association with cognitive functioning (measured with the Mini-Mental State Examination and the Mattis Dementia Rating Scale) than would total GDS scores.

Method

Sample

The present study's sample was derived from a clinical database containing information on 608 clients aged 65 years or older of a depression day-hospital treatment program serving a psychogeriatric population from 1985–1999. Data for 34 participants were trimmed, due to multivariate non-normality, extreme divergence from the remainder of the sample in terms of depression severity, or sufficient cognitive impairment to render their responses suspect. Hence, the present analyses utilized data from 574 participants ($M = 76.0$ years, $SD = 6.2$), including 401 women ($M = 75.8$ years, $SD = 6.0$) and 171 men ($M = 76.5$ years, $SD = 6.4$), with gender not reported for 2 participants.

Approximately one third of the participants had been born in Canada (171), with a similar number born in Poland (154), or in other countries (146), respectively. Only 221 of the 574 participants reported speaking and understanding English fluently, with 352 somewhat less fluent in English. Most participants had attended or completed high school (245), with somewhat fewer having gone no further than elementary school (168), and far fewer having gone on to college or university (89). In terms of psychiatric history, participants had an average of approximately 3 psychiatric episodes each, with an average of just under two Axis I diagnoses each. This included a majority with clinical depression (415) and smaller numbers with cognitive impairment (127), an anxiety disorder (77), substance abuse (41), Axis II pathology (52), Axis II traits (15), or past suicidal behavior (56).

Procedure

Upon admission to the depression day-hospital program, each participant was administered the *Geriatric Depression Scale* (GDS) and *Mini-Mental State Examination* (MMSE) by a Case Manager, the *Hamilton Rating Scale for Depression* (HAM-D) by a Psychiatrist, and the *Mattis Dementia Rating Scale* (MDRS) by a Psychologist.

Results

Descriptive statistics will be presented initially, followed by the findings of the factor analyses and the validation results. The present study's sample demonstrated moderate to high levels of depression, as illustrated by GDS ($M = 19.8$, $SD = 5.8$) and HAM-D ($M = 18.6$, $SD = 6.8$) scores; and a moderate level of cognitive functioning, as illustrated by MMSE ($M = 26.3$, $SD = 3.0$) and MDRS ($M = 124.1$, $SD = 14.9$) scores. None of the measures used in the present study evidenced excessive skewness or kurtosis.

Factor analyses

There is some debate over the acceptability of applying Factor Analysis with Pearson correlation coefficients to dichotomously scored data such as GDS items (e.g., Liang, 1984; Loo, 2000; D.L. Streiner, personal communication, 2000). Given the exploratory nature of the current study, Factor Analyses were conducted using Pearson correlations (as in Salamero and Marcos, 1992) and tetrachoric correlations (as suggested by Liang, 1984), and their results compared.

An initial principle components analysis was conducted examining the factor structure of the GDS. The resulting component matrix yielded 8 factors with eigenvalues greater than unity, and accounted for 55% of the variance of GDS scores. Scree output revealed a strong first factor, and a possible presence of either a 3 or 7-factor structure. Exploratory factor analyses were conducted next, forcing 3, 4, 5, 6, and 7 factors, utilizing orthogonal (varimax) rotation, in order to deter-

mine the most reasonable and parsimonious factor structure for the measure. The resulting four-factor structure (see Table 1) emerged as the most acceptable model in terms of parsimony, reasonableness, face validity, and internal consistency, with Cronbach alpha coefficients of .80, .69,. 66, and. 61 for component subscales measuring Depression, Anxiety/Emotional Lability, Social Restriction/Depletion, and Cognitive Complaints, respectively. This model accounted for approximately 38% of the variance of GDS scores, demonstrated concordance with published findings (e.g., Sheikh et al., 1991), and supported the first and second hypotheses of the present study. These factors were then submitted, in turn, to an orthogonal factor analysis, in order to examine for potential higher-order factors. The results demonstrated a single higher-order factor, termed Geriatric Depression, with an eigenvalue greater than one, that explained 51% of the total variance of GDS scores.

Table 1
CDS Component matrix with varimax rotation

Item #	Component			
	1	2	3	4
3. Feels life is empty	**.79**			
2. Dropped activities	**.77**			
15. Wonderful to be alive	**.59**			
17. Feels pretty worthless	**.55**			
16. Feels downhearted and blue	**.54**	.43		
9. Often feels happy	**.50**			.31
5. Hopeful about future	**.49**			
22. Situation is hopeless	**.49**			
7. Often in good spirits	**.43**			.34
1. Basically satisfied with life	**.42**			
19. Finds life exciting	**.39**			.36
27. Enjoys getting up in morning	**.33**			.31
23. Most people better off	**.29**			
11. Often restless and fidgety		**.65**		
6. Bothersome thoughts		**.61**		
24. Gets upset over little things		**.55**		
12. Prefers to stay at home		**.52**		
8. Fears something bad		**.51**		
18. Worries about past		**.45**		
25. Often feels like crying		**.43**		
10. Often feels helpless	.37	**.40**	.37	
4. Often gets bored	.30	**.36**		
28. Avoids social gatherings			**.72**	
13. Often worries about future			**.71**	
20. Hard to start new projects			**.58**	
21. Feels full of energy			**.43**	
29. Easy to make decisions			**.39**	.34
30. Mind is clear				**.66**
26. Trouble concentrating				**.65**
14. Has memory problems				**.63**
Percentage of variance accounted for	13.38	9.47	8.04	6.77

Note. Items were ordered in decreasing order of factor loadings. Only items with factor loadings above. 30 on one (or more) factor(s) were included for clarity of presentation. Bolded loadings indicate items for the respective Depression (1), Anxiety/Emotional Lability (2), Social Restriction/Depletion (3), and Cognitive Complaints (4) factors.

The previous factor analysis was repeated utilizing tetrachoric correlations, forcing a four-factor model, as above. The resulting subscales revealed complex factor loadings, explained only 26% of the overall variance, and yielded much lower internal consistency than the previous model, with two components evidencing unacceptable internal consistency. Hence, the factors derived from the initial factor analysis were utilized in the validation analyses.

Validation

Correlational analyses were conducted in order to examine the concurrent validity of GDS factor scores with existing measures of depression (HAM-D) and cognitive impairment (MMSE and MRSD), respectively. The results demonstrated that the correlation between the GDS Depression subscale and HAM-D total scores ($r = .21$, $p < .01$), while non-significant, exceeded that between the HAM-D and GDS total scores ($r = .17$, $p < .01$, Fisher's $Z = .95$, ns), providing modest support for the third hypothesis of the present study. Moreover, while univariate ANOVAs revealed that GDS total scores did not significantly predict diagnoses of clinical depression, the GDS Depression subscale evidenced a non-significant trend towards such a relationship ($M = 8.4$, $SD = 2.8$ for the depressed and $M = 7.8$, $SD = 3.1$ for non-depressed participants, $F_{(1,466)} = 3.3$, $p = .07$).

The validation findings demonstrated no association between GDS and either MMSE or MDRS scores ($r = .00$ and $r = -.02$, ns; and $r = .03$; $r = -.03$, ns) for GDS total scores and GDS Cognitive Complaints subscale scores, respectively. The GDS Cognitive Complaints subscale only slightly improved the relationship between the GDS and measures of cognitive functioning, providing very limited support for the fourth hypothesis of the present study. Finally, there were no significant differences in either GDS total or GDS Cognitive Complaints subscale scores based on the presence of diagnoses of cognitive impairment ($F_{(1,517)} = .07$, ns, and $F_{(1,504)} = .85$, ns, respectively), failing to support the fifth hypothesis of the present study.

Summary

The present study demonstrated a multidimensional factor structure for the Geriatric Depression Scale. Internal reliability and modest concurrent validity were demonstrated for factors assessing Depression, Anxiety/Emotional Lability, Social Restriction/Depletion, and Cognitive Complaints. The results of this study were limited by the use of a retrospective methodology, and by the poor intercorrelations among the measures used in the present study, possibly due to restricted-range effects resulting from sampling largely depressed and relatively cognitive-intact seniors. These limitations notwithstanding, the findings of the present study support the multidimensional exploration of GDS protocols in a clinical population, and discourage the clinical practice of exclusively utilizing GDS total scores in diagnostic decision-making as to depression status. Further research is needed examining the predictive validity of the proposed factor structure with additional measures of depression, anxiety, and cognition, and replicating this study among more heterogeneous and less-impaired samples of seniors.

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24. Depression and recovery after acute ischemic stroke: Initial data on lacunar versus other stroke types

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Disruption of subcortical–frontal circuits is thought to play a role in the pathogenesis of depression, and is more likely to occur with lacunar versus other stroke types (atherothrombotic or cardioembolic). Neurological recovery occurs earlier with lacunar stroke. We hypothesized that lacunar stroke patients would be more likely to develop depression, and that affective recovery would occur earlier. In an observational study with 28 male veterans (61% lacunar; 39% other stroke types), scores on the NIH Stroke Scale, Geriatric Depression Scale, Mini-Mental, and Barthel Index were equivalent at baseline. Seven of 17 patients with lacunar stroke (41%) and 3 of 11 patients with other types (27%) were depressed at baseline. Patients with lacunar stroke showed greater motor and affective improvement at 3 months after onset.

Report

Recent literature has implicated direct neural connections between subcortical and frontal cortical regions in depressive symptoms associated with neurological disorders, including the pathophysiology of stroke. The cognitive domains most affected with these depressive symptoms include attention, short-term memory, and psychomotor speed. Language, perception, and spatial abilities may be preserved, unless affected by poor attention, motivation, or organizational abilities (Mayberg, 2000).

A number of other studies have shown subcortical–cortical distinctions in emotion and memory processes (Baker, 1996). The working model of depression presented by Mayberg (2000) implicates the failure of coordinated interactions between subcortical–cortical (limbic-cortical) pathway networks. An imbalance in activity between subcortical/limbic/paralimbic regions and neocortical/frontal regions accompanies depression. Treatment for depression has the effect of rebalancing the activity in these regions. Pre-treatment hypermetabolism in the intermediate rostral anterior cingulate region—with connections to both subcortical and frontal cortical regions—is seen in treatment responders.

Nih/ninds criteria have identified four major ischemic stroke types: lacunar, large vessel atherosclerotic, cardioembolic, and uncertain/other. Studies have suggested that cognitive impairment after stroke is related to stroke type, as well as to vascular risk factors and other host features (Desmond et al., 2000). These authors compared groups with vascular dementia ($n = 68$) and without any dementia ($n = 334$) at 3 months after ischemic stroke. They found that lacunar (or 2.43; ci 0.97–6.06) and atherosclerotic (or 3.27; ci 1.27–8.37) versus other stroke type were each associated with patients in the vascular dementia group. Depression at 3 months was associated with the vascular dementia group when entered into the model as a covariate (or 3.31; ci 1.26–8.73).

A recent review has shown much less support for the hypothesis of left versus right hemisphere lesion location in post-stroke depression (Carson et al., 2000). Chemerinski, Robinson, and Kosier (2001) found that patients with post-stroke depression who showed improvement in depression at follow-up also showed more recovery in functional activities of daily living (adls). Perhaps stroke type and associated vascular risk factors may help in understanding changes in mood and cognition, as well as motor and functional recovery after stroke.

For this observational study, lacunar strokes were considered to be associated with small vessel disease and were compared to atherosclerotic (large vessel) and cardioembolic stroke types. Since lacunar lesions are more likely to be subcortical, and thus to disrupt subcortical–frontal pathways, we hypothesized that lacunar stroke patients would be more likely to develop depression than those with other stroke types. In addition, because of the type of ischemic changes that occur with lacunar stroke, we thought that affective recovery would be seen earlier in the lacunar group. Using initial data in this brief report, we compared participants with lacunar stroke to those with other stroke types in terms of neurological (motor), affective, cognitive, and functional recovery.

Methods

At an enrollment visit 1–4 weeks after onset of acute ischemic stroke, 28 male veteran patients (mean age 71; caucasian 75%, african american 25%) were examined by a neurologist and psychologist; and completed several scales: the nih stroke (nihss), hachinski, mini-mental (mmse), geriatric depression (gds), barthel index (barthel), clinical dementia rating (cdr), and sf-36 health-related quality of life (physical: pcs) and (mental: mcs). The measures were repeated during a follow-up visit at 3 months after stroke onset. A clinical interview and medical record review at enrollment and follow-up aided in determining stroke type and presence of depression and/or dementia.

Results

Baseline and 3 months after onset

At enrollment, nihss scores ranged from 0 to 12 (mean 4.5; $SD = 3.3$). Barthel scores averaged 89.9 ($SD = 17.3$). Thus, this initial sample is characterized by mild stroke severity. At baseline, 61% ($n = 17$) of participants had lacunar strokes, while 39% had atherosclerotic ($n = 10$) or cardioembolic ($n = 1$) stroke. Based on interview and gds scores, ten participants (36%) were considered to have post-stroke depression at baseline. Eleven participants (39%) had post-stroke dementia at baseline, based on interview, mmse, and cdr. Five participants had both conditions, while 12 had neither condition.

At baseline, stroke type and depression resulted in four groups: lacunar depressed ($n = 7$), lacunar non-depressed ($n = 10$), other depressed ($n = 3$), and other non-depressed ($n = 8$). Over the first 3 months after onset, 4 patients with lacunar stroke became depressed, while 3 recovered. No patients with other stroke types became depressed, while 2

recovered. At the 3 month time point the number of patients in the four groups included: lacunar depressed ($n = 8$), lacunar non-depressed ($n = 9$), other depressed ($n = 1$), and other non-depressed ($n = 10$) ($\chi^2 = 4.4$, $p < .05$).

Mean scores for the study measures at enrollment were generally comparable for lacunar ($n = 17$) versus other ($n = 11$) stroke type: *nihss* (4.5 vs. 4.5); *hachinski* (10.9 vs. 9.5); *gds* (7.8 vs. 5.9); *mmse* (25.9 vs. 25.2); *barthel* (90.6 vs. 88.9); sf-36 *pcs* (32.4 vs. 33.6), and sf-36 *mcs* (50.9 vs. 50.5). The hachinski scores, representing more vascular symptoms associated with dementia, and the gds depression scores were slightly higher for the lacunar group.

Mean scores for the depressed ($n = 10$) and non-depressed ($n = 18$) groups at enrollment were: *nihss* (4.5 vs. 4.5); *hachinski* (11.9 vs. 9.5); *GDS* (12.6 vs. 3.8); *MMSE* (25.9 vs. 25.5); *Barthel* (88.0 vs. 91.0); SF-36 *PCS* (34.4 vs. 37.9), and SF-36 *MCS* (42.5 vs. 55.6). As would be expected, gds depression scores ($t = -4.3$, $p < .001$) and sf-36 mcs mental/emotional health-related quality of life scores ($t = 2.6$, $p < .05$) were worse for the depressed group. Hachinski scores were also worse ($t = -3.4$, $p < .003$) for the depressed group.

Change scores

Fig. 1 ($n = 22$) compares the percentage of change in raw scores on selected study measures from baseline to 3 months after onset. The difference in raw scores is given as a percentage of the possible range in scores on the measures. Positive change represents improvement. The lacunar group ($n = 15$) shows more improvement in neurological (motor) recovery (nihss) and mood (gds), and less change incognition (mmse) and functional ability (barthel) improvement inmental/emotionalquality of life (sf-36 mcs; not shown) was similar.

A comparison of percentage of change in raw scores from baseline to 3 months after onset (not shown) for patients who were depressed ($n = 7$) or not depressed ($n = 15$) at enrollment showed comparable neurological (motor) recovery, greater improvement on measures of depression ($t = -3.0$, $p < .01$), cognition, functional ability, and mental/emotional quality of life (sf-36 mcs; $t = -3.5$, $p < .01$) for the depressed group.

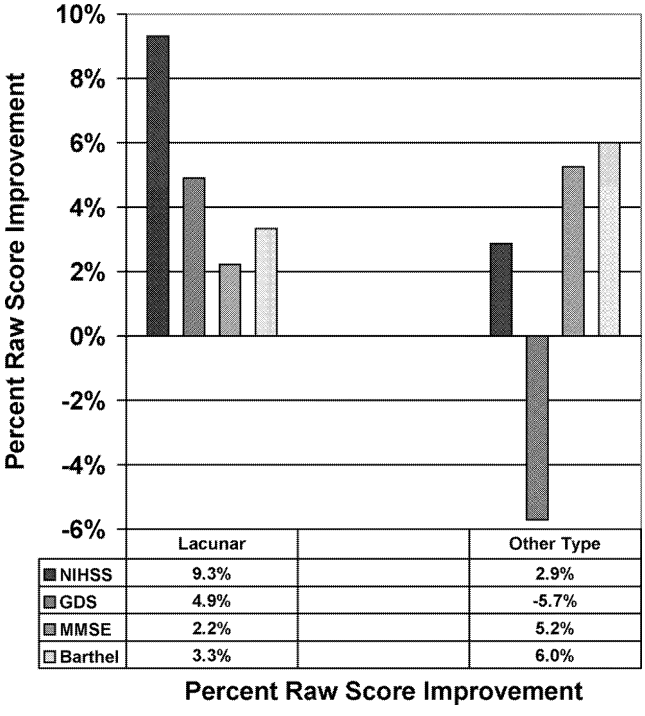

Fig. 1. Three month recovery after stroke.

Conclusion

In this preliminary brief report, with a very small pilot sample, patients with lacunar stroke showed greater improvement than the group with other stroke types on neurological and depression measures. The lacunar stroke group showed somewhat less cognitive and functional improvement.

Suprisingly, a post-hoc comparison of initially depressed and non-depressed patients showed that even though neurological recovery was equivalent, the depressed group actually improved more than the non-depressed group on measures of depression, cognition, function, and mental/emotional quality of life. Depressed patients were treated for their post-stroke depression.

The finding that a greater percentage of patients in the lacunar group (24% vs. 0%) became depressed during the first three months after onset, while an equal percentage of both groups (18%) recovered, would support the hypothesis of greater disruption of subcortical–frontal circuits after lacunar stroke as a pathophysiological mechanism in post-stroke depression.

The greater association of depression with lacunar stroke at baseline (70%) compared to other stroke type (30%), the fact that all depressed patients were treated, and the association of improvement in depression with improvement in cognition, function, and quality of life in the post-hoc comparison suggests that treatment of depression in patients with lacunar stroke may play a particularly important role in their overall recovery.

The improvement in cognition associated with improvement in depression is consistent with the concept of dementia of depression, and with the normalization of metabolic activity in cortical (dorsolateral pre-frontal) regions that would be expected to accompany recovery from depression, according to the working model of depression described in Mayberg (2000).

While the current sample size is too small to draw any conclusions, some initial trends have emerged. Statistical analyses will be conducted when sample size allows for adequate statistical power. Especially interesting will be examining the interaction between change in post-stroke depression and change in post-stroke dementia for various stroke types. Future-related research will include clinical trials of exercise among stroke patients, as well as among persons with vascular mildcognitive impairment and vascular depression from hypertensive small vessel disease. Dose-response effects of rehabilitation treatment on functional improvement, over and above neurological recovery, will help in understanding affective, cognitive, and motor recovery after various types of ischemic stroke.

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25. Emotional and cognitive changes after stroke: Course and correlation

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In this study we examined emotional and cognitive changes after first-ever ischemic unilateral stroke in 77 patients, at 3 and 15 months post-onset. Moreover 61 control subjects were tested with the same time-interval. The Hospital Anxiety and Depression Scale was used to measure anxiety and depression. Moreover memory for faces, verbal memory, and reasoning were assessed. Both patient groups showed changes in depressive mood, memory for faces, and non-verbal reasoning as compared to the control group, irrespective of the side of the lesion. Stroke did not seem to effect level of anxiety. Only few correlations between emotion and cognition appeared to be significant, remarkably, in the patient groups, these implied that an increase in anxiety or depression is related to an increase in cognitive performance.

Report

Stroke can cause profound changes in emotion and cognitive capacities. Post-stroke depression is a common consequence of stroke and has frequently been studied. The prevalence, though, varies largely with the selection of patients and diagnostic criteria. The relation between side of lesion and depression after stroke is not consistent across various studies (Singh, Herrmann, & Black, 1998). Anxiety and depression often co-occur, and anxiety was found in 23% of a community-based stroke population by Johnson et al. (1995). Beside emotional changes, cognitive disorders frequently occur after stroke. In this study we examined emotional (depression and anxiety) and cognitive (memory and reasoning) changes after stroke, their course over time and especially their relation.

Methods

Subjects

A community-based patient group ($n = 77$), who suffered a clinically first-ever unilateral ischemic stroke, was included in the study. Patients were recruited from 100 general practitioners (gp's) and the stroke-unit of the academic hospital groningen in The Netherlands. Side of stroke was verified with ct-scan findings. All patients were examined at three months ($t1$) and 15 months ($t2$) post-stroke. A control group ($n = 61$), recruited from 4 practices of gp's, was tested with the same time interval. The patient and control groups did not differ in age ($t = 1.65$, $p = .10$), education ($z = -.79$, $p = .432$), or gender ($\chi^2 = .09$, $p = .77$). The data were analysed splitting up the patients into a left ($n = 41$) and a right ($n = 36$) hemisphere group. Age, education and gender did not differ between the patient groups.

Material

Depression and anxiety were measured using the hospital anxiety and depression scale (hads) (Zigmund and Snaith, 1983).

To be able to measure a community-based group, without excluding the aphasic patients, a non-verbal intelligence test was used in order to measure reasoning: the son-r 5 1/2 -17 (Snijders, Tellegen, & Laros, 1989). Three subtests were used: mosaics (spatial abilities), categories (abstract reasoning), and stories (concrete reasoning), and added to a total score for analyses.

A non-verbal memory test was constructed, in which people had to learn ten pairs of faces (photographs) during five consecutive trials. After 25 min the delayed recall was tested (Gerritsen, Deelman, & Berg, 2000). The well-known auditory verbal learning test (avlt) was used to measure verbal memory.

Statistical analyses

All analyses were carried out using three groups: control, left hemisphere, and right hemisphere patients. The group differences were tested using oneway ANOVA, with least square differences (lsd) post-hoc analyses. Within group course over time was tested with paired t tests. Pearson's correlation was used to establish the relation between the emotional and cognitive data. All tests for significance were two-tailed.

Results

Anxiety and depression

At $t1$ and $t2$ the groups differed significantly on the depression scale from the hads ($t1$ $f = 14.67$, $p = .000$; $t2$ $f = 3.79$, $p = .025$). Post-hoc analyses showed that at the right hemisphere patients ($t1$ $p = .000$; $t2$ $p = .038$) as well as the left hemisphere patients ($t1$ $p = .000$; $t2$ $p = .016$), were more depressed than the control group, but they did not differ from each other. Paired t testing (2-tailed) showed no significant improvement in level of depression in any of the three groups.

Level of anxiety did not differ between the groups on either time of measurement. Still anxiety did significantly decrease in the right hemisphere group ($t = -2.07$, $p = .046$).

Memory and reasoning

Reasoning was significantly different between the three groups on $t1$ ($f = 5.68$, $p = .004$) as well as $t2$ ($f = 3.71$, $p = .027$). Post-hoc testing revealed that both left ($t1$ $p = .004$; $t2$ $p = .036$), and right ($t1$ $p = .008$; $t2$ $p = .018$) hemisphere patients had lower scores than the control group. No significant differences between the patient groups were found, on $t1$ and $t2$. The improvement over time was significant in both patient groups (rh $t = -2.10$, $p = .044$; lh $t = -2.52$, $p = .016$), but not in the control group. The improvement could therefore, be counted for as (incomplete) recovery of reasoning in the patient groups.

The immediate recall of memory for faces also revealed a significant group difference on both $t1$ ($f = 4.54$, $p = .012$) and $t2$ ($f = 3.75$, $p = .026$). Again the differences between the right hemisphere patients ($t1$ $p = .036$; $t2$ $p = .016$) and the left hemisphere patients versus the control group ($t1$ $p = .006$; $t2$ $p = .038$), were significant, but to our surprise there were no differences between both patient groups. Over time, within the groups, testscores of the control group ($t = -3.06$, $p = .003$) and the left hemisphere patients ($t = -2.82$, $p = .008$) improved significantly. The delayed recall scores were different for the groups only on $t1$ ($f = 4.71$, $p = .011$). Post-hoc analyses

Table 1
Significant correlations (Pearson's) between emotion and cognition on $t1$ and $t2$, and the course over time ($t2 - t1$, $t2$ minus $t1$). IR, immediate recall; DR, delayed recall

Time	Group	Related variables	Correlation	p
$t1$	LH	Anxiety & SON-R 1/2 -17	.53	.000
	Control	Depression & SON-R 1/2-17	−.38	.004
	Control	Depression & AVLT	−.28	.027
$t2$	RH	Anxiety & Faces IR	.36	.032
	LH	Anxiety & SON-R 1/2 -17	.37	.022
$t2 - t1$	RH	Depression & AVLT-DR	.39	.027
	Control	Depression & AVLT-IR	−.28	.030
	Control	Depression & AVLT-IR	−.29	.029

showed that the right hemisphere group did not differ from the control group, or from the left hemisphere patients. The left hemisphere patients on the other hand did perform worse than the control group ($p = .003$). They improved comparing $t1$ and $t2$ ($t = -3.09$, $p = .004$).

Much to our surprise there was no difference between the three groups on the avlt, on either time of measurement, for the immediate nor the delayed recall. Moreover there were no differences over time within the three groups.

Depression and cognition

The relation between anxiety and depression and cognitive disorders was established at $t1$ and $t2$, moreover the $t1 - t2$ difference scores were correlated. Very few correlations appeared to be significant; only the significant correlations are presented in Table 1.

All the correlations in the patient groups were in a positive direction, indicating that the higher the anxiety or depression score, the better the cognitive performance. In the control group the correlations found, showed a negative relation between depressive mood and the cognitive measures.

Conclusions

This study shows that unilateral first-ever stroke leads to both emotional and cognitive changes, irrespective of the side of the lesion. Mainly in the cognitive domains patients improve to some extend, between 3 and 15 months, but the depressive mood and impairments in problem solving and memory for faces seem to be lasting late after stroke. However, stroke patients are not impaired on all emotional and cognitive domains tested in this study. In contrast to what we had expected the patients do not show more anxiety than the healthy age-peers, moreover they perform just as well on the avlt as the control group does.

There does not seem to be a clear relation between depression and anxiety on one hand, and memory and problem solving on the other. Remarkable, though, was the finding that the few significant correlations that were found in the patient groups were in a positive direction. Considering the opposite meaning of higher cognitive and higher hads scores, this indicates that when one improves in one domain (cognitive or emotional), one gets worse in the other. Most strongly, and persistent over time, was the correlation between anxiety and reasoning in the left hemisphere group: higher anxiety seems to be related to higher problem solving abilities in this patient group.

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26. Course of stroke-related and non-stroke-related depressive mood in unilateral right and left hemisphere stroke patients

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Stroke-related depressive mood and mood not attributed to the stroke event are described for right and left hemisphere stroke patients at 3 (T1) and 15 months (T2) post-stroke. The results show that for the patient group total depression scores improve from T1 to T2. Non-stroke-related depressive mood of patients does not differ from depressive mood of controls and shows no improvement in time. Only right hemisphere stroke patients show significant improvement in stroke-related depression scores. From T1 to T2, six stroke subjects develop a depressive mood. Lack of recovery seems to affect the development of stroke-related depressive mood in left hemisphere subjects, while major life events appears to affect the emergence of a depressive mood in right hemisphere subjects.

Report

Depressive mood is quite prevalent in late life, but affects approximately one-quarter of community dwelling subjects after stroke (House et al., 1991; Lenze et al., 2001). The relationship between depressive symptoms and lateralization of lesion appears to be inconsistent across different studies (Singh, Hermann, & Black, 1998). The impact of stroke on mood seems to be a complex interaction of the direct effect of brain damage, the way subjects cope with its consequences and other circumstances in the lives of patients. Within this study the course of depressive mood is described for left and right hemisphere stroke patients and a community sample of elderly subjects without brain damage. An attempt has been made to divide post-stroke depressive mood into a part not related to stroke and a part related to the stroke event by attribution of patients themselves.

Methods

Subjects

The patient group included in this study consisted of 88 first-ever, unilateral, ischemic stroke patients. Patients were collected through the aid of 100 general practitioners (GP) from the northern part of the Netherlands and by the aid of the stroke unit of the Academic Hospital Groningen. Side of ischemic damage was checked with CT-scan findings: 41 patients had right hemisphere damage (RH), 47 patients left hemisphere damage (LH). A group of 70 control subjects were recruited among the population of four practices of GPs. Subjects with previous neurological damage or a history of psychiatric disturbances were excluded. Stroke patients and control subjects were interviewed twice, with an interval of approximately one year. First measurement of stroke patients was at 3 months post-stroke (T1), the second at 15 months post-stroke (T2). Stroke patients and controls did not differ in age ($M = 65.4$, $SD = 11.4$ vs. $M = 67.0$, $SD = 12.1$, $t = .85$, $p = .40$) or gender (65% vs. 55% men, $X^2 = 1.6$, $p = .21$).

Material

The Hospital Anxiety and Depression Scale (HADS) was used to measure depressive and anxious mood (Zigmond & Snaith, 1983). Only the depression sub-scale was analyzed in this study. A cut-off score of 5 was used to divide subjects into depressive or non-depressive (Johnson et al., 1995). After each item of the HADS, stroke subjects were asked if the reported mood was attributed to the stroke event. Depression scores can thus be summed to a stroke-related score and a score not attributed to the stroke event. Both scores were divided by the number of items to obtain a mean score.

At T2, all subjects were asked which life events had occurred the previous year. They could also rate the impact of the life event on their lives with scores ranging from (0) none to (5) very much. Stroke patients were also asked to rate their amount of recovery after stroke, ranging from (7) very good recovery to (1) no recovery, decline in health.

Results

Comparison of depressive mood at T1 and T2

The results showed significant higher total depression scores for stroke patients compared to control subjects on both times of measurement (T1 $M = 3.4$, $SD = 3.1$ vs. $M = 1.1$, $SD = 1.5$, $t = -5.9$, $p = .00$; T2 $M = 2.5$, $SD = 3.1$ vs. $M = 1.4$, $SD = 2.0$, $t = -2.7$, $p = .01$). At T1, 25 stroke patients and 3 control subjects scored above cut-off. At T2, numbers above cut-off were 14 for the stroke patients and 3 for control subjects. These numbers differed significantly at both T1 and T2. Mean non-stroke-related depression scores of the patient group did not differ significantly from mean depression scores of the control group. Besides, left-hemisphere patients did not differ from right hemisphere patients on total depression scores, post-stroke or non-stroke-related depression at T1 or T2.

Course of depressive mood

Comparison of scores on T1 and T2 showed a small, but non-significant, deterioration of mood for the control group ($t = -1.9$, $p = .07$). In contrast, total depression scores of stroke patients improved significantly ($t = 2.1$, $p = .04$). Further analyses showed that non-stroke-related mood of patients remained at the same level from T1 to T2 ($t = 0.6$, $p = .56$), while post-stroke mood improved significantly ($t = 3.2$, $p = .002$). As Fig. 1 illustrates, significant improvement of post-stroke depressive mood was only present for right-sided stroke patients ($t = 2.6$, $p = .01$), while improvement did not reach significance in left-sided stroke patients ($t = 1.9$, $p = .06$).

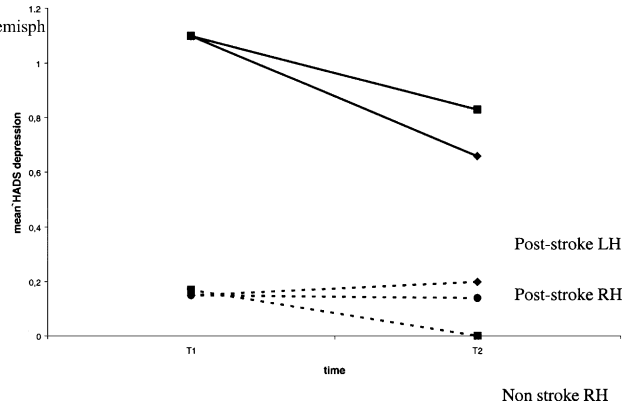

Fig. 1. Stroke-related and non-stroke-related depressive mood for right and left hemisphere stroke patients and control subjects at T1 and T2.

From T1 to T2, 2 control subjects (3%) and 6 stroke patients (7%, LH $n = 3$, RH $n = 3$) made a transition from non-depressive to depressive and exceeded the cut-off with three or more scale points. Further inspection of stroke patients developing depression showed that that all new depression of right hemisphere stroke patients was non-stroke related, while all new left hemisphere depression was attributed to the stroke event.

Comparison of the reported life events of new depression cases showed that all six patients reported significant greater life event impact scores than non-cases or existing depression cases ($Z = -2.1$, $p = .04$). For right hemisphere subjects these were life events not related to the stroke event, such as death of one's partner. Left stroke patients reported illnesses of themselves as life events with high impact scores. Besides, new left hemisphere depression cases reported significant less recovery after stroke than non-cases or existing depression cases ($Z = 2.7$, $p = .02$).

Conclusions

This study showed that a first-ever stroke has a great impact on depressive mood of both right and left hemisphere stroke patients, especially at 3 months post-stroke. From 3 to 15 months after stroke, patients improved in post-stroke depressive mood. However, stroke patients remained significantly more depressed than control subjects. A small group of stroke subjects developed a depressive mood during the first year post-stroke. Both stroke-related and non-stroke-related factors played a role in the development of depression. While left hemisphere stroke patients mentioned less recovery and other illnesses after stroke, right hemisphere stroke patients mentioned a greater impact of non-stroke-related life events.

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27. Mania following deep brain stimulation (DBS) in movement disorders: A report on two cases

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Deep brain stimulation (DBS) is a novel neurosurgical intervention for late-stage Parkinson's disease (PD) and essential tremor. Acute and chronic depressogenic effects, as well as mood lability with irrepressible crying and laughter, were reported following the procedure. We report here on one PD patient and one dystonic patient with secondary parkinsonism, both included in a prospective study on safety and efficacy of DBS in movement disorders, who presented an inaugural episode of mania, in the direct aftermath of bilateral high frequency stimulation of the subthalamic nucleus or the internal globus pallidus. These observations point to distinct effects of DBS on mood and are discussed in the light of current knowledge of the role of the basal ganglia in emotional processing.

Report

Background

Deep brain stimulation (DBS) is a novel neurosurgical treatment for late-stage Parkinson's disease (PD) and essential tremor. The method consists of implanting stimulators in the subthalamic nucleus (STN), the internal globus pallidus (Gpi), or the thalamus, hence creating reversible functional lesions through high frequency stimulation. This procedure is effective on motor dysfunction, with minimal cognitive impact. Transient acute depression has been observed in a PD patient, after acute stimulation of the left substantia nigra (Bejjani et al., 1999), and we reported elsewhere our observation of depressogenic effects in a series of PD patients under chronic STN-DBS. Complex effects on mood were reported by others, including mood swings, irrepressible crying and laughter (Kumar, Krack, Mc Viecker, & Benabid, 1999). These observations have raised the possibility of direct effects of the procedure on mood regulation. We report here on two patients, who presented an inaugural episode of mania, in the direct aftermath of DBS implementation.

Methods

Both patients were participants in a prospective, study on safety and efficacy of deep brain stimulation (DBS) in movement disorders. In this study, all patients were assessed prior and at regular intervals following DBS, using standardized instruments for motor (Unified Parkinson Disease Rating Scale, UPDRS), cognitive (according to Core Assessment Program for Surgical Interventional Therapy for PD, CAPSIT-PD), and mood status (Hamilton, and Montgomery Asberg Depression Rating Scales). Additional psychiatric assessments were performed to follow and manage the remarkable mood evolution of the two patients described here.

Patient 1

A 51-year-old man with a 17-year history of PD, underwent bilateral DBS of the Subthalamic nucleus (stimulation parameters: 2.5 V, 185 Hz, 90 ms). Psychiatric history revealed previous non-treated, minor depressive episodes, but no personal or familial history of bipolar disorder. Motor improvement after surgery allowed antiparkinsonian medication withdrawal (pre-operative off/on motor UPDRS 38/8 was improved to a stable score of 12). Neuropsychological evaluation pre- and post-operatively did not show any significant changes. For two months post-operatively, he presented a non-psychotic manic episode, fulfilling DSM-IV criteria, with sustained euphoria, increased self-esteem, frequent calls to friends, and he volunteered as supervisor in a school. Each adjustment of stimulation parameters was followed by urges to cry, replaced by the manic state. At 3 months, the stimulation was switched off for 6 h, according to motor protocol. Since then, the manic symptoms did not reappear. He started with intermittent, then persistent feelings of worthlessness and sadness, which progressively worsened until he became suicidal, fulfilling DSM-IV criteria for a major depressive episode. He mentioned feelings of unreality at times, but had no psychotic symptoms. Stimulating more distally worsened motor scores without changing mood (stimulation parameters: 2.5 V, 185 Hz, 60 ms). All symptoms were successfully treated with fluvoxamine, but recurrence of depressive episodes occurred at 7, 16, and 20 months post-operatively.

Patient 2

A 46-year-old woman with a 10-year history of toxic bilateral pallidal necrosis, with secondary parkinsonism and severe right hemidystonia, underwent bilateral DBS of the internal globus pallidus (stimulation parameters: 2 V, 130 Hz, 60 ms). She had no familial history of affective disorders, but personal history of non-bipolar depressive episodes, in remission at the time of the intervention. During one month post-operatively, she presented a manic state, with elation in mood, flight of ideas, and increased self-esteem. She felt full of energy and had a reduced need for sleep. She was very interested in her outlook, and described heightened perceptions of noises and colors, but had no hallucinations or psychotic symptoms. Even though the neurosurgical procedure had barely an impact on her motor symptoms (UPDRS pre/post-operatively: 37/37-43), she reported a feeling of well being she had never experienced before. At week 5, she became irritable, and less interested in her treatment. Her mood improved with augmentation of the stimulation intensity (stimulation parameters: 3 V, 130 Hz, 90 ms). She was stable for one month and then presented a depressive relapse, successfully treated with amitriptyline (her previous maintenance therapy). At 2 years follow-up, there was no relapse and no manic symptoms recurred.

Discussion

We report here on two patients who presented an inaugural episode of mania, occurring in the direct aftermath of high frequency stimulation of the STN or the Gpi for movement disorders. Both patients had previous minor or major depressive episodes, but no personal or familial history of bipolar disorder. According to bipolar disorder's epidemiology, a first episode of mania after the age of 46 (or 51) is unlikely and mania is a rare event. The occurrence of the manic

episode in strong temporal relation with the implementation of the stimulation points to a proper effect of the stimulation; however, the underlying mechanisms remain unknown.

The STN and the Gpi are control structures, thought to regulate, the activity of the basal ganglia-thalamo-cortical circuits, classically described as five parallel (two motor, two associative, and one limbic), segregated circuits (Alexander, Delong, & Strick, 1986). Anterior cingulate cortex (ACC), orbito-frontal cortex (OFC), ventral striatum and ventral pallidum are the main relay of what is now considered as several limbic sub-loops. A somatotopic organization of the STN, and the internal globus pallidus, was demonstrated in animal studies, with motor, associative and limbic territories, supporting the hypothesis of a regulation not only of motor, but also of associative and limbic circuits. Single cell recording of the STN in PD patients seems to confirm this somatotopic organization in humans. Though, DBS of the STN or the Gpi could have mood effects, mediated by cortico-subcortical limbic loops. Interestingly, in stroke patients, mania was associated with right orbitofrontal, basotemporal, basal ganglia, or thalamic lesions and a disruption of fronto-subcortical connections, more specifically of the right orbitofrontal loop was suggested as a possible mechanism. This putative mechanism could be present in our cases, related to the lesion-like effect of DBS. More complex effects could be related to interconnections between loops, present at different levels including the STN: an open-interconnected scheme has been proposed, in which the STN, among other structures, could play a role in the integration of sensorimotor, associative and limbic informations (Joel & Weiner, 1997). If such processing takes place at the STN or Gpi level, one can expect complex effects on mood when DBS targets these structures.

So far, only motor activation paradigms were used in neuroimaging studies, with PD patients under STN or Gpi-DBS, showing that effective stimulation was modulating the activity of motor cortical areas (supplementary motor area and dorsolateral prefrontal cortex), but also of cingulate cortex and cerebellum (Ceballos-Baumann et al., 1999). Future studies using cognitive and mood activation paradigms could address more specifically the putative effects of DBS on associative and limbic loops and their cortical correspondents. These observations add to our knowledge of the role of the basal ganglia in mood regulation, but further investigation of the function and organization of the frontal striato-thalamo-frontal circuits as well as the mechanism of action of DBS are still preliminary to interpret their significance.

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28. Regional cerebral metabolism is influenced by age, anxiety, and melancholia in major depressive disorder

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Metabolism has correlated negatively with severity of both depression and anxiety in Major Depressive Disorder (MDD). Moreover, melancholic status has been shown to be associated with biological markers including HPA axis dysregulation. SPM-PET and MRI analyses were carried out on 67 MDD patients (20–60 years). Metabolism in independent regions in both limbic and frontal areas correlated negatively with age and severity of anxiety, while thalamic, occipital, and temporal regions correlated positively with age. Age also correlated negatively with paralimbic, basal ganglia, and temporal regions. In general, these regions did not overlap with those showing reduced grey matter concentration with age. Regions of metabolic activity and clinical correlates may help to select antidepressant treatments in the future.

Report

Studies of cerebral glucose metabolism in major depressive disorder (MDD) have generally provided support for claims that a prefrontal-limbic circuit is dysregulated in depression and may be altered by various antidepressant treatments (Mayberg et al., 1999). Nevertheless, there are many inconsistencies in findings across studies, which may be attributed to small sample size, heterogeneity among patient samples, variations in techniques of image analysis or scanning methodologies.

When age has been considered in study design, investigators have tended to study a relatively small sample of patients. For similar pragmatic reasons (particularly small sample size and/or patient heterogeneity), investigators have rarely examined the impact of symptom severity, particularly symptoms of depression and anxiety, or depressive subtype on metabolic activity or cerebral blood flow.

In contrast, a series of investigations into the effect of healthy human ageing on cerebral glucose metabolism, blood flow or regional cerebral oxygen consumption has produced relatively consistent results (Moeller et al., 1996; Petit-Taboue, Landeau, Desson, Desgranges, & Baron, 1998). In a large study of the metabolic topography of normal aging, Moeller and colleagues reported one pattern of increasing hypofrontality and a second pattern of increasing cerebellar, brain stem, and basal ganglia metabolism with increasing age. Subsequent investigators (Petit-Taboue et al., 1998) have consistently noted similar reductions in regional glucose metabolism, especially in dorsolateral and medial prefrontal cortices, including the anterior cingulate (BA 24/32), parietal, and temporal regions.

In the present protocol, in addition to sub-characterisation of major depressive disorder (MDD) into melancholic and non-melancholic sub groups, we sought to determine the effects of age, severity of depressive and anxiety symptoms in male subjects who met defined criteria for MDD and were currently in a major depressive episode (MDE). The study was approved by the Centre for Addiction and Mental Health Research Ethics Board.

Subjects

Subjects were 67 right-handed men (mean age: 37.6 ± 10.2 years; age range: 20–60 years) who met criteria for major depressive disorder (MDD) which was further divided into melancholic and non-melancholic subtypes, based on the Structured Clinical Interview for

DSM-IV. Inclusion criteria included a score of $\geqslant 18$ on the 17-item Hamilton Rating Scale for Depression (HRSD) (mean: 24 ± 3.3) body mass index within 20% of age adjusted averages and no recent exposure to antidepressant treatments (3 months for electroconvulsive therapy, 8 weeks for fluoxetine, and 4 weeks for all other antidepressant agents). Concurrent DSM-IV diagnoses or prescription of additional psychotropic medication were exclusion criteria. A measure of severity of concurrent anxiety symptoms was provided by the Hamilton Rating Scale for Anxiety (HRSA) (mean: 16.5 ± 4.5). After providing a complete description of the study to all subjects, written informed consent was obtained. Average number and duration of previous depressive episodes were 1.7 ± 2.4 and 70 ± 108 weeks, respectively. Duration of current depressive episode was 79.8 ± 110.2 weeks.

Statistical methods

Statistical Parametric Mapping software version 1999 (SPM 99) was employed to undertake image analysis. Regional brain metabolism in 67 images was correlated with age, HRSD (severity of depression), HRSA (severity of anxiety), number of previous episodes, total duration of previous episodes (weeks), and duration of current episode (weeks). In addition, brain metabolic differences between the 38 melancholic and 28 non-melancholic patients were examined (data for classification were unavailable for one subject). Global normalisation was performed with ANCOVA and voxel threshold was set to 0.01 ($p < 0.01$). Only a corrected cluster level $p < .05$ was considered statistically meaningful and the atlas of Talairach and Tournoux was used to localise brain regions. Additionally, the Statistical Package for the Social Sciences version 10 (SPSS 10) was used for statistical analyses of the clinical scores after testing for normal distribution and Bonferroni correction was applied for multiple comparisons.

Results

Melancholic and non-melancholic subgroups

When the 38 melancholic subjects (age range: 20–59 years, mean age: 38.8 ± 9.7 years) were compared with the 28 non-melancholic subjects (age range: 20–60 years mean age: 36.0 ± 10.9), the melancholic group had significantly higher severity scores on HRSD. There were no significant differences between the two subgroups in severity of anxiety (HRSA), age, number of previous episodes, total duration of previous episodes, and duration of current episode.

Significant metabolic increases in the melancholic group were observed in dorsal and anterior insula, precentral gyrus, postcentral gyrus, inferior parietal lobe, superior and transverse temporal gyri in the left brain compared to the non-melancholic sample. Additionally, there were no areas that showed a significant reduction in metabolism in the melancholic group compared to non-melancholic group (Fig. 1).

Severity of depression, anxiety, and metabolism

There was a significant correlation between severity of depression according to HRSD and severity of anxiety according to HRSA severity scales ($r = .56, p < .001$). Neither HRSA nor HRSD correlated with age, total number of prior episodes nor duration of current episode.

There was a significant correlation between regional brain metabolism and severity of anxiety (HRSA), but not severity of depression (HRSD). Our data showed that anxiety correlated negatively with metabolism in medial, middle, and inferior frontal gyri in both hemispheres. Additionally, in the left-brain, there were negative correlations between anxiety and metabolism in subgenual cingulate and anterior insula. There were no positive correlations between severity of anxiety and regional brain metabolism (Fig. 1).

Age and regional metabolism

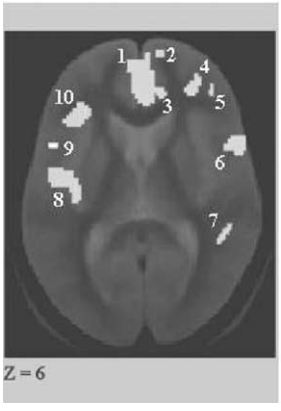
The relationship between age and metabolism varied across brain regions: a large area of prefrontal cortex extending from insula to anterior cingulate, temporal and premotor areas correlated negatively with age ($p < .05$). There was a positive correlation between age and metabolism in the basal ganglia (pallidum and caudate), thalamus, certain limbic regions (posterior cingulate, amygdala, hippocampus, and parahippocampus), as well as precuneus and cuneus (in parietal and occipital lobes) ($p < .001$) (Fig. 1).

Grey matter concentration and age, and hrsa

Atrophy and decreased metabolism with age occurred concomitantly in inferior frontal gyrus (BA 47),and superior temporal gyrus (BA22). Additionally, concentration in middle frontal gyrus (BA 11) and inferior frontal gyrus (BA47) decreased with a decrease in HRSA (Fig. 1).

Comments

This report contributes to further elucidation of MDD according to symptom profile and clinical subtype. Similar changes with age were observed in frontal and temporal regions in our MDD patients and in healthy controls reported elsewhere. In contrast, MDD patients in this study displayed increased activity in the thalamus, which have not previously reported. The implications of these findings for treatment selection require further consideration.



1,6,9: Met/Age Neg Correlation
2,3,4,10: Met/HRSA Neg Corr controlled for age
5,7: Atrophy/age
8: Melancholic Status, increase

Region Key
1) Medial Frontal Gyrus (BA 10), and Cingulate Gyrus (BA 24/32)
2) Medial Frontal Gyrus (BA 10)
3) Cingulate Gyrus (BA 24/32)
4) Middle Frontal Gyrus (BA 46)
5) Inferior Frontal Gyrus (BA 45/46)
6 / 9) Precentral Gyrus (BA 6)
7) Middle Temporal Gyrus (BA 21)
8) Insula (Anterior and Posterior)
10) Precentral Gyrus (BA 6), and Anterior Insula

Fig. 1.

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29. When two hemispheres are not better than one: Effects of worry on interhemispheric processing

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This study examined the influence of individual differences in worry on interhemispheric processing of happy and angry faces. In a divided visual field study, participants indicated whether the emotional expression of a laterally presented face matched the expression of a face in the same visual field (within-field match) or the opposite visual field (across-field match). Individuals scoring low on a trait measure of worry displayed a highly significant advantage for detecting across-field matches versus within-field matches, consistent with prior findings that interhemispheric division of labor is advantageous. High worriers, in contrast, displayed no interhemispheric advantage. This group difference was not affected by whether the matches involved happy or angry faces. The findings suggest that altered interhemispheric communication may be related to cognitive deficits associated with worry.

Report

Utilization of both the left and right cerebral hemispheres often leads to enhanced cognitive performance, compared to conditions in which only a single hemisphere is required to perform a task (Banich, 1995). Presumably, performance is improved due to the additional processing resources available when both hemispheres are involved in a task. Though many studies have examined how interhemispheric processing advantages vary according to the computational complexity and attentional demands of the task (Banich, 1995), few studies have examined individual differences in interhemispheric communication. Interhemispheric interaction may be especially relevant to understanding cognitive processing deficits in anxiety and worry, which have often been conceived as involving inefficient utilization of cognitive resources (e.g., Eysenck, 1992). Deficient utilization of bi-hemispheric resources may provide one mechanism for the inefficient cognitive processing associated with anxiety.

Consistent with this notion, a recent study reported that increasing trait levels of worry were associated with a reduction in the interhemispheric processing advantage (Compton & Mintzer, 2001). The authors argued that worry may interfere with communication of information between the hemispheres, increasing the costs of interhemispheric processing relative to within-hemisphere processing. An alternative possibility is that worry may impede interhemispheric communication of emotionally irrelevant information, while facilitating interhemispheric communication of emotionally relevant information. This might be the case if worry biases cognitive processing priorities in favor of emotionally relevant information. Because the prior study employed a non-emotional letter-matching task, the possibility of differential interhemispheric communication of anxiety-relevant information has not yet been addressed.

To test these two competing predictions regarding the influence of worry on interhemispheric communication, the present study used a task that required matching facial expressions of emotion either within a single hemisphere or between hemispheres. Matches are typically detected faster between hemispheres than within a hemisphere, reflecting the advantage of interhemispheric division of labor. If worry hinders interhemispheric communication in general, then worriers should display a reduced interhemispheric advantage in matching facial expressions of emotion, regardless of the specific emotional expression. Alternatively, if worry facilitates the interhemispheric communication of anxiety-relevant information, then worry may enhance the interhemispheric processing advantage for matching angry faces.

Methods

Participants

Forty-six right-handed undergraduates (29 women, 17 men) completed the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990) and an interhemispheric face-matching task. Subjects were divided by a median split into High and Low worry groups based on the PSWQ scores.

Face-matching task

Stimuli included nine digitized black and white photographs, three male posers displaying neutral, happy, and angry expressions (Ekman & Friesen, 1976). The stimulus array for each trial consisted of three faces arranged in a triangular formation, with two faces above the fixation point and one below the fixation point. Each face subtended $3° \times 2°$ of visual angle. The top two faces were centered 2.5° above fixation and 5° to the left and right of fixation. The bottom face was centered 2.5° below fixation and 2.5° to either the left or the right of fixation. The task was to indicate whether the bottom face depicted the same emotional expression as either of the top two faces.

Half of the trials were matches, in which the bottom face matched the emotional expression of one of the top two faces, and half were mismatches, in which the bottom face matched neither of the top two. The bottom face could bear either a happy or an angry emotional expression, and it could appear in the left visual field (LVF) or the right visual field (RVF). Most importantly, a match could occur within a visual field, with both matching items on the same side of the midline and thus presented to a single hemisphere, or a match could occur across visual fields, with one member of the pair on the left and the other on the right side of the m dline. Recognizing an across-field

match requires interhemispheric communication, whereas recognizing a within-field match does not.

The task, run by E-Prime software (Psychology Software Tools), included 576 trials, divided into 6 blocks of 96 trials following 32 practice trials. Each trial included a 1000-ms fixation point, followed by a 200-ms presentation of the stimulus array and finally by a 1500-ms fixation point during which responses were collected. The participant was instructed to press a key only when the emotional expression on the bottom face matched the expression on either of the top two faces.

Results

Accuracy (the proportion of matches correctly detected) was analyzed by ANOVA with the between-subjects factor of Group (High vs. Low Worry) and within-subjects factors Emotion (Angry vs. Happy face), Interhemispheric Condition (Across- vs. Within-field match), and Visual Field of top matching item (VF; LVF vs. RVF).

Accuracy was higher overall for across-field trials ($M = .71$) than for within-field trials ($M = .67$; $F(1,44) = 23.94$, $p < .0001$), reflecting an interhemispheric advantage in processing that is consistent with previous findings for difficult cognitive tasks (e.g., Banich, 1995). However, the degree of this interhemispheric advantage depended on worry group (Group × Interhemispheric Condition, $F(1,44) = 8.12$, $p < .01$). While the interhemispheric advantage was highly significant in the Low Worry group ($F(1,22) = 26.76$, $p < .0001$), it was not significant in the High Worry group ($F(1,22) = 2.37$, $p > .10$). Means are presented in Fig. 1.

Regarding the emotionality of the faces, accuracy was higher overall for happy faces ($M = 0.74$) than for angry faces ($M = 0.64$; $F(1,44) = 39.38$, $p < .0001$). However, the 3-way interaction of Group, Interhemispheric Condition, and Emotion did not approach significance ($F < 1$). That is, there was no evidence that the reduced interhemispheric advantage in the High Worry group depended on the emotionality of the facial expression.

An unpredicted finding was that the worry groups differed in perceptual asymmetry for happy faces. The significant 4-way interaction among Group, Interhemispheric Condition, Emotion, and VF ($F(1,44) = 4.92$, $p < .05$) was broken down to examine within-field trials and across-field trials separately. VF asymmetries reflecting hemispheric specialization are expected on within-field matches but not on across-field matches, because on across-field trials one matching item is presented to each hemisphere. Accordingly, the 3-way interaction among Group, Emotion, and VF was significant for within-field matches ($F(1,44) = 4.98$, $p < .05$), but not for across-field matches ($p > .25$). Examination of within-field trials revealed that the difference between worry groups was isolated to the happy faces (Group × VF, $F(1,44) = 7.96$, $p < .01$ for happy faces). For happy faces, low worriers displayed a LVF/right hemisphere advantage ($F(1,22) = 8.41$, $p < .01$; $M = .74$ for LVF, $M = .65$ for RVF), whereas high worriers displayed no significant VF advantage ($F < 1$; $M = .74$ for LVF, $M = 0.76$ for RVF). For angry faces, there was no overall VF advantage ($M = .62$ for LVF, $M = .61$ for RVF; $F < 1$) and the VF advantage did not depend on worry group ($F < 1$).

To confirm the findings from the ANOVA, a regression analysis examined the relationship between PSWQ score and the across-hemisphere advantage (across-field accuracy minus within-field accuracy). The analysis revealed a significant negative correlation ($r = -.35$, $F(1,44) = 5.98$, $p < .02$), confirming that as the worry score increased, the advantage of interhemispheric processing decreased.

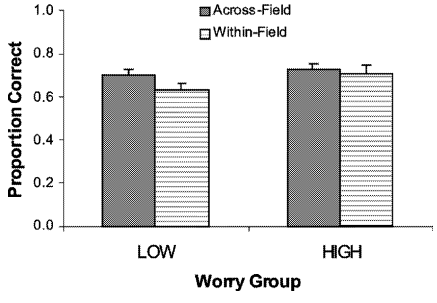

Fig. 1. Proportion of across-field and within-field matches correctly detected, as a function of worry group. Low worriers, but not high worriers, display a significant across-field advantage.

Discussion

The main finding was that a division of labor between the hemispheres was beneficial for individuals scoring low on a self-report measure of worry, but not for those scoring high on the worry measure. These results confirm and extend the findings of Compton and Mintzer (2001), who previously reported that high worriers did not benefit from interhemispheric processing in a non-emotional task. The present study demonstrated that the absence of an interhemispheric advantage in worriers did not depend on whether the information to be communicated between hemispheres was emotionally pleasant or emotionally threatening. Though high worriers differed from low worriers in failing to show a right-hemisphere advantage for matching happy faces, the happy versus angry expression appeared to have no effect on interhemispheric performance in either group. This finding appears to rule out the possibility that interhemispheric communication of emotionally relevant information is facilitated in worriers. Instead, the findings indicate that worry-prone individuals fail to show interhemispheric processing advantages regardless of the stimulus type.

These findings suggest that individuals characterized by a high level of worry may be deficient in the utilization and coordination of interhemispheric resources. One possibility is that the "cognitive load" imposed by worry interferes with the executive control necessary for efficient interhemispheric communication. An alternative hypothesis warranting further research is that within-hemisphere processing may be especially efficient in worriers, thus reducing the relative advantage of dividing processing between the hemispheres. This alternative possibility is partly supported by aspects of the present data indicating that within-hemisphere performance was slightly (but non-significantly) better in worriers than non-worriers; however, this possibility is inconsistent with previous data (Compton and Mintzer, 2001) indicating that worriers and non-worriers differed more in across-field than within-field processing. Both studies agree that the relative advantage of across-field processing is significantly reduced in worriers, and future studies will be required to determine to what extent this is due to deficient interhemispheric communication or enhanced within-hemisphere processing. Future studies should also explore the connection between reduced interhemispheric performance advantages and other cognitive deficits associated with worry.

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30. A nonlinear study of EEG in patients with affective disorder

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The aim of this study is to investigate the nonlinear characteristics of electroencephalogram (EEG) in patients with affective disorder via higher-order statistics (HOS). The Bispectral Index (BI) is proposed as a nonlinear quantification to identify if BI could be used as a discriminating statistics to demonstrate the nonlinearity in the EEG. The difference between the bicoherece patterns of EEG in healthy subjects and patients with affective disorder is expected to reflect some mechanism of the underlying brain wave based on the hypothesis that nonlinearity may manifest the mechanistic difference. Both depressives and maniacs are investigated and compared with normal controls. The results indicate that the nonlinear analysis based on BI can provide the means of investigating the brain electrical activities of patients with affective disorder.

Report

In recent years the analysis of human EEG by using the nonlinear methods has received increased attention and has emerged as an important advance in understanding the underlying mechanism of brain electrical activities (Li et al., 2001). The presence of nonlinear behaviors in various physiological and pathological states, such as schizophrenia, dementia and epilepsy, has been discussed. Since there have been more evidences indicating the existence of nonlinear and non-Gaussian behavior of the EEG (Ning & Bronzino, 1998; Shen, Chan, Sun, & Beadle, 2000), it is necessary to adopt non-traditional method to address the nonlinearity of the EEG for the purpose of better describing the patients with affective disorder. The bispectrum, unlike the traditional spectral analysis, provides the quadratic phase coupling (QPC), which makes it a particularly relevant and useful tool while analyzing nonlinear interactions among the different rhythms of EEG. We suspect that such interaction like Bispectral Index (BI) can be helpful in identifying the changes in affective states of the brain. This study test the hypothesis that BI of EEG will reveal and help quantitative brain's response to affective disorder.

The focus of the present study is the rhythm's nonlinear interaction relationship for the EEG in patients of both depressives and maniacs via BI to characterize the nonlinearity of EEG. The different EEG segments were studied to obtain the evidence of QPC phenomenon of the brain wave.

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Method

Selection of subjects and EEG recording

The subjects included 23 volunteer normal controls, 22 depressive patients, and 27 mania patients. The normal controls were healthy male graduate students and researchers volunteer, aged between 20 and 36 (average age 26.8). They had no history of any neurological or psychiatric disease and were not taking any drugs for more than one month. The 22 depressive patients, aged between 22 and 46 (average age 32.5), were not medicated and the 27 mania patients, aged between 24 and 49 (average age 35), were also not medicated. The EEG for both depressives and maniacs were from the patients in the Mental Health Care Centre of Shantou University and diagnosed as the depressive and mania, respectively, according to the CCMC-α-R standard. The EEG collection were performed in an acoustically and electrically shielded room where the subjects were lie comfortably on the bed by using the NIKHON EEG-4200 system. EEG data were recorded from 14 electrodes mounted on the subject's scalp according to the international 10-20 system and were sampled at 100 Hz. The reference electrode was placed on the tip of the nose and grounded through linked earlobes. Artifact rejection was performed off-line by an experienced EEG expert who visually inspected the recordings.

Bicoherence analysis

The bispectrum of each stationary segment of EEG was estimated after dividing it into appropriate number of records. The bispectrum $B_x(f_1, f_2)$ of an EEG $x(t)$ is defined (Shen et al., 2000) as

$$B_x(f_1, f_2) = \frac{1}{M}\sum_{i=1}^{M} X^{(i)}(f_1)X^{(i)}(f_2)X^{(i)*}(f_1 + f_2), \tag{1}$$

where $X^{(i)}(f)$ is the Fourier transform of the ith segment of $x(t)$ and * denotes the complex conjugate. The Bicoherence Index (BI), also called the normalized bispectrum, is defined as follows:

$$\mathrm{bic}(f_1 + f_2) = \frac{B_x(f_1, f_2)}{\left[\frac{1}{M}\sum_{i=1}^{M}\left|X^{(i)}(f_1)X^{(i)}(f_2)\right|^2\right]\left[\frac{1}{M}\sum_{i=1}^{M}\left|X^{(i)}(f_1 + f_2)\right|^2\right]}. \tag{2}$$

The theoretical value of bicoherence index lies between 0 and 1, where 0 is non-significant and 1 indicates the highest significant QPC of the EEG.

Results and discussion

To guarantee that the estimate of BI has a satisfied resolution and small variance, more than 64 segments of 6.4 s EEG epochs of each subject were used. The average BI of EEG is calculated within the specified rhythm band in the bifrequency plane of bicoherence. The maximum peak of bicoherence and its location in bifrequency plane were also estimated. The statistical results via BI for normal controls, depressives, and maniacs were shown in Table 1.

The statistical results in Table 1 show that the average BI within the α-band in bifrequency plane for both depressives and maniacs are smaller as compared with that for the normal controls. The experimental result indicates more QPC phenomena exist in the α-band of the bifrequency plane for the healthy EEG. In addition, the maximum bicoherence peak exists within the α-band of the bifrequency plane for the normal controls whereas the main bicoherence peak occurs in the θ-band of the bifrequency plane for both two kinds of patients with affective disorder. The increase in the average BI measure for the

Table 1
Comparison of average BI and bicoherence peaks for 3 kinds of subjects

Measurements	Normal controls	Depressives	Maniacs
Average BI value within the α-band	0.72 ± 0.083	0.38 ± 0.036	0.41 ± 0.09
Average BI value within the θ- and δ-bands	0.39 ± 0.084	0.52 ± 0.12	0.55 ± 0.14
Location of the maximum BI peak in bifrequency plane	$(10 \pm 1,\ 10 \pm 1)$ Hz	$(4 \pm 2,\ 4 \pm 2)$ Hz	$(5 \pm 2,\ 5 \pm 2)$ Hz
Average value of the maximum bicoherence peak	0.82 ± 0.08	0.43 ± 0.07	0.49 ± 0.08

normal controls shows that the OPC among the α-rhythm's frequency components is more significant under the normal brain function state. The BI in patients with affective disorder presents decreased amplitudes and widespread distribution in bifrequency domain as compared with normal controls. This result reflects that the quadratic nonlinearity in the EEG generating process is more pronounced under the normal brain state. The α-rhythm is the dominant electrical activity and the frequency components in α-band have a fixed frequency and phase relationship. Moreover, for the EEG of patients with affective disorder their QPC presence can be found in a wide range of bifrequency domain. However, there was not very significant bicoherence peak detected. The statistical results imply that there exists a well orderly relationship of the brain electrical activities under the normal brain function state, while the orderly relationship for both of the frequency components and the phase of the EEG were significantly declined if the brain function state has changed into the affective disorder like depressive and mania. Finally, the statistical results with BI analysis may provide us the information that both depressives and maniacs can be classified as a similar category from a point of view of electrophysiology and the nonlinear index. The affective disorder causes the decreasing capacity of the information processing in the brain and significantly depress the orderly nonlinear relationship of the frequency components of the EEG within the α-band.

The results indicate that the EEG should be treated as a nonlinear process and the higher order correlation or BI of EEG can provide more useful information. In this study, we provide the first direct evidence of the presence of quadratic nonlinearity involved in the EEG of patients with affective disorder. Since the mechanism of affective disorder electrical activity is still not clear, more subjects and further study are required to investigate the nonlinearity of the EEG. Still more investigation remains to be done to see whether the QPC nonlinear phenomenon is associated with the neurological state of the human.

Conclusion

This study has demonstrated that the nonlinear analysis based on BI can provide the means of investigating the brain electrical activities of patients with affective disorder. The advantage of the proposed method includes that the BI can reveal the difference of the nonlinear relationship of the EEG between the normal controls and the patients with emotion disorder. The BI can be considered as a reference for evaluating the EEG under different brain function states. The significant BI within the specified rhythm band strongly indicates the presence of quadratic nonlinear interaction in the EEG generator for both healthy subjects and the patients with affective disorder.

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31. Brain stem evoked potential correlates of trait and state anxiety in normal adult volunteers

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The present study examined the relationship between anxiety and brain stem auditory evoked potentials (BAEPs) in 54 female university students who were assessed on the Spielberger State-Trait Anxiety Inventory (STAI). Latencies and amplitudes of BAEP peaks I, III, and V were examined for three (72, 80, and 88 dB) click intensities prior to brief (120 s) auditory noise (75 dB) exposure, and for one intensity (88 dB) post-noise exposure. Amongst the findings observed, shorter pre-noise peak V latencies were associated with higher state anxiety while noise-induced peak V amplitude increments were associated with higher trait anxiety. These findings provide some tentative support for the notion that BAEPs may be sensitive to individual differences and acute anxiety-evoking stressors.

Report

Rationale

Brain stem neurons are known to modulate physiologic and behavioral arousal and their aberrant functioning has been implicated in a number of mood and anxiety disorders associated with putative arousal abnormalities. Although the scalp-recorded brain stem auditory evoked potentials (BAEPs), utilized routinely in a variety of contexts in clinical medicine, appear to offer a suitable non-invasive means for probing relationships between brain stem neural elements and anxiety, these electrical potentials have for the most part been shown to be relatively invariant with respect to inter- and intra-individual differences in psychological processes (attention, memory, perception) and arousal (sleep/wake) states. Two recent studies conducted in normal adults have, however, shown latencies of BAEP peak V (reflecting activity in lateral lemniscus or inferior colliculus) to be sensitive to individual differences in trait anxiety and for peaks I (reflecting activity of the auditory nerve), III (reflecting activity of lower pons), and V to be differentially affected by transient changes in state anxiety as reflected by latency alterations following acute exposure to a moderately intense (auditory noise) stressor (Petiot, Parrot, Smolik,

Petiot, & Lobreau, 1994) and administration of a single dose of an anxiolytic (benzodiazepine: alprazolam) agent (Parrot, Petiot, Morizot, Petiot, & Smolik, 1999). In this current study, BAEPs were examined before and after auditory noise presentation in a sample of women assessed for trait (reflecting dispositional anxiety-proneness) and state (reflecting anxiety at a transient point in time) anxiety.

Method

Subjects

Fifty-four right handed female ($M = 19.2$ years, $SD = 1.1$) university students were recruited from introductory psychology classes. Volunteers had no current or prior neurological, psychiatric or alcohol–drug abuse history and, with the exception of contraceptives ($n = 26$), were not taking any medications. Volunteers, assessed for auditory thresholds with a 1000 Hz tone, exhibited normal hearing at 20 dB.

Procedure

In a single laboratory test session, which included BAEP recordings, completion of the Spielberger State-Trait Anxiety Inventory (STAI: Spielberger, 1983), and noise rating scales, data collection was carried out in five sequential steps: (1) the recording of BAEPs in response to 3 click intensities at 72, 80, and 88 dB (SPL); (2) completion of the State (S-Anxiety) anxiety form (STAI Form Y-1); (3) the binaural headphone presentation of 76 dB (SPL) auditory broad-band "white" noise for 120 s; (4) the recording of BAEPs in response to 88 dB (SPL) clicks and (5) the completion of the trait (T-Anxiety) form (STAI-Form Y-2) and auditory noise rating (ANR) scales.

Instruments

The STAI consists of 2 separate (S-Anxiety and T-Anxiety) forms of 20 statements each. Volunteers rate each statement as being descriptive or not descriptive of themselves, using a 4-point likert scale ranging from (1) 'not at all' to (4) 'very much so'. The sum of the scores (minimum score 20, maximum score 80) for the S-Anxiety form reflects how anxious an individual feels at the present moment (i.e., at time of ratings) and the summed score for the T-anxiety form reflects how anxious an individual generally feels on a day-to-day basis. All T-anxiety and S-anxiety scores were found to be within normal limits.

ANR measurement of reactivity to the auditory noise involved rating the noise for subjective "loudness", and its effect on "irritability" and "anxiety." Each was rated by marking a 95 mm visual analogue scale anchored at one end by the phrase "not at all" and at the other end by the word "extremely."

BAEPs

BAEP recordings, taken from the midline vertex (Cz) and ipsilaterally referenced left ear lobe (AI) electrodes (impedances <2 k□), were amplified with a gain of 200,000 and bandpass frequency filter settings of 100 Hz–2000 kHz. Each of the 3 stimulus intensity presentations (calibrated, as was intensity of auditory noise, with a Bruel and Kjaer type 2204 sound level meter) consisted of a series of 2000 rarefaction clicks (0.1 ms duration) delivered monaurally (left ear) at a rate of 11.1 s through telephonic TDH-39 shielded headphones. Each trial was sampled at 200 □s intervals for a 10 ms (beginning 1 ms prior to click onset) epoch. Single trial epochs with voltages exceeding 95% of the amplification gain were rejected from the final average. All final averages for each subject in this analysis were artifact-free and were comprised of 2000 trials.

For peaks I, III, and V, identified as the most positive peaks between 1.3–2.1, 3.4–4.2, and 5.1–6.3 ms, respectively, the following measures were taken: (1) latency, time in ms from click onset to maximum peak amplitude; (2) amplitude from baseline, height of peak (□V) relative to pre-stimulus baseline; and (3) peak-to-trough amplitude, height of peak (□V) relative to the preceding negative peak and (4) inter-peak-latency (IPL), time in ms, between peaks I–III, III–V, and I–V.

Analyses

For each study measure, two sets of analyses were carried out, one to examine the relationship between extracted measures and T-anxiety scores and the second to examine their relationship to S-anxiety scores. For the first analyses, volunteers were sub-grouped ($n = 18$ per group) as either Low T (mean score = 28.2, range 23–22), Middle-T (mean score = 35.6, range 32–39) or High-T (mean score = 46.5, range 39–60) and for the second analyses, subjects were sub-grouped ($n = 18$ per group) as either Low-S (mean score = 23.56, range 21–26), Middle-S (mean score = 29.3, range 26–32) or High-S (mean score = 41.1, range 32–66). Analyses of baseline BAEPs involved split-plot analysis of variance (ANOVA) procedures with group (×3) and intensity (×3) as between- and within-group factors, respectively. Noise reactivity was analyzed by subjecting different scores (post-noise peak values minus pre-noise peak values for 88 dB-elicited BAEPs) to one-way ANOVAs. Each ANR scale was also analyzed with one-way ANOVAs and all significant ($p < .05$) effects were followed-up with Tukey HSD tests.

Results

As with previous literature, significant (pre-noise) intensity effects were observed for I, III, and V peak latencies and peak I and III amplitudes, with increasing intensity resulting in shorter latencies and larger amplitudes. No significant group effects were observed with T-anxiety analyses but follow-up of a significant group intensity interaction ($F(2, 100) = 2.8$, $p < .05$) for peak V latency found longer ($p < .05$) latencies for the Low-S group at 72 dB ($M = 5.9$ ms, $SD = .27$) and 80 dB ($M = 5.8$ ms, $SD = .24$) than the High-S group at 72 dB ($M = 5.7$ ms, $SD = .24$) and 80 dB ($M = 5.6$ ms, $SD = .24$). Follow-up analyses of a significant group × intensity interaction ($F(4, 98) = 4.4$, $p < .01$) also found ($p < .05$) longer III–V IPI's for the Low-S ($M = 1.9$ ms, $SD = .18$) group compared to the High-S group ($M = 1.7$ ms, $SD = .19$).

S-anxiety groups did not differ with respect to BAEP or subjective reactivity to auditory noise but T-anxiety groups exhibited differences with respect to both measures. Significant group differences were found for subjective 'anxiety' ratings ($F(2) = 3.1$, $p < .05$) elicited by the noise, with follow-up tests showing High-T volunteers reporting greater noise-induced anxiety ($M = 60.2$ mm, $SD = 24.9$) than the Low-T ($M = 38.0$ mm, $SD = 30.2$) volunteers ($p < .05$). Differences in noise-induced peak I latencies ($F(2) = 5.3$, $p < .01$), peak V (baseline to peak) amplitudes ($F(2) = 3.2$, $p < .05$) and I–III IPIs ($F(2) = 3.9$, $p < .01$) were observed. Compared to Low-T volunteers who exhibited only a slight decrease ($M = -.02$□V, $SD = .16$) in peak V amplitudes, both Medium-T ($M = .12$ □V, $SD = .22$) and High-T groups ($M = .12$ □V, $SD = .22$) exhibited significant ($p < .05$) increases in amplitudes of this peak. For peak I, the Medium-T group showed a significant ($p < .05$) lengthening of latencies ($M = .03$ ms, $SD = .11$) compared to the High-T group who showed a shortening of latencies ($M = -.02$ ms, $SD = .73$) with noise exposure. Also significant ($p < .05$) was the difference between High-T and Medium-T volunteers in I–III IPIs, with the former group showing a lengthening ($M = .04$, $SD = .08$) and the latter showing a shortening ($M = -.05$, $SD = .08$) of this interval.

Conclusion

In general, the results of this study tended to verify previous work reporting relationships between anxiety and BAEP recordings. Psychometrically assessed state anxiety at the approximate time of BAEP recordings was significantly associated with peak V latency, with higher ratings of self-reported anxiety being associated with shorter latencies of this peak. Volunteers with higher trait anxiety (vs. low trait anxiety volunteers) reported greater anxiety ratings during the noise exposure, and noise exposure resulted in larger peak V amplitudes in volunteers with medium and higher trait anxiety (vs. low trait anxiety volunteers).

Although generators of early peaks I and III have been argued to contribute to peak V, available human evidence suggests peak V is generated in the high pons or low midbrain (lateral lemniscus or inferior colliculus) (Chiappa, 1997). Hyper-excitation of the noradrenergic (NA) enriched pontine locus coeruleus nuclei has been implicated in pathological anxiety (Charney et al., 1984) and it is conceivable that both endogenous and exogenous (noise)-induced normal NA variations in this region may have mediated the anxiety and peak V alterations seen here in normal volunteers.

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32. Behavioural and neuroendocrine correlates of hemispheric asymmetries in benzodiazepine receptor binding induced by postnatal handling in the rat

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Early postnatal handling enhances the development of cerebral lateralization in rats, particularly for emotion-related behaviours. Handling stimulation also initiates numerous adaptive changes in stress physiology and coping ability. We employed receptor autoradiography to examine the effects of handling on hemispheric asymmetries in central benzodiazepine (BZ) receptor binding. Across prefrontal and hippocampal regions, handling caused a rightward shift in BZ binding, particularly in hippocampal CA1 and dentate gyrus. Binding asymmetry index in these regions (favouring the right brain) was significantly correlated with increased investigation of a novel environment, consumption of novel palatable food and reduced neuroendocrine responses to restraint stress. It is suggested that increased inhibitory tone in right hemispheric stress-regulatory regions prevents excessive emotional and neuroendocrine reactivity in stressful or anxiety-provoking situations.

It has been known since the studies of Denenberg (1981) that early environmental stimulation ("handling") in rats enhances the cerebral lateralization of emotion-related behaviours, such that the right hemisphere assumes predominant control of such processes. The same handling procedure also induces lasting adaptive changes in neural and endocrine stress-regulatory systems and a reduction in anxiety-related behaviours, which have been shown to be mediated by enhanced early maternal stimulation (e.g., Caldji et al., 1998). Taken together, this raises the possibility that the development of cerebral lateralization in specific brain systems may be importantly linked with emotion-related behaviours and physiological adaptation to stress.

In the present study, we employed quantitative receptor autoradiography in handled and non-handled rats to examine patterns of hemispheric asymmetry in adult benzodiazepine (BZ) receptor binding in selected brain regions. This system was targeted due to the anti-anxiety properties of BZs and the ability of BZs to dampen neuronal activation associated with stress. The results suggest that handling does induce a lateralized shift in BZ receptor binding which correlates with both behavioural and neuroendocrine indices of stress.

Methods

Handling procedure

In the handling (H) treatment (performed on each of the first 14 days of life), Long-Evans moms were removed from the litter and placed in an adjacent cage. The litter of pups was then transferred to a separate cage. After 15 min, the pups then the moms were returned to the homecage. In the nonhandled condition (NH), litters were left completely undisturbed during this period except for one cage cleaning on day 8. Following weaning on day 22, male pups were housed in same-treatment pairs until testing as adults.

Behavioural tests

At three months of age, rats were videotaped in dim lighting in a holeboard apparatus ($60 \times 60 \times 40$ cm), consisting of an elevated floor with nine equally spaced holes (5 cm diameter). The number of holes visited and investigated with a nose-poke was taken to indicate the exploratory/investigative response to a novel environment, also reflective of reduced anxiety. We also assessed the response to a novel appetitive stimulus by monitoring the consumption of (Eagle Brand) sweetened condensed milk diluted 4:1, delivered in a standard water bottle and homecage for a single one hour exposure.

Stress testing

Rats were placed for 20 min in Plexiglas rodent restrainers with blood samples taken from the tail vein at 0, 20, and 80 min representing basal, peak and stress recovery time points, respectively. Plasma samples were later analysed for levels of the stress hormones adrenocorticotropic hormone (ACTH) and corticosterone using radioimmunoassay double antibody kits (ICN Pharmaceuticals). Pilot studies showed that while H and NH rats did not differ in ACTH levels following acute restraint stress, H rats alone habituated significantly to this neuroendocrine stress response when examined during a fifth daily restraint. We therefore sampled the present rats on the fifth restraint session, so that brain receptor differences could be associated with this highly adaptive physiological state.

Autoradiography

Immediately following blood sampling, rats were killed by decapitation and brains rapidly removed and frozen for autoradiographic determination of benzodiazepine ([^{3}H]flunitrazepam) receptor binding, as described by Caldji et al. (1998). The primary regions of interest

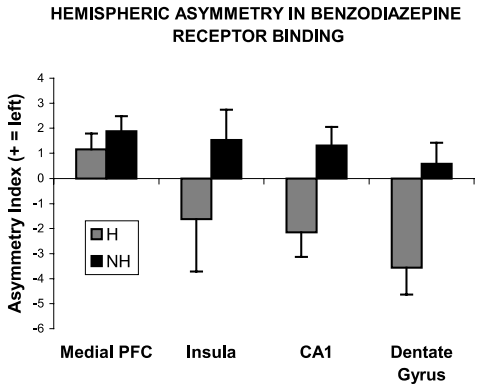

Fig. 1. Across regions examined, H treatment was associated with a significant shift to the right in [^{3}H]flunitrazepam binding density, relative to NH rats ($F_{1,14} = 8.87$, $p = 0.010$). There was also a significant effect of Region, but no Group × Region interaction ($n = 8$ rats/group).

were hippocampus and prefrontal cortex (PFC), given their roles in glucocorticoid feedback regulation and emotion-related behaviours. Left and right brain structures were analysed separately and a hemispheric asymmetry index computed for each region as $(L - R)/(L + R) \times 100$. All procedures conformed to the guidelines of the Canadian Council of Animal Care and McGill University animal utilization protocols.

Results

Fig. 1 summarizes the mean (±SEM) hemispheric asymmetry measures in the four brain regions examined. While handling resulted in a significant rightward shift in BZ binding across structures, this difference was most notable in hippocampal CA1 region and dentate gyrus. Total (average of left and right) BZ receptor binding was not affected by handling treatment in any structure (data not shown), despite generally higher levels of binding in hippocampal vs. cortical regions. As well, regional total binding levels were not significantly correlated with any behavioural or neuroendocrine measures. In contrast, regional binding *asymmetries* were significantly associated with such measures. Across animals, the asymmetry index in dentate gyrus was correlated with holeboard exploration ($r = -.53$, $p = 0.034$), sweetened milk consumption ($r = -.68$, $p = 0.003$) and peak ACTH stress response ($r = .60$, $p = 0.023$). Hippocampal CA1 asymmetry was correlated with sweetened milk consumption ($r = -.81$, $p < 0.0005$), peak ACTH stress response ($r = .58$, $p = .028$) and ACTH stress recovery levels ($r = .59$, $p = .027$). In other words, individual asymmetries in BZ binding favouring the right hemisphere are associated with increased exploratory activity in a novel environment (reduced anxiety), consumption of novel palatable food and reduced HPA reactivity (or enhanced habituation) in response to repeated mild stress.

Discussion

The adaptive long-term effects of early handling stimulation have previously been well documented and shown to involve numerous neural and neuroendocrine mechanisms (e.g., Caldji et al., 1998). However, the issue of hemispheric asymmetry is rarely considered in such studies. The present findings highlight the importance of considering this factor in assessing the long-term consequences of early developmental manipulations. For example, we report that H treatment did not affect total BZ receptor binding (average of left and right) in hippocampal and prefrontal regions, confirming the findings of Caldji et al. (1998). However, H did significantly affect the hemispheric distribution of BZ receptor binding, and these individual hemispheric asymmetries were related to behavioural indices of novelty/anxiety and neuroendocrine stress adaptation.

Our findings indicate that relatively greater right-sided BZ binding (either greater number of binding sites or greater affinity for ligand) is related to reduced anxiety in response to novel situations as well as reduced stress-induced neuroendocrine responsivity or enhanced negative feedback regulation. Both the hippocampus and medial prefrontal regions are known to be sites where glucocorticoids exert negative feedback regulatory control over hypothalamic–pituitary–adrenal (HPA) axis function. Recent animal studies focusing on the medial PFC have demonstrated that the right hemisphere is especially important in the activation of both autonomic and neuroendocrine responses to stress and that lesions of right but not left medial PFC result in an anxiolytic behavioural profile (Sullivan & Gratton, 1999, 2002). These studies also suggest that excessive neuronal activity of right medial PFC leads to an increased vulnerability to the pathological effects of stress.

The central BZ receptor site is part of the GABA-A receptor complex and activation of the BZ site facilitates GABAergic inhibition. As such, increased right-sided BZ binding in key stress-regulating structures may have a net effect of allowing more efficient inhibition of neural and behavioural responses to stressful situations. While the above studies focused on medial PFC, a similar situation may exist in hippocampus which projects heavily to (and has close functional relationships with) medial PFC. Moreover, a recent study has shown that an early handling procedure (exposure to novelty) very similar to the present one, induces a permanent enhancement in hippocampal volume specific to the right hippocampus (Verstynen, Tierney, Urbanski, & Tang, 2001) and that the same early manipulation confers an enhanced sensitivity to the effects of glucocorticoids on neuronal function in the right hippocampus compared to the left (Tang, personal communication).

It is suggested that an increase in inhibitory tone in key right brain limbic and cortical regions conferred by early handling, renders such animals better equipped to prevent excessive right brain activity, otherwise leading to heightened emotionality and stress reactivity. Such findings further support the contention that disorders of emotion involving hyperfunctional stress-regulatory systems (namely depression and anxiety) are associated with a relative excess of right prefrontal and associated limbic activity (for review, see Sullivan & Gratton, 2002).

Acknowledgments

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33. States of awareness associated with memory for emotional and neutral pictures in older and younger adults

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The present study used the remember/know/guess paradigm to investigate age differences in states of awareness associated with recognition memory for emotional and neutral pictures. Both younger and older adults reported more "remember" responses for negative than for neutral pictures. Positive pictures were associated with more "remember" responses than neutral pictures in younger, but not in older, adults. In addition, older adults reported less "remember" responses than younger adults for emotional (positive and negative), but not for neutral, pictures. These findings suggest that the tendency of emotional stimuli to create rich recollective experience is weakened in older adults. Several findings suggest that rich recollections of past events (as reported by "remember" responses) tend to occur less often in older than in younger adults (see Gardiner & Richardson-Klavehn, 2000 for a review). This has been demonstrated for neutral but not for emotional stimuli. Yet, recent findings indicate that emotional stimuli tend to be richly re-experienced in memory more often than neutral ones in younger adults (Ochsner, 2000). It may be that the modulating effect of emotion on recollective experience is preserved in older adults and that memory deficits associated with ageing are less pronounced for emotional than for neutral stimuli. Alternatively, emotional stimuli could make older adults focus on their feelings rather than on the perceptual details of the stimuli (Hashtroudi, Johnson, Vnek, & Ferguson, 1994) and this may impair recollection. The purpose of the present study was to examine these propositions by investigating states of awareness associated with memory for positive, negative, and neutral pictures in older and younger adults.

Methods

Subjects

Subjects were 20 older adults (M age = 64.5, $SD = 2.4$, range = 60–68) and 20 younger adults (M age = 22, $SD = 2.1$, range = 18–25).

Materials

The stimuli consisted of 40 positive, 40 negative, and 40 neutral photos from the IAPS (Lang, Greenwald, Bradley, & Hamm, 1993). These photos were divided in two sets (A and B) of 60 photos (20 positive, 20 negative, and 20 neutral). The use of sets A and B as studied or nonstudied items was counterbalanced across participants. Stimuli were placed in a pseudorandom but fixed order such that no more than two photos with the same valence occurred in succession. To counterbalance for order effects, the photos were presented in one order for half the subjects and in the reverse order for the other half. Also, 10 filler items were placed at the beginning and end of the list. For the recognition test, the 120 photos of sets A and B were presented in a pseudorandom but fixed order such that no more than two "old" or "new" photos occurred in succession. The photos were presented in one order for half the subjects and in the reverse order for the other half.

Procedure

Subjects were asked to rate the photos on seven-point scales along each of three dimensions: valence (1, very negative; 4, neutral; 7, very positive), arousal (1, very weak; 4, moderate, 7, very strong), and visual complexity (1, not at all complex, 4, moderately, 7, very complex). The photos were presented on a computer screen approximately 60 cm in front of them. On each trial, a fixation cross appeared in the center of the screen for 750 ms. After a 500 ms pause, a photo appeared on the screen for 2 s. When it disappeared, the rating scales for valence, arousal, and visual complexity appeared successively. Subjects made each rating in this order and the next trial began as soon as the last rating had been completed.

Two weeks later, subjects were presented with an unexpected recognition test. For each photo, they had to decide whether they had seen it during the rating session. Furthermore, they had to report whether their recognition was of the remember (R), the know (K) or the guess (G) variety (Gardiner & Richardson-Klavehn, 2000). Briefly, they were told that an R response should be given to any picture which, at the time it was recognized, brought back to mind something they had consciously experienced at the time it was presented. In contrast, they were asked to make a K response if the photo felt familiar but they were unable to recollect details of its prior exposure. Finally, they were asked to make a G response if they were unsure whether or not the photo had been presented in the study phase.

Results

To allow analysis of R, K, and G responses as a function of valence, we classified the pictures according to the ratings of valence subjects had made during encoding. The third of the pictures with the highest mean ratings were classified as positive, the third of the pictures with the lowest mean ratings were classified as negative, and the third of the pictures with ratings in between were classified as neutral. The mean proportions of R, K, and G responses as a function of valence and age are presented in Table 1.

Separate age (old vs. young) × valence (negative, neutral, and positive) analyses of variance (ANOVAs) were performed on R, K, and G responses. For R responses, the ANOVA revealed a main effect of age, $F(1, 38) = 22.63$, $p < .001$, a main effect of valence, $F(2, 76) = 73.36$, $p < .001$, and an age × valence interaction, $F(2, 76) = 21.05$, $p < .001$. Planned comparisons indicated that both younger and older adults made more R responses to negative than to both positive and neutral pictures (all ps $< .05$). In contrast, positive photos received more R responses than neutral ones in younger ($p < .001$) but not in older adults ($p = .10$). Further comparisons indicated that younger adults made more R responses than older adults for both negative ($p < .001$) and positive ($p < .01$) pictures, but not for neutral ones ($p = .19$).

The ANOVA performed on K responses demonstrated an effect of valence, $F(2, 76) = 33.71$, $p < .001$, and an age × valence interaction, $F(2, 76) = 4.82$, $p < .05$. In both younger and older adults, neutral and positive pictures received more K responses than negative pictures (all ps $< .05$). In contrast, neutral pictures received more K responses than positive ones in younger ($p < .01$) but not in older adults ($p = .26$). Further comparisons revealed that older adults made more K responses than younger adults for negative photos ($p < .05$), but not for positive and neutral photos (ps $> .07$). Finally, there was an effect of valence on G responses, $F(2, 76) = 14.71$, $p < .001$, but no age × valence interaction, $F(2, 76) = 1.66$, $p < .20$.

Table 1
Mean proportions of R, K, and G responses as a function of valence and age

		Young			Old		
		Negative	Neutral	Positive	Negative	Neutral	Positive
R	Hits	.74	.32	.47	.38	.25	.30
	FAs	.01	.01	.02	.05	.01	.03
K	Hits	.11	.35	.26	.19	.30	.26
	FAs	.03	.02	.05	.08	.05	.08
G	Hits	.04	.13	.10	.07	.11	.11
	FAs	.06	.04	.06	.07	.08	.08

Discussion

The results of the present study show that the effect of emotion on recollection is modulated by age differences. Consistent with a previous study (Ochsner, 2000), positive and negative pictures were richly recollected more often than neutral ones in younger adults. In contrast, older adults reported more R responses for negative but not for positive pictures. Furthermore, they reported less R responses than younger adults for emotional but not for neutral pictures. This is somewhat surprising given that age is generally associated with a decrease in R responses. However, Perfect, Williams, and Anderton-Brown (1995) found that the decrease in R responses in older adults disappeared when elaborative encoding was encouraged. The instructions we used in the present study encouraged such a detailed encoding by drawing attention to various aspects of the stimuli (their visual complexity, valence, and intensity) and this could explain the absence of age differences in the recollection of neutral stimuli. In contrast, older adults had a deficit in recollective experience for emotional stimuli. Despite the instructions which tried to draw attention to both emotional and perceptual details of the stimuli, it may be that, when confronted with emotional stimuli, older adults tend to focus on their feelings to a greater extent than younger adults. In consequence, less resources would be available to encode perceptual and contextual details of the stimuli and hence rich recollections would be less likely to occur. Future studies will be needed to examine this proposition.

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34. Coactivation of the amygdala and hippocampus predicts better recall for emotional than for neutral pictures

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Emotional events tend to be better remembered than nonemotional events. This memory-enhancing effect of emotion has been attributed to a modulatory influence of the amygdala on the hippocampus during encoding and consolidation (*modulation hypothesis*). We investigated this hypothesis using event-related fMRI. During scanning, subjects encoded pleasant, unpleasant, and neutral pictures under incidental learning conditions, and after scanning, they recalled details of the pictures. Confirming the memory-enhancing effect of emotion, emotional pictures were better recalled than neutral pictures. Compared to neutral pictures, encoding of emotional pictures was associated with activations in several regions, including amygdalar, anterior cingulate, parietal, and occipitotemporal regions. In the case of pictures that were subsequently remembered, emotional pictures were associated with greater activity in both the amygdala and the hippocampus than neutral pictures. These results are consistent with the modulation hypothesis, and shed light on the neural mechanisms of the memory-enhancing effect of emotion.

Report

Emotionally charged events tend to be better remembered than nonemotional events. This difference has been attributed to a modulatory effect of the amygdala on the hippocampus during memory encoding and consolidation (*modulation hypothesis*, e.g., McGaugh, 2000). This hypothesis is based mainly on animal evidence, but some functional neuroimaging evidence with humans is also available (Hamann, 2001). Here, we explore the neural mechanisms underlying the formation of emotional memory using event-related fMRI.

We measured two effects: the *emotion effect* and the *subsequent memory effect*. The *emotion effect* refers to brain activity that is greater for emotional than for neutral stimuli. Previous functional neuroimaging studies have identified emotion effects in several regions including the amygdala, prefrontal cortex, anterior cingulate, posterior parietal, and insula (Davidson & Irwin, 1999). The *subsequent memory effect* refers to encoding activity that is greater for items that are subsequently remembered than for items that are subsequently forgotten. Previous event-related fMRI studies have identified subsequent memory effects in hippocampal and prefrontal regions (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998). On the basis of emotion and subsequent memory effects we investigated two issues.

1. *Co-activation of the amygdala and hippocampus during emotional encoding*. Previous neuroimaging studies have reported that amygdalar activity was correlated with the number of subsequently remembered emotional items (for a review, see Hamann, 2001). However, the modulation hypothesis assumes not only an amygdalar activation, but also an effect of the amygdala on the hippocampus, and therefore it predicts that both the amygdala and the hippocampus are involved in emotional encoding. To investigate this issue,

we compared activity in these regions for subsequently remembered emotional and subsequently remembered neutral pictures, using event-related fMRI.

2. *The role of the amygdala in the processing of pleasant stimuli.* Neuroimaging studies of emotion have strongly associated the amygdala with the processing of unpleasant stimuli, but it is less clear how this region is involved in the processing of pleasant stimuli (Davidson & Irwin, 1999). To investigate this issue, we measured amygdalar activity during the processing of pleasant and unpleasant pictures.

Methods

Participants

Fourteen young (mean age = 24.3 years) healthy right-handed female Duke University students/staff participated in this study. All subjects gave informed consent to a protocol approved by the Duke University Institutional Review Board. Female participants were chosen because previous studies using similar stimuli have found that women are more physiologically reactive to emotional stimuli, and because women are more likely to report intense emotional experiences.

Materials

Stimuli consisted of a pool of 180 pictures selected mainly from the International Affective Picture System (IAPS) and complemented with additional neutral pictures equated for complexity and human presence. IAPS pictures are rated on a nine-point scale both in terms of emotional arousal (1, calm and 9, excited) and emotional valence (1, unpleasant; 5, neutral; 9, pleasant). Based on these scores, we selected 60 high-arousing and pleasant, 60 high-arousing and unpleasant, and 60 low-arousing and neutral pictures. The pleasant and unpleasant pictures differed from each other in terms of emotional valence, but not in terms of emotional arousal, whereas both pleasant and unpleasant pictures differed from neutral pictures in terms of both arousal and valence.

Behavioral methods

Similar to the procedure we employed in a previous event-related potential (ERP) study (Dolcos & Cabeza, submitted), subjects completed six consecutive study blocks of 30 pictures each (10 pleasant, 10 unpleasant, and 10 neutral), randomly presented using an LCD projector. Pictures were presented for 3 s, and followed by a 12-s fixation. Participants were instructed to rate the pictures for pleasantness, using a three-point scale (1, unpleasant; 2, neutral; 3, pleasant). No subsequent memory test was mentioned during encoding, so that learning was incidental. Following the scanning session, subjects performed a 45 min cued-recall test, in which they were provided with a written cue for each of the pictures, and had to describe in writing as many details as they could remember. Subjects were asked to provide enough details so that an outsider could identify each picture and discriminate it from similar studied pictures. Only pictures whose description was detailed enough to allow both identification and discrimination were classified as remembered.

fMRI methods

Anatomical scanning. Thirty-four axial high-resolution T1-weighted structural images were acquired with a 450-ms TR (repetition time), a 9-ms TE (echo time), a 24-cm FOV (field of view), a 256^2 matrix, and a slice thickness of 3.75 mm. Forty-six coronal T1-weighted images were then acquired using the same imaging parameters.

Functional scanning

Thirty-four contiguous gradient-echo echoplanar axial images (EPIs) sensitive to blood-oxygen level dependent contrast were acquired using the same slice prescription described above for the near-axial structural images. The EPIs were acquired as follows: TR = 3 s, TE = 40 ms, one radio frequency excitation, FOV = 24 cm, image matrix = 64^2, and flip angle (FA) = 90°. Slice thickness was 3.75 mm, resulting in cubic 3.75-mm^3 isotropic voxels.

Image preprocessing

All image preprocessing and statistical analyses were performed using SPM99. Functional images were corrected for acquisition order, and realigned to correct for motion artifacts. Anatomical images were coregistered with the first functional images for each subject, and both anatomical and functional images were spatially normalized to a standard stereotactic space. Functional images were spatially smoothed using an 8-mm isotropic Gaussian kernel.

Statistical analyses. For each subject, task-related activity was identified by a convolving vector of the onset times of the stimuli with a synthetic hemodynamic response and its temporal derivative. The general linear model, as implemented in SPM, was used to model the effects of interest. Group analyses were conducted using random-effects models, as follows. To identify brain areas involved in emotional processing, we compared brain activity for pleasant, unpleasant, and neutral pictures (emotion effect). To reveal brain regions involved in successful encoding operations, we compared brain activity for subsequently remembered and subsequently forgotten pictures (subsequent memory effect). The significance threshold was set at $p < .001$, uncorrected ($t > 3.85$). Additionally, ANOVAs were performed on percent signal change measures extracted from regions of interest (ROIs) drawn on amygdala and hippocampus using custom software from the Brain Imaging and Analysis Center of Duke University.

Results

Behavioral results

As expected, recall was better for emotional pictures (pleasant: 54%, unpleasant: 54%) than for neutral pictures (40%). An ANOVA yielded a significant picture type effect ($F(2, 13) = 73.07, p < .0001$), and post-hoc contrasts indicated that recall of pleasant and unpleasant pictures was similar ($p > .05$) and higher than recall of neutral pictures (both $p < .001$).

fMRI results

Emotion effect

Compared to neutral pictures, emotional pictures (pleasant and unpleasant) were associated with activations in several regions including amygdalar, anterior cingulate, lateral parietal, precuneus, and occipitotemporal regions (see Fig. 1A). The amygdala was activated by both unpleasant and pleasant pictures, and in the right amygdala activity was greater for unpleasant than for pleasant pictures (see Fig. 1B).

Subsequent memory effect

Compared to forgotten pictures, remembered pictures were associated with activations in hippocampal, prefrontal, temporal, and occipital regions. Compared to remembered neutral pictures, remembered emotional pictures elicited greater activity in both the amygdala and the hippocampus (see Figs. 1C and D).

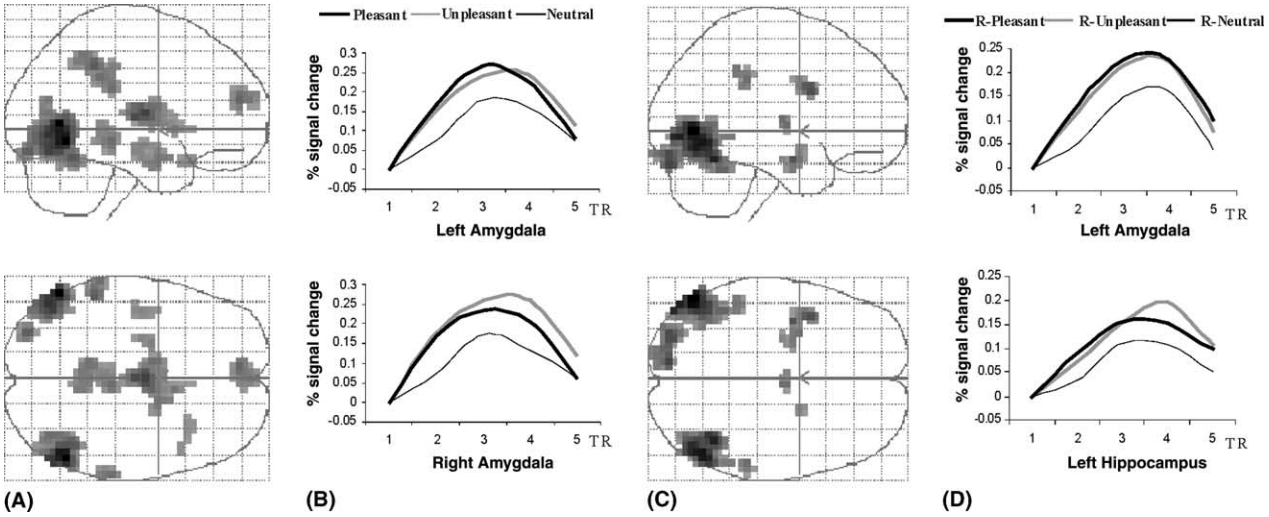

Fig. 1. (A) Regions more active for emotional than for neutral pictures. (B) Percent signal change in the amygdala. (C) Regions more active for remembered emotional than for remembered neutral pictures. (D) Percent signal change in the amygdala and hippocampus. Activations are displayed at $p < .005$, uncorrected. R, remembered; TR, repetition time.

Discussion

The main result of the study was the finding that both the amygdala and the hippocampus were more activated for remembered emotional than for remembered neutral pictures. This finding provides strong support for the modulation hypothesis. Neural activity of these two structures paralleled the difference in memory performance, which was greater for emotional than for neutral pictures. These results suggest that emotional stimuli exert their beneficial effect on memory performance by enhancing activity in the medial–temporal lobe system.

A second finding of the present study is that, when the emotional stimuli are equated for arousal, the amygdala is involved in the processing of both positive and negative emotions. At the same time, the finding that the right amygdala was more activated for unpleasant that for pleasant pictures is consistent with evidence suggesting that the amygdala is particularly sensitive to negative emotions (Davidson & Irwin, 1999). Thus, the present results suggest that the amygdala is involved in the processing of both positive and negative emotions, and that the right amygdala may have some preference for negative emotions.

Acknowledgments

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35. Effect of divided attention on the memory benefit for negative as compared to neutral words

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Individuals are better able to remember in rich detail (“recollect”) negative as compared to neutral stimuli. No studies have addressed whether divided attention alters this benefit. We examined the effect of divided attention on memory for negative versus neutral words. Divided attention at encoding reduced the ability to recollect negative words (Experiments 1 and 2) and to remember source information (Experiment 3); divided attention at retrieval had no effect. Even with divided attention at encoding, however, memory for negative words was better than for neutral words. Automatic and attention-demanding processes at encoding may contribute to the memory benefit for negative items.

Report

Background and motivation

Declarative memory is typically better for negative than neutral stimuli. This benefit may result from an increased ability to remember, in rich detail, negative as compared to neutral stimuli. Thus, Ochsner (2000) found that negative stimuli are better recollected (i.e., participants feel they are re-experiencing the item when they encounter it on a recognition test) than neutral stimuli. Similarly, Doerksen and Shimamura (2001) found that individuals remember more “source” information (i.e., contextual details of an item’s presentation) for negative than neutral words.

No study has investigated whether processes at encoding or retrieval contribute to this enhanced memory for negative as compared to neutral items. Nor has any study addressed whether automatic or intentional processes at encoding enhance recollection of negative stimuli. Automatic (non-conscious) orienting toward emotional items (Williams, Mathews, & Spencer, 1996), or intentional semantic or autobiographical elaboration (Doerksen & Shimamura, 2001; Phelps, Labar, & Spencer, 1997) could contribute to the recollective enhancement effect.

Divided attention, particularly at encoding, reduces subsequent memory for emotionally neutral items. Specifically, it reduces the ability to recognize words based on detailed recollections, while leaving relatively intact the ability to recognize items based on more automatic assessments of familiarity. To date, no studies have examined whether this effect of divided attention extends to emotionally negative items.

Present study

We report results of three behavioral experiments examining how attentional modulation affects memory for negative and neutral words. We asked whether the recollective enhancement for negative items was affected by adding a distractor task at encoding or retrieval, and whether the two manipulations had an additive effect. The divided attention manipulation also allowed us to investigate whether automatic processes (not disrupted by divided attention) contribute to the enhancement effect.

Experiment 1

Methods

At encoding, 18 participants (ages 18–30) saw either negative or neutral words (matched for word frequency, familiarity, and imageability), which they rated as highly negative, somewhat negative, or neutral. Participants concurrently performed either an "easy" auditory discrimination task (i.e., two rhythmic patterns were clearly distinct and easy to discriminate) or a "hard" task (i.e., two rhythmic patterns were similar and difficult to discriminate); they were asked to press a button every time the pattern changed. Encoding was performed in 30-s blocks, and participants were informed before each block whether the auditory discrimination would be easy or hard. At retrieval, participants saw previously presented words and an equal number of new words. They were asked to indicate whether they "remembered" the word from the list (had a detailed recollection or feeling of re-experience), "knew" the word was on the list (without specific recollection), or believed the word to be "new" (not presented). While retrieving words, they performed the easy or hard discrimination task, as during encoding.

Results and conclusions

Negative items were associated with more "remember" responses and "recollective" responses (computed following Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998) than neutral items in the "easy" encoding and retrieval condition (t test, $p < .01$). This result with words, together with the results of Ochsner (2000) with pictures, suggests that the recollective benefit for negative information is present across stimulus types.

During encoding, reaction times to the rhythmic pattern changes were slower when they occurred during the presentation of a negative as compared to a neutral word (t test, $p < .05$). In studies using only negative words, others have reported slowing of the secondary task at retrieval compared to encoding. Researchers have taken this slowing as evidence that retrieval requires obligatory processes that cannot be switched to the secondary task. Following this logic, we suggest that the slower reaction times to the change in rhythmic pattern that occurred during encoding of negative words may signify obligatory processes (perhaps automatic orienting toward negative stimuli) that do not occur with neutral stimuli.

Although this reaction time difference contributes to our understanding of the types of processes that occur when encoding negative as compared to neutral stimuli, the confound between reaction time and stimulus valence prevented a direct comparison of the effect of divided attention on negative as compared to neutral stimuli.

Experiment 2

Methods

The 18 participants (ages 18–30) were shown neutral and negative words, randomly intermixed, and were asked to rate each as "abstract" or "concrete." They were told that it was important to pay attention to the auditory task, and to press a button whenever the pattern changed. Other encoding and retrieval methods were identical to Experiment 1.

Results and conclusions

Reaction times were similar for neutral and negative words, allowing comparison of the effects of divided attention. Participants who encoded and retrieved words with the easy distractor task responded "remember" or "recollected" (Yonelinas et al., 1998) a significantly greater proportion of negative than neutral items ($p < .05$, Fig. 1). This effect became a trend ($p < .10$) when items were encoded with the difficult distractor task. Retrieving words with the hard versus the easy distractor task did

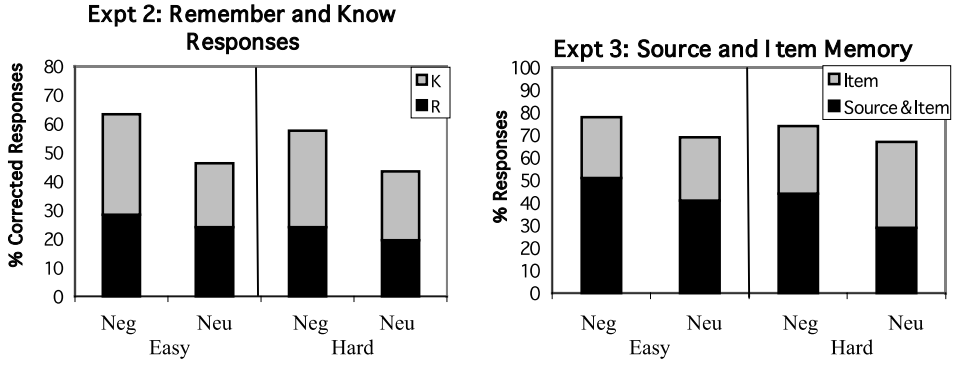

Fig. 1. Encoding words with the hard versus the easy discrimination task (collapsing across retrieval condition, top) reduced the ability to recollect negative and neutral stimuli. It also disrupted memory for source information (bottom). It did not, however, eliminate the memory benefits for negative as compared to neutral items.

not affect performance, regardless of the encoding condition. Anova conducted for "r" or "recollection" responses indicated a significant effect of the easy versus the hard condition (fewer "r" or "recollection" responses with divided attention at encoding, $p < .05$), an effect of valence (more "r" or "recollection" responses for negative words, $p < .05$), but no interaction between condition and valence. Corrected recognition (hits—false alarms) was greater for the negative than neutral stimuli in all conditions ($p < .01$). Anova indicated a significant effect of valence (better memory for negative than neutral stimuli, $p < .01$), condition (poorer memory in hard encoding conditions, $p < .01$), and no interaction between valence and condition.

Modulating attention at encoding impacts memory for negative and neutral words, but does not diminish the overall memory benefit for negative as compared to neutral stimuli. It also does not eliminate the recollective benefit for negative stimuli.

Experiment 3

Methods

This experiment used a "source memory" paradigm: the 18 participants (ages 18–30) saw words presented in blue or red ink (half of the words were negative, half were neutral) and rated each as "abstract" or "concrete". Attention manipulations were identical to experiment 1. Participants then took a recognition test (with no distractor task) in which they (a) indicated whether a word was "old" or "new," and (b) for words rated "old," decided whether the word had been written in red or blue ink.

Results and conclusions

Consistent with Doerksen and Shimamura (2001), in the easy encoding condition, participants showed a source memory benefit for the negative as compared to the neutral words ($p < .01$). This benefit remained when words were encoded with the difficult distractor task ($p < .01$). Anova computed either for overall memory (source or item) or source memory indicated main effects of valence (negative, neutral, $p < .01$), and encoding condition (easy, hard, $p < .01$), but no valence by condition interaction.

Encoding words with the hard versus the easy distractor task reduced the ability to remember source information for negative and neutral items. It did not, however, diminish the memory benefit for negative as compared to neutral items.

General conclusions

The results from three experiments clarify (a) whether processes at encoding or retrieval enhance memory for negative stimuli, and (b) whether the memory benefit for negative items results from automatic or attention-demanding processes.

Divided attention at encoding reduced recollection, or source memory, for negative and neutral items; divided attention at retrieval did not. Attention-demanding encoding processes appear critical to memory formation for negative and neutral stimuli. These processes could include semantic (reliant on left inferior prefrontal regions), or autobiographical elaboration (recruits posterior cingulate and orbitomedial frontal regions). Modulation of attention may reduce the processing that occurs in these brain regions.

Despite this overall effect of divided attention at encoding on memory for negative stimuli, attention modulation did not eliminate the memory benefit for negative stimuli. Recognition (summing "remember" and "know," or "source" and "item" scores), recollection, and source memory were better for negative than neutral stimuli, even with divided attention. There may be obligatory, or relatively automatic processes, that occur during the encoding of negative stimuli. Such processes could include amygdaloid modulation of lower-level perceptual areas. Amygdaloid modulation of higher-level regions (e.g., hippocampal formation, prefrontal cortices) may also lead to better memory for negative stimuli, even in instances where attentional resources are taxed.

These results suggest that in everyday life, we may be less likely to remember an emotional event vividly if our attention is diverted. Nonetheless, given the same attention-demanding situation, we may be better able to recall emotional than neutral events.

Dividing the attention of young adults can equate their performance with older adults in a full attention condition. Normal aging and divided attention in young adults may therefore have similar effects on memory enhancement for emotional stimuli. Consistent with this view, other data from our laboratory suggest that although older adults show poorer memory than young adults (in full attention conditions), their memory enhancement and recollective benefit for negative stimuli are comparable in magnitude to the effects seen in young adults.

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36. Autobiographical episodic re-experiencing: A prospective fMRI study

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Participants prospectively created a pool of everyday autobiographical episodes by keeping an audio-journal over a 6–8 month period. They were later presented with a random sample of these recordings while being scanned with fMRI. This paradigm provided a higher degree of experimental control than is typical for studies of autobiographical memory. The recordings evoked a strong feeling of autobiographical episodic re-experiencing. This conscious state was associated with a left-lateralized network of medial frontal, ventrolateral frontal, lateral temporal, retrosplenial, and anterior thalamic activations. This pattern was observed when contrasted with conditions controlling for the impersonal narrative aspects of the recordings and undated self-referential information. It therefore indicates the neural correlates of autobiographical mental time travel, a state of consciousness unique to humans.

Report

Withdrawn.

37. Memory for emotional and everyday events: The role of noradrenaline and cortisol

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Studies report enhanced memory for traumatic events, but not for neutral information concerning the event. This was attributed to noradrenaline elevation in the brain during trauma. Following emotions, however, noradrenaline *and* cortisol are secreted. Significantly increased, or decreased, cortisol levels were showed to impair memory for neutral events. We attempted to determine the role played by noradrenaline and cortisol while negative and neutral information were memorized. Memory was measured while blocking noradrenergic receptors and inhibiting cortisol's secretion. Men received placebo ($n = 11$), propranolol ($n = 10$; blocker of noradrenergic receptors), or metyrapone ($n = 10$; inhibitor of cortisol's secretion). Two neutral and one emotional segment composed the story viewed. Propranolol did not impair memory for emotional and neutral information, while metyrapone affected memory for neutral and emotional segments, but more for neutral than emotional information.

Report

September 11th attacks will be engraved on people's memory for a very long time. This flashbulb memory phenomena is defined as the vivid recollection one has of striking events because of the high level of surprise and emotional arousal these events create (for a review, see Lupien & Brière, 2000). Studies demonstrated that witnesses to violent crimes have enhanced memory for the traumatic event, i.e., Assailant, weapon, but not for the neutral information concerning the event, e.g. The surroundings (see Lupien & Brière, 2000). Flashbulb memories have been attributed to noradrenaline elevations in the brain during the negative experience. Central noradrenaline has been shown to sustain attention, which elaborates encoding and enhances recall of traumatic events (Cahill, Prins, Weber, & Mcgaugh, 1994). Proving the importance of noradrenaline in memorizing negative events, Cahill et al. (1994) demonstrated, in humans, that blockade of peripheral and central β-adrenergic receptors during the encoding of a negative story inhibited the enhanced memory for negative information without affecting memory for neutral information.

Following traumatic events, however, not only is there secretion of catecholamines, but there is also cortisol secretion (Lupien & Brière, 2000). High cortisol levels have been associated with memory deficits for neutral information in humans (Lupien & Brière, 2000). Recently, Lupien et al. (in press) demonstrated that decreasing cortisol levels with metyrapone, an inhibitor of cortisol's synthesis, also impairs recall for neutral information in humans. Significantly increased or decreased circulating levels of cortisol therefore seem to prevent the successful memorizing of neutral events. No study ever measured the impact of cortisol on memory for negative events.

A paradox thus persists in psychoneuroendocrine research as to the specific role of noradrenaline and cortisol in enhancing or decreasing memory for emotional and neutral events. We attempted to determine the specific role played by these two hormones during the memorization of negative and neutral information, memory was measured while blocking noradrenergic receptors in one condition, and while inhibiting cortisol secretion in the other. We hypothesized that blocking peripheral and central β-adrenergic receptors would impair memory for negative information, but not for neutral information. On the other hand, inhibiting cortisol secretion would impair memory for neutral information, but not for emotional information.

Methods

Thirty-one men, university students aged between 18–35 years, participated in the study. Participants were submitted to physical and psychological examinations, and routine laboratory screening. Participants had no medical problems, no medication use, no abnormalities on laboratory test and no active or life-time history of psychiatric disorders (dsm-iv criteria). Subjects were randomly distributed in a placebo group ($n = 11$), a 40 mg propranolol group ($n = 10$; blocker of β-noradrenergic receptors), or a 750 mg metyrapone group ($n = 10$; inhibitor of cortisol secretion). Groups did not differ with respect to age, body mass index and education level (all $ps > .1$).

An incidental memory task, developed according to the memory test used by Cahill et al. (1994), was administered. Subjects watched a 11-slides story presented on a computer screen. The first 4 slides constituted phase 1 of the story and presented neutral information. Phase 2 (slides 5–8) presented negative information and phase 3 (slides 9–11) presented neutral information. Narratives accompanying phases 1 and 3 were neutral, while narratives accompanying phase 2 were emotionally negative. After viewing the story, subjects rated how emotional they thought the story was on a scale of 0 = not emotional to 10 = very emotional. Delayed recall of the story occurred one week later.

During the protocol, baseline blood samples were taken at 6:20 a.m. and 6:40 a.m. the metyrapone group received a first dose at 6:45 a.m. the placebo and propranolol groups were given placebo pills at 6:45 a.m. at 9:45 a.m., pulse and blood pressure were taken and the placebo group received a placebo, while the medication groups received their respective drugs. propranolol was administered once, compared to metyrapone, because only one dose of propranolol is needed to block β-adrenergic cell receptors (Cahill et al., 1994), while two doses of metyrapone are needed to inhibit cortisol secretion (Lupien et al., in press). at 10:00 a.m., subjects had breakfast and at 10:20 and 10:45 a.m., blood samples were collected at 10:45 a.m., one hour after propranolol was administered, measures of pulse and blood pressure were taken and subjects viewed the story. cardiac activity was measured at 9:45 and 10:45 a.m. because propranolol should, one hour after its administration at 9:45 a.m. (Cahill et al., 1994), decrease pulse and blood pressure, which are regulated through peripheral β-adrenergic cell receptors. at 10:55 a.m., a last blood sample was collected. blood samples were taken to measure cortisol levels and ensure that metyrapone inhibited cortisol secretion. cortisol was analyzed by radioimmunoassay kit (medicorp, Canada).

Results

Physiological data

Percent change was calculated between 9:45 and 10:45 a.m. timepoints for pulse and blood pressure. the anovas revealed no significant impact of treatment on pulse and blood pressure (all $ps > .1$). the anova performed on cortisol levels revealed a significant interaction between treatment and sample ($f(8, 112) = 8.30$, $p < .0001$). simple effects performed on this interaction revealed that cortisol levels varied significantly across samples in the placebo and metyrapone groups, but not in the propranolol group ($fs(4, 112) > 3.75$, $ps < .006$). tuckey mean comparisons showed that cortisol levels significantly decreased after metyrapone treatment (samples 10:20, 10:45, 10:55), when compared to baseline. in the placebo group, cortisol levels increased from the 6:40 to the 10:45 and 10:55 samples, possibly due to the administration of breakfast at 10:00 a.m. propranolol had no effect on cortisol levels (all $ps < .05$).

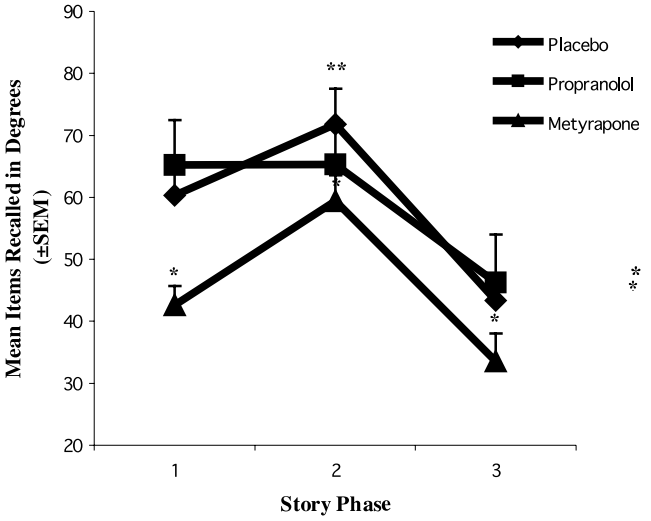

Fig. 1. Mean ($\pm SEM$) items recalled per phase for all three groups. *, Significantly different from the placebo group, $p < .04$. **, Significantly different than phases 1 and 3, $p < .02$.

Cognitive data

Fig. 1 presents memory performance for all three groups memory test results demonstrated a significant main effect of treatment ($f(2, 28) = 3,\ 13,\ p < .05$). planned comparisons revealed that the metyrapone group recalled significantly less emotional and neutral information than the placebo group ($p < .04$). However, the propranolol group recalled as many emotional and neutral information as the placebo group ($p > .1$). We also found a significant main effect of story phase ($f(2, 56) = 24.65$, $p < .0001$) as shown in Fig. 1, all groups recalled significantly more emotional information (phase 2) than neutral information (tuckey, $p < .02$). Finally, ratings of emotional reactions to the story did not differ between groups ($f(2, 28) = .48$, $p > .1$), and all subjects found the story emotionally negative.

Discussion

The results of this study showed that propranolol does not impair memory for emotional information, which suggests that emotional memory does not solely rely on noradrenaline secretion in contrast, a marked diminution in cortisol levels in the metyrapone group decreased memory performance when compared to the placebo group interestingly, metyrapone affected memory for both emotional and neutral information, but more so for neutral than emotional information.

As expected, metyrapone was efficient in lowering cortisol levels, without affecting pulse and blood pressure. propranolol had no impact on cortisol, neither did it yield the expected decrease in cardiac activity an hour after its administration. The absence of propranolol's effects on cardiac variables was surprising since we used a similar pharmacological dose, 40 mg, as Cahill et al. (1994). but this absence of a significantly decreased cardiac activity could be explained by the fact that pulse and blood pressure only vary by 10% under the influence of low dosages of β-blockers (Giudicelli & Witchitz, 1988).

Memory test results showed that the propranolol group recalled as many emotional and neutral information than did the placebo group. These memory results diverge from those reported by Cahill et al. (1994), who showed diminished recall for emotional information relative to neutral information of a negative story after the administration of propranolol. The absence of women in our sample, compared to Cahill et al. (1994), who had more women than men in their groups, could explain the discrepant findings obtained. Estrogen enhances noradrenaline secretion (Giudicelli & Witchitz, 1988), so it is possible that women in the high estrogen phase of their menstrual cycle or using contraceptive pills could have contributed significantly to the increased emotionality effect on recall of the placebo group in Cahill's study. Also, propranolol blood concentrations are increased by contraceptive pills, thus optimizing the β-blocker's pharmacological action (Giudicelli & Witchitz, 1988). Women using contraceptive pills in the propranolol group could have contributed to the inhibitory effect of propranolol on emotional memory in Cahill's study.

Memory results for the metyrapone group demonstrate how important cortisol is for optimal cognitive abilities since a lack of cortisol impairs memory not only for neutral information, but also for emotional information. This suggests that cortisol may be implicated in memory for emotional information. Noradrenaline, however, would be related to the physiological activation felt during emotion, and not as much to the memorizing of the negative event. Our results offer an interesting parallel with post-traumatic stress disorder (ptsd) patients (Nutt, 2001). Cortisol levels of those patients are abnormally low, while their noradrenaline levels are significantly high. Ptsd patients show important attentional and memory deficits, and have difficulty processing efficiently emotional stimuli. The low cortisol levels found in ptsd patients have been associated to their inability in dealing with traumatic situations.

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38. Theory of mind deficits in nonverbal learning disability and the role of the right cerebral hemisphere

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We assessed five children on Theory of Mind, nonverbal abilities, and intellectual functioning tasks. Three of the children who were identified as having a Nonverbal Learning Disability (NLD) demonstrated impairment on higher order Theory of Mind (ToM) tasks and on nonverbal tasks even though their verbal skills were in the average to superior range. Results are discussed in terms of the relationship between nonverbal abilities, Central Drive for Coherence, and Theory of Mind, as well as the role of the right-cerebral hemisphere as one of the potential, common mediating structures for these functions.

Report

Individuals with Nonverbal Learning Disability (NLD) are hypothesized to have a right-hemisphere (RH) deficit and present with visual–spatial impairments, inability to appreciate humor, and difficulty assessing emotional states and social cause-and-effect relationships. There appears to be an association between the kind of social and cognitive impairments found in these individuals and those associated with theory of mind (TOM) impairment. TOM is the ability to attribute mental-states (intentions, beliefs, desires, and emotions) to oneself and

to others and to predict behavior accordingly. Researchers indicate that by age 4 or 5, children share with adults basic mental-state concepts and view people as mental beings who experience desires and beliefs.

Leslie (1987) suggests that TOM development is dependent upon the normal development of an innate mechanism, ''the TOM module,'' that underlies the cognitive ability of producing metarepresentations. Where primary representations are beliefs about the world, metarepresentations are secondary representations that are suspended from the world and embedded in relationships, such as think and pretend. As such, the social and communication problems evidenced NLD individuals may reflect an impairment in the ability for metarepresentation.

Rourke (1987) argues that impairments in intermodal-integration cause the socio-emotional problems seen in individuals with NLD. Frith and Happé (1994) refer to this as a deficit in ''central coherence,'' that is, an inability to integrate separate pieces of information into meaningful wholes. A weak drive-for-coherence may lead to deficits in TOM, which in turn, can cause the socio-emotional problems that lead to their social isolation, depression and increased risk for suicidal behavior. Research indicates that, RH damaged patients have difficulty with intermodal-integration, story integration, joke completion, pragmatics, interpersonal skills, and TOM (Siegal, Carrington, & Radel, 1996).

The present study aimed to examine ''TOM'' abilities in individuals with NLD to further the understanding of the nature of their psychosocial deficits. The following hypotheses were tested: (1) NLD children will show deficits in TOM even when their verbal IQ is average or above; (2) they will be less accurate on questions requiring mental-state attribution compared to control questions and vs. age-matched controls; (3) they will perform more poorly than controls on a set of higher-order ToM Strange-Stories even when they are able to pass control physical-stories.

Method

Participants

Five children (MA, JG, ED, ML, and JL) were included in the study. Three (MA, JG, and ED) were identified as having NLD, and two 6:11 year-olds were included as comparison participants (ML and JL), matched to the youngest NLD (MA) for age, sex, grade, and Full-Scale IQ.

Neuropsychological/academic results revealed that all NLD children were impaired on visual-spatial/nonverbal tasks (PIQ, WISC-III; JLO; TONI-3), scored significantly lower on arithmetic vs. reading (WRAT 3), and presented with average to high-average verbal skills (VIQ, WISC-III).

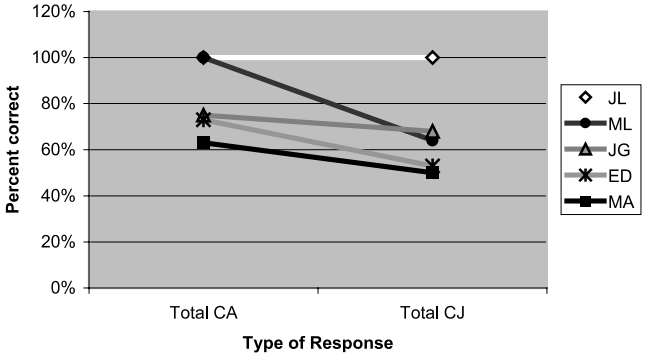

Fig. 1. Percentage of correct responses among the five participants to the ''Accuracy'' questions and the ''Justification'' questions of the higher-order strange-stories. *Note*: CA, correct ''Accuracy'' responses; CJ, correct ''Justification'' responses; JL, typical control (6:11 year-olds); ML, verbally impaired control (6:11 year-olds); JG, NLD (11:10 year-olds); ED, NLD (10:02 year-olds); MA, NLD (6:11 year-olds).

JG (oldest NLD, 11:10) was included in order to examine age as a contributing factor to the failure of NLD participants on TOM tasks. ED (DX: agenesis of corpus collosum) was specifically selected to examine Rourke's hypothesis regarding deficits ''accessing'' RH systems in NLD, providing a comparison involving a child with an NLD profile and known brain insult implicating the RH (see Fig. 1).

Control JL showed no discrepancy between his verbal and nonverbal abilities and scored within the average to high-average range on all measures. JL was included to provide representational data for a healthy same-age comparison.

ML was selected because of the discrepancy between his significantly lower VIQ and higher PIQ, to examine the relationship between verbal and nonverbal abilities and TOM. He also scored significantly higher on arithmetic than on reading. With lower verbal and reading abilities and preserved visual-spatial/nonverbal intelligence ML's cognitive profile was considered to be indicative of verbal impairment, and opposite to that of MA (NLD).

Materials

First-order TOM tasks

Included ''Smarties'' and ''Sally-Anne'' tasks, and required attribution of mental-states to oneself or to another, making ''first-order attributions'' (a mental-state about the state of the world). These tasks begin to be mastered by the age of four.

Second-order TOM tasks

Included ''Jenny's-Cookie'' and ''John's-Crayon'' tasks and required recursive thinking (the ability to understand that people have beliefs about others' beliefs). Participants had to predict a person's thoughts about another person's thoughts, making 'second-order attributions' and predict their behavior accordingly. This ability develops closer to age 6 or 7.

Both First- and Second-order tasks included Control, Belief, and Justification questions.

Higher-order strange-stories

Included 16 stories: ''Pretend,'' ''Lie,'' ''White-Lie,'' ''Figure-of-Speech,'' ''Joke,'' ''Persuade,'' ''Irony,'' and ''Double-Bluff,'' and required higher-order TOM abilities such as the ability to understand hidden emotions and motives, irony, and so on. The stories described simple social situations and involved understanding motivations for utterances that were not literally true and could be inferred using contextual information such as situational context and speaker's tone. The stories were unambiguous so that only one interpretation could be made and examined participants' ability to understand hidden intentions and emotions through understanding of jokes, lies, irony, and so on. Children are not expected to pass such tasks until the age of six or seven. Each story included two questions: Accuracy Question (is it true what the character says?), and Justification Question (why does she\he say that?).

Control physical-stories

Included four stories that did not involve any mental-states.

Results and discussion

All participants passed the First-order and all the physical-control tasks. Two of the three NLD participants, and the VI Control had

difficulty with the Second-order tasks. All NLD participants showed difficulty on both the Accuracy and the Justification questions of the Higher-order stories (Accuracy: 62–75%; Justification: 50–68%). The VI Control, however, showed difficulty only on the Justification questions (Accuracy: 100%; Justification 64%), while the typical Control passed all higher-order Accuracy and Justification questions (Accuracy: 100%; Justification 100%). Furthermore, all NLD participants failed both the Accuracy and the Justification part of the Irony Story, and, MA (youngest NLD) failed both the Accuracy and the Justification parts of the Joke, Double-Bluff, and the Irony stories.

Unlike the NLD children, both controls realized that the literal meaning of the speakers' utterances did not make sense and were able to utilize the contextual information to make accurate judgments about the accuracy of the utterances. NLD children, however, took most of the utterances to be literally true and utilized this false information to guide their judgement regarding the characters' true intention and motivation. For example, in a "Joke-story" where a boy tells her friend who has a huge dog "You don't have a dog you have an elephant", MA, (youngest NLD) said that the utterance was true and that the boy said this because "it was too big for a dog."

NLD participants attempted to explain the characters' intentions by attributing inappropriate mental-states to the characters. Their responses may be taken as context-inappropriate answers that fit the utterance in isolation but not in the story context given. NLD participants were unable to utilize the story context to first, make an accurate judgment about the accuracy of the utterance and, second, to attribute an appropriate mental-state to the story character which could be inconsistent with his/her overt behavior (utterance).

Results parallel previous findings that RH damaged individuals are capable of making inferences, but the inferences they make about social/emotional content do not apply in the particular context (Gardner, Brownell, Wapner, & Michelow, 1983). Researchers also suggest that the ability to contextualize the interpretation of an emotion may require sensitivity to the relationships among emotions which depends on spatial-organizational RH based strategies.

Frith and Happé (1994) argue that the fundamental problem in TOM impairment is a deficit in "central cohesion." They argue that information needs to be integrated in order to form correct interpretations of events. NLD Individuals who have poor RH resources may be unable to do this because they lack this central drive. The fact that NLD participants scored lower on the Accuracy questions and showed characteristically inappropriate mental-state justifications may suggest that a deficit in central coherence is a more universal/persistent impairment in NLD than the inability to attribute mental-states alone.

Conclusions

This study suggests that NLD children may have an intact system for accessing verbal information. Their success on first-order TOM and control tasks and their average or higher verbal IQ indicates an intact general language ability, semantic storage, and retrieval skills. Studies indicate that children's acquisition of language is fundamental to their TOM development. However, what may be important is not so much the acquisition of the meanings of words (semantics) or the ability to put words together in grammatically correct order (syntax), but the ability to 'use language' intentionally to communicate (pragmatics)—the way intentions of language users are coded and interpreted.

Poor RH resources may have impaired the NLD participants' ability to make the correct inferences in the more novel and complex situations characterizing some of the stories, including their ability to integrate and utilize contextual information. Results suggest that problems in the attribution of emotions and mental-states may not be solely related to verbal IQ, but also to nonverbal abilities and perhaps RH dysfunction.

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39. Patients with ventromedial prefrontal lesions show impaired affective theory of mind

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It has been previously suggested that deficits in theory of mind (ToM) may account for the aberrant behavior observed in patients with venromedial (VM) prefrontal damage. However, inconsistent results have been reported. The present study examined the hypothesis that patients with VM lesions are impaired in the *affective* rather than *cognitive* facets of ToM. The performance of patients with localized lesions in the VM was compared to that of control subjects. Three ToM tasks differing in the level of emotional processing involved were used: second-order false belief; understanding irony; 'faux pas.' The results indicated that patients with VM lesions were significantly impaired in irony and faux pas but not in second-order false belief, as compared to posterior patients and healthy controls.

Report

Withdrawn.

40. Do central dopaminergic systems intervene in human motivation and reward sensitivity?

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Parkinson's disease provides a good model to assess this hypothesis. Twenty-three PD patients were compared, in both the "on" and "off" states, to 28 controls, using: (1) an Apathy Scale; (2) Stimulus-Reward Learning, Reversal and Extinction tasks; and (3) a Gambling task. PD patients were mildly apathetic and impaired on Stimulus-Reward Learning and Reversal in both states. They progressed in the Gambling task during the first but not the second assessment, whatever the state. Only apathy was more severe in the "off" state. These results suggest (1) the implication of striato-frontal loops in human motivation and reward sensitivity, and (2) complex relationships between these affective factors and dopamine.

Report

Motivation is a conscious or unconscious factor, which incites the subject to act (Marin, 1990). It intervenes during all stages of behavioral planning: determination of aim, selection, and elaboration of responses and evaluation of consequences of action. Conversely, motivation and planning are influenced by the ability to identify the behavioral relevance and the reinforcing value of stimuli in the environment and to take into account the difference between the anticipated and the obtained reward. Motivation and sensitivity to reinforcement are therefore central processes for adaptive orientation of behavior.

The computation to adopt the appropriate behavior may be explicit when the rule is clear and the same reward is regularly associated with the same stimulus, as in Stimulus-Reward Learning. Rolls, Hornak, Wade, and McGrath (1994) created a laboratory task, where the reward contingencies may be unexpectedly reversed (Reversal) or extinguished (Extinction) when subjects have explicitly learned the stimulus-reward association. The ability to reverse the stimulus-reward-response association suggests a form of ''affective'' flexibility, whereas the ability to withhold a response is rather related to control of impulsiveness.

In real life, however, outcomes in terms of reward or punishment are more uncertain. Bechara, Damasio, Damasio, and Anderson (1994) designed a task, the so called Gambling task, which resembles the decisions made in real life. The task includes four decks of cards, two of them being disadvantageous (high gains and unpredictable higher penalties), whereas the other two are advantageous (small immediate gains and lower penalties). Normal subjects progressively learn to choose the advantageous decks. This behavior is largely implicit, since bias towards the selection of advantageous choices occurs before the subject becomes aware of the goodness or badness of his or her choice and a great proportion of normal controls does not reach awareness.

Animal studies implicate limbic structures (amygdala and orbitofrontal cortex) in motivation, reinforcement associated learning, ''affective'' flexibility and control of impulsiveness. The ventral striatum, which connects the limbic and frontal executive systems via the ''orbitofrontal'' and ''cingulate'' loops is also involved. In addition, the mesolimbic and the nigrostriatal dopaminergic systems, which modulate the activity of these loops, would intervene in signaling changes or errors in the prediction of rewarding events. In humans, reinforcement associated learning, ''affective'' flexibility and control of impulsiveness have been shown to be impaired by orbitofrontal lesions, whereas apathy or loss of motivation, in the absence of depression, has been observed in the case of lesions of the basal ganglia. Is apathy related to decreased sensitivity to reinforcement? Are the striato-frontal loops involved in reinforcement associated learning in humans? Does dopamine intervenes in affective flexibility? Parkinson's disease (PD), which alters the mesocorticolimbic dopaminergic system and consequently impairs the function of the ''orbitofrontal'' and ''cingulate'' loops, may help to answer these questions. Indeed, apathy has been observed in PD and might worsen the cognitive and behavioral difficulties of these patients.

The aims of the study were to investigate motivation and sensitivity to reinforcement in non-demented and non-depressed PD patients and to evaluate the influence of dopaminergic therapy by comparing patients in the ''on'' (with L-Dopa) and ''off'' (without L-Dopa) states.

Twenty-three patients hospitalized in the Neurology Department of the Salpêtrière Hospital for therapeutic equilibration or candidature for subthalamic nucleus deep brain stimulation were recruited for the study. Inclusion criteria were idiopathic, persistence of a good reactivity to L-Dopa, absence of dementia (score = 130 on the Mattis Dementia Rating Scale) or depression (score = 20 on the Montgomery and Asberg Depression Rating Scale), ability to be tested not only in the ''on'' state (maximum therapeutic effect of dopaminergic treatment), but also in the ''off'' state (after about 12 h of therapeutic withdrawal). Twenty-eight control subjects without neurologic or psychiatric disorders, matched to the patients for age and sex, were recruited. A comparison of the two groups confirmed the existence of both a mild dysexecutive syndrome and a tendency for more dysthimic disorders in patients.

There were two assessments with a gap of 24 h for patients and controls. They were presented in the same order: Apathy Scale, Stimulus-Reward Learning (hereafter referred to as Stimulus-Reward Learning 1) and Reversal, Gambling task, new Stimulus-Reward Learning (hereafter referred to as Stimulus-Reward Learning 2), and Extinction.

Several experimental variables were impaired in patients with PD. Their score on the Apathy Scale was higher than that of control subjects, confirming that apathy may be observed in PD, even in non-demented and non-depressed patients. Apathy was mild, since the mean score for patients was lower than the cut-off pathological score of 14. However, six patients in the ''off-first'' subgroup and three patients in the ''on-first'' subgroup had pathological scores, giving an overall percentage of 39%. Although the patients of our study were not clinically depressed, there was a mild but significant correlation between the Apathy Scale and MADRS scores, probably due to anhedonia, a common factor in the two scales.

Stimulus-Reward Learning was also impaired in patients. In normal controls, it required only a few trials and errors. The acquisition was conscious (at the end of the first learning all controls said that they had to touch a stimulus and not to touch the other one) and easily transferred to another pair of patterns (the second Stimulus-Reward Learning task attained a ceiling effect and was nearly perfect by the end of the first assessment). This reinforcement associated learning was maintained in the second part of the experiment. When compared to controls, the performance of PD patients was impaired in both Stimulus-Reward Learning tasks, although they were able to learn and transfer the rule of reinforcement to a new pair of patterns, since their performance was normalized before extinction in the second assessment. In controls, reversal improved in the second assessment, where it was nearly optimal. This was not the case for the Extinction task, suggesting that it is easier to explicitly reverse the stimulus-reward association than to inhibit all responses. The difference between patients and control subjects was highly significant for Reversal and just significant for Extinction. These results are in favor of a deficit in ''affective'' flexibility rather than in control of impulsiveness and are in line with those of a recent study obtained with more cognitively complex tasks of probabilistic and concurrent reversal.

The progression of performance of control subjects was slower on the Gambling task in agreement with the results of Bechara. Only 50% of controls were conscious of the difference between the advantageous and disadvantageous decks of cards. These results confirm the more implicit dimension of the reinforcement learning in the Gambling task. On this task, PD patients performed in a similar manner to control subjects in the first assessment, but did not progress further in the second assessment. It may be hypothesized that a decrease in motivation or in sensitivity to reinforcement impairs the mobilization or maintenance of attentionnal resources required by this particular type of implicit learning.

To summarize, patients with PD were impaired in motivation, in explicit and implicit reinforcement associated learning, and in ''affective'' flexibility. Interestingly, there was no correlation between these affective deficits. This is likely due to the diversity of the neuropsychologic processes involved: subjective feeling versus objective performance, explicit versus implicit reinforcement associated learning, ''affective'' flexibility versus learning.

The different sensitivity of these deficits to dopaminergic therapy is also indicative of the diversity of the underlying neurophysiologic mechanisms. The Apathy Scale improved in the ''on'' state. This dopaminergic reactivity of apathy has not been shown before. By contrast, explicit Stimulus-Reward Learning and Reversal were not

sensitive to dopaminergic therapy. This would appear surprising bearing in mind that enhancement of central dopaminergic innervation improves working memory and "cognitive" flexibility, at least in the early stages of the disease, and that various experimental studies in primates have implicated dopamine in reinforcement associated learning. A possible explanation is that dopaminergic depletion is more severe in the nigrostriatal system than in the mesocorticolimbic system. The high doses of L-Dopa required to compensate for the depletion of the motor system would exceed the depletion of the affective system and would consequently disturb its function.

The lack of effect of dopaminergic therapy in the Gambling task is noteworthy, given the hypothesis of error prediction of reward (Hollerman & Schultz, 1998). This kind of implicit learning would require processes of long term consolidation, probably poorly sensitive to the short term fluctuations of dopaminergic therapy.

In conclusion, these results implicate the "orbitofrontal" and "cingulate" striato-frontal loops in human motivation, explicit and implicit sensitivity to reinforcement, and "affective" flexibility. They also underline the complexity of relationships between these affective factors, due to the participation of various neuropsychologic and underlying dopaminergic mechanisms.

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41. Modulation of orbitofrontal activity by prior knowledge of emotional stimuli: A positron emission tomography study in humans

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In a previous PET-study (article in preparation, Geday et al., data presented at HBM 2001) we found that novel emotional pictures activated the right orbitofrontal region less than closely match neutral pictures. This supported the "default mode of brain function" theory according to which the main task of the orbito-prefrontal region is to maintain attention and to choose between relevant inputs from other brain areas, because salient messages from the few temporal emotion-reco-gnising areas made the choice of attention easy. Our test hypothesis was, that a shift from novel to known pictures should diminish the orbitofrontal deactivation, because it would receive messages from areas both associated with memory and emotion. Thus making the choice of attention equally difficult for the emotional and the neutral pictures. We compared blood flow in the orbitofrontal cortex in one group where the test persons were watching novel pictures, and one where they were watching already known pictures. As expected, significantly less right orbitofrontal deacivations was found in the "known-pictures" group, to confirm that the subject were engaged in memory processing significant activations were found in the left retrosplenial cortex.

Report

Since Harlow's description in 1848 of the spectacular accident of Phineas Gage, and the profound consequences it had for his social behaviour, the importance of the orbitofrontal cortex has been well recognised. Damasio claims in his "somatic marker hypothesis" the orbitofrontal cortex to be critical for the integration of emotion and cognition (Damasio, 1995). Others like Rolls have focused on the region's role in emotion-related learning, and suggest, that orbitofrontal cortex' main task is to represent the magnitude of a given reward or punishment (Rolls, 2000). A recently published study however suggests another function. According to the "default mode of brain function" theory, there is a well organised, baseline default pattern of neuronal activity in the passive brain. This pattern is suspended during specific goal directed behaviours, and the main task of the orbito-prefrontal region is to maintain attention and to choose between relevant inputs from other brain areas (Raichle et al., 2001). In a previous PET-study (article in preparation, Geday et al., data presented at HBM 2001) we found that novel pictures of emotional situations or facial expressions activated the right orbitofrontal region less than pictures of closely match neutral situations or facial expressions. In our view these findings supported the "default mode of brain function" theory. This, because salient—and from an evolutionary point of view—high priority messages from the temporal emotion-recognising areas made the choice of attention easy.

If this were so, we would expect, that a shift in visual stimuli from novel to known pictures should diminish the orbitofrontal deactivation. The orbitofrontal cortex would here not just receive high-priority messages about the emotional valence of all pictures from the extrastriate cortices, but from other areas like the retrosplenial cortex (Maddock, 1999), associated with memory and emotion as well. Thus making the choice of attention more equally difficult for the emotional and the neutral pictures.

To investigate this in a PET-paradigm we compared blood flow in the orbitofrontal cortex in two groups. One group where the test persons were watching novel emotionally charged pictures and novel neutral pictures. And one, where they were watching already known pictures, which they themselves before had rated in terms of emotional valence. We focused on the interaction between novel/known pictures and emotional valence. Our primary regions of interest were the right orbitofrontal region and left retrosplenial region.

Methods

Subjects

Eight male subjects (mean age: 43 years, *SD*: 11.5 years) took part in the study in the "novel"-group, 5 male subjects (mean age: 39 years, *SD*: 9.8 years) took part in the study in the "known"-group. All subjects were unmedicated, with no psychiatric or neurological illness.

PET scan acquisition and analysis

Subjects received a total of 500 Mbq of $H_2^{15}O$ as a fast i.v. bolus (<5 s) through an antecubital cannula for each of the scans, and activity was measured during a 90-s time window. Stimuli were presented the whole scanning window. PET images were reconstructed after correction for scatter and measured attenuation correction. The 47 3.1-

mm thick slices were filtered to 16 mm FWHM isotropic (Hanning filter cut-off frequency = 0.15 cycles/s). PET images were realigned using the Automatic Image Registration (AIR) software to correct for head movements between the scans. For anatomical localisation of activation sites, T1-weighted magnetic resonance imaging (MRI) was performed on a GE Sigma 1 T scanner providing slices of 1.5-mm thickness. The first PET image was co-registered to each individual's MRI. PET and MRI data were mapped into standardised stereotaxic space (Talairach and Tournoux) using a nine-parameter affine transformation.

T-statistical maps were calculated after a pixel-by-pixel regression of PET volumes using the local voxel *SD*. The blood flows measured while subjects were watching neutral pictures were used as baseline scans and regressed voxel for voxel against the blood flows measured, while they were watching emotional pictures (pleasant and unpleasant). These results were then voxel for voxel regressed for grouping (novel versus known). Corrected *p*-values for local maxima were calculated according to the method described by Worsley et al. for image volumes with a non-uniform *SD*.

Stimulus

The Empathy Picture System (EPS) was used to test our hypothesis. Each of the picture series in EPS consists of 30 images selected from international newspaper photo-databases. All images in all series are showing real-life persons in real-life events. The series are generated in a $3 \times 2 \times 2$ factorial design involving three levels of valence (pleasant, neutral, and unpleasant) and two groupings (predominantly facial expression and predominantly situation). Each of these six conditions was made in two different versions. The pictures in each series are of different individuals, but all have the same grouping and valence. The complexity of the pictures is sought to be the same across the valence-categories within the groups.

All pictures were pre-tested on a group of eight normal controls to insure the validity of the groups. If all controls agreed that a given picture belonged to one of the groups ("facial" or "situation") the picture was accepted. These pictures were sorted in the valences (pleasant, neutral, or unpleasant) by the investigator.

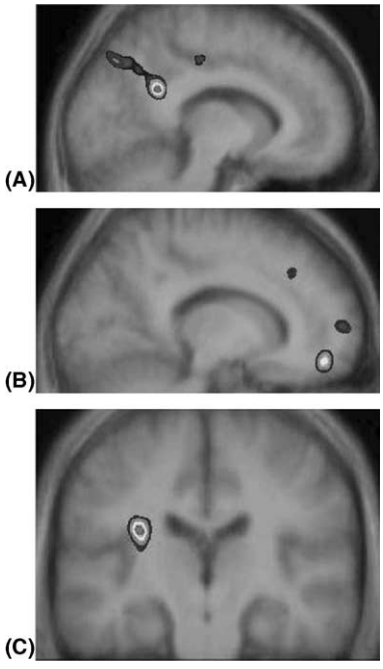

Fig. 1.

Experimental design

For the subjects in the "novel"-group the 12 series were presented in a randomised order. During each scan only one series was shown. The 30 pictures were presented one at a time on a 21 in. monitor placed 70 cm from the subject's face. Each presentation lasted 3 s, and was immediately followed by the next. The subjects were instructed to look carefully at the pictures. No explicit recognition or categorisation was required. After every scan, the subjects were asked if they agreed upon the face/situation category and valence just shown (e.g., "Do you agree that you have seen pictures of people in situations you felt were unpleasant?").

The five subjects in the "known"-group first evaluated the face/situation category and valence of the pictures individually. From these evaluations four neutral (two predominantly facial and two predominantly situation) and four emotional (facial + pleasant, facial + unpleasant, situation + pleasant, and situation + unpleasant) series each of 30 pictures were made. They were scanned the same way as the "novel" group. After the scans, all subjects were asked if they felt the emotional pictures as strongly as when they saw them the first time.

Results

Five percentage corrected, significant activations were found in left retrosplenial cortex, where prior knowledge increased the difference in blood flow between neutral and emotional pictures (searchvolume 40,000 mm^2) (Fig. 1A).

Five percentage corrected, significant activations were found in the right orbitofrontal cortex where prior knowledge increased the difference in blood flow between neutral and emotional pictures (searchvolume 35,000 mm^2) (Fig. 1B).

Outside our ROI, activations just below the significance threshold were found in the left insula, where prior knowledge decreased the difference in blood flow between neutral and emotional pictures (searchvolume, cortical gray matter: 500,000 mm^2) (Fig. 1C).

Conclusions

Our findings supports the test hypothesis, that the orbitofrontal cortex' main task is choose between inputs from other brain areas. That our test-persons in the "known-pictures" group actually were engaged in an emotional memory-retrieval processing, was supported by the fact that we were able to show, that prior knowledge as expected increased the emotional activation in the retrosplenial cortex. Insula activation has in several other studies been shown to relate to the magnitude of an elicited emotion. We believe the below threshold activation of the left insula, may reflect the fact that our test-persons considered the emotional pictures more arousing the first time, than the second.

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42. Can emotions help us reason? Two positron emission tomography studies using a training paradigm

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Three main questions are currently under debate in the cognitive psychology of reasoning: Do we reason logically? Why do we make reasoning errors? Can emotions help us reason? This report presents a synthesis of two already-published brain-imaging studies (Houdé et al., 2000, 2001) which, when matched to each other via an intergroup comparison, offer new insight into these issues. Our data indicate that in certain cases, the brain is not logical, but takes the path of least effort by recruiting a perceptual network to solve logical task. The results also show that emotion plays a key-role: a brain region linked to emotions and self-feeling (the right ventromedial prefrontal cortex) was involved in inhibiting a perceptual bias in order to gain access to deductive logic.

Report

As recently summarized by Kosslyn and Rosenberg (2001), three main questions are currently under debate in the cognitive psychology of reasoning: Do we reason logically? Why do we make reasoning errors? Can emotions help us reason? This report presents the synthesis of two already-published positron emission tomography (PET) studies (Houdé et al., 2000, 2001) which, when matched to each other via an intergroup comparison, shed some new light on these issues.

In a previous PET study we scanned the same subjects twice during a logical task (a conditional rule falsification task), before and after a training in error inhibition. The first scan was on a pretest session during which they performed the task with a reasoning bias (so called "perceptual matching bias") leading to errors. After training, the same subjects were pet scanned again, while performing the task logically. The main finding was a striking shift in the cortical anatomy of reasoning from the posterior part of the brain (ventral and dorsal pathways) to a prefrontal network. A key issue raised by this first study was that it did not separate (a) the logicoemotional impact [emotion/self-feeling, Damasio, 1999] of the matching-bias inhibition training and (b) the effect of the logical explanation of the training task, i.e., the logic per se necessarily included in any procedure about a deductive reasoning task. So, the crucial brain-imaging experiment we then conducted consisted in applying exactly the same paradigm to a new group of subjects, but trained this time in logic only, that is, without the logicoemotional warnings about error inhibition—a "cold" kind of training. The aim was to subtract the pet training-effect thus obtained (impact of logic per se) from the previous one, in order to isolate the logicoemotional effect of the first type of training.

Methods

Twelve right-handed male students (mean age 22, age range 19–26) were selected on the basis of their matching-bias response on the conditional rule falsification task. They were divided in two groups, one given logicoemotional training ($n = 8$) and the other trained in logic only ($n = 4$). The NrCBF (normalized regional cerebral blood flow) of each subject was scanned six times with $H2^{15}O$ PET (Siemens ECAT-HR+) while performing the conditional rule falsification task, three times before training (PET1: pretest session) and three times after training (PET2: posttest session), either in logic-emotion or in logic only. For each group, a training-effect map was computed by subtracting the averaged NrCBF map obtained before training (pretest) from that obtained after training (posttest). Then, an intergroup comparison was computed by subtracting the logical training-effect map from that of the logicoemotional training effect. It was masked (inclusive) by logic-emotion group activations to cancel out deactivations. The activation significance threshold was set at $Z_{\min} = 4.6$ ($p < .05$, corrected for multiple comparisons).

Results and discussion

Behavioral measurements indicated that the 12 subjects in both training groups exhibited a perceptual matching bias on more than 90% of the pretest items. During the posttest, the logic-only group still exhibited the bias on more than 90% of the items, whereas the logic-emotion group responded logically on more than 90% of the items. These findings demonstrate that the error-to-logical shift appeared only after logicoemotional training in matching-bias inhibition, which confirms the specific behavioral impact of this self-feeling procedure, and hence also confirms the validity of using a group trained in logic only as a control. In this group, no error correction took place after training, which means that despite the logical explanation of the training task, the subjects could not avoid the trap on the posttest. It thus appears that training in logic per se is insufficient—"too cold"—to trigger a biased-to-logical shift.

In addition, the neuroimaging data revealed essentially that the right ventromedial prefrontal cortex (involved in emotions and self-feeling), the right pulvinar, and the bilateral peristriate cortex (reflecting the filtering of visual information irrelevant to the current task) were activated in the logic-emotion group only (see Table 1). We also observed the activation of a left prefrontal area located at the junction of the precentral gyrus and the middle frontal gyrus (involved both in object and in spatial working memory; here, the logical abstraction of the stimuli's properties). Interestingly, from the famous case of Phineas Gage in the

Table 1
Extent, anatomical localization (MNI Brain Template), stereotactic coordinates, and local maxima z scores of areas detected in the inter-group comparison of the two training-effect maps, i.e., logic-emotion group ($n = 8$) (from Houdé et al., 2000) minus logic-only group ($n = 4$) (from Houdé et al., 2001)

Volume (cm^3)	Anatomical localization	Coordinates (mm)			Z score	Corrected p vlaue
		y	z			
2.7	R ventromedial prefrontal/ anterior cingulate	20	54	0	6.40	.000
1.9	R pulvinar	12	−32	−4	5.21	.003
5.4	Peristriate	0	−98	−20	5.49	.001
0.3	L peristriate	−22	−98	−18	4.67	.033
2.6	L precentral gyrus/middle frontal gyrus	−32	2	36	4.91	.012

19th century (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994) to Damasio's patients today (Damasio, 1999), neuropsychological data clearly indicates that right ventromedial prefrontal damage is consistently associated with impairments of reasoning/decision making, emotion, and feeling. For the first time, the present results demonstrate the direct involvement, in neurologically intact subjects, of a right ventromedial prefrontal area in what puts the mind on the "logic track," where it can implement the instruments of deduction to good use.

With regards to Kosslyn's three questions mentioned at the beginning of this report, the findings of our two PET studies indicate that in certain cases, the brain is not logical, but spontaneously takes the path of least effort by recruiting a network that is strongly anchored in perception. This demonstrates the materiality of reasoning biases. Through neuroimaging, we were able to understand why the human brain, as sophisticated as it is, can make logic errors. But the results presented also pointed out the plasticity of the brain, in this case, its capacity to inhibit a reasoning bias and activate deductive logic (Houdé et al., 2000). Furthermore, the role of emotion was demonstrated by showing that a brain region linked to emotions and self-feeling was involved in inhibiting a bias in order to gain access to logic (Houdé et al., 2001). It would be interesting in future research to test the role of emotion in our training paradigm by recording the skin conductance response, thereby combining neuroimaging, cognitive psychology, and psychophysiology.

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43. Emotional and social consequences of orbitofrontal and non-orbitofrontal lesions of the prefrontal cortex

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Damage to the prefrontal cortex has been associated with aberrant social and emotional functioning, including inability to recognise emotion in others, lack of empathy, and poor insight. This study is a comparison of day to day difficulties in the social, emotional, and cognitive domains following neurosurgical lesions to the orbitofrontal and non-orbitofrontal prefrontal cortex. Standardised scales and a newly devised measure were rated by both patients and controls and compared with their informants' ratings. In comparison with control subjects, patients with orbitofrontal cortex damage tended to have more difficulties and underestimate their limitations in socio-emotional functioning. In contrast patients with non-orbitofrontal prefrontal cortex damage had a reduced capacity for insight and greater impairment in activities with cognitive demands.

Report

Damage to the prefrontal cortex is associated with impaired emotional and social interactions such as angry outbursts, increased lability, relationship difficulties, insensitivity, and sexual disinhibition. Possible explanations for such social problems include impaired ability to recognise emotions in others, a lack of empathy, poor insight, and other changes in emotional functioning.

Patients with ventral frontal lobe damage have been shown to have impairments in the identification of facial and vocal emotional expression, in comparison with a non-ventral damaged patient group. These deficits were found to correlate with observable changes in behaviour such as disinhibition, irritability, and aggression (Hornak, Rolls, & Wade, 1996). Another social difficulty displayed by this patient group is a reduction in empathic reactions, which play a role in the exhibition of pro-social behaviours and inhibition of anti-social behaviours towards others.

Although the demands of some social situations inevitably involve higher-level cognitive abilities, it appears that socio-emotional mechanisms may be affected independently of executive functions. Dubois et al. (1995) describe patients with impaired abstract reasoning, perseveration, poor planning, and strategy formation following damage to the dorsolateral prefrontal cortex. In contrast, lesions in the orbitomedial prefrontal cortex have been observed to lead to impaired affective processes and social interactions (e.g., Saver & Damasio, 1991). Further support for dissociable cognitive and affective subsystems is provided by a study measuring regional cerebral glucose metabolism in patients with dorsolateral or ventromedial prefrontal cortex damage (Sarazin et al., 1998). Impairments on cognitive tasks were correlated with metabolism in the dorsolateral prefrontal cortex and anterior cingulate cortex. Behavioural disturbance was associated with metabolism in the orbitofrontal cortex and frontopolar cortex. However no attempt has yet been made to compare patients' everyday social behaviour according to lesion site in the prefrontal cortex.

This study endeavoured to provide a comparison of real life social and emotional versus cognitive and instrumental difficulties following discrete neurosurgical lesions to the orbitofrontal and non-orbitofrontal prefrontal cortex. This was done using self- and informant-report measures.

A second aim was to explore further the subtleties of social and emotional difficulties using a newly devised self- and informant-rated questionnaire examining dysfunction including the inability to recognise emotion and empathise with others. Fractionation of areas of difficulty was investigated.

The third aim was to examine capacity for insight into difficulties. Previous studies have investigated awareness of difficulties in traumatic brain injury clinical samples, where there may be additional diffuse non-prefrontal cortex damage. Prigatano, Altman, and O'Brien (1990) found that traumatic brain injury patients' judgements of competency in activities of daily living were generally in line with their relatives' ratings. However, patients underestimated their deficiencies in emotional and interpersonal interactions. This study sought to determine whether there were differences in capacity for insight in different domains of everyday functioning in orbitofrontal and non-orbitofrontal cortex patient groups.

Method

Participants

Group ($n = 25$) patients who had undergone neurosurgery exclusively in the prefrontal cortex were recruited. Exclusion criteria included other non-prefrontal cortex damage, a history of learning disabilities, current psychotic illness, alcohol or drug dependence.

On the basis of MRI scans and neurosurgeons reports, the patients were subdivided into a group ($n = 15$) who had orbitofrontal damage (with or without additional medial and dorsolateral damage) and $n = 10$) who had no orbitofrontal damage (i.e., only medial and/or dorsolateral damage). The patient group were matched for sex, age, and IQ as measured by the revised National Adult Reading Test with normal controls ($n = 25$). All participants nominated a friend or relative who completed informant versions of the measures ($n = 50$).

Measures

Three 5-point Likert scale questionnaires were completed by each participant:

1. Patient Competency Rating Scale (PCRS), a 30-item questionnaire forming subscales assessing proficiency in activities of daily living (ADL), cognitive, interpersonal, and emotional domains.
2. Dysexecutive Questionnaire (DEX) from the Behavioural Assessment of Dysexecutive Syndrome test battery, a 20-item questionnaire with three-factors measuring the behavioural, cognitive, and emotional problems.
3. Socio-Emotional Questionnaire (SEQ), a 30-item questionnaire devised for this study containing 5 items to assess ability to recognise basic emotions in others (happy, sad, fear, anger, disgust), 5 items to assess empathy for these emotions, and 20 items with face validity chosen to cover a wide range of social and affective symptoms.

Results

Analysis of socio-emotional questionnaire

A factor analysis of the items for the informant version of the measure was conducted using the principal components method with varimax rotation. A five factor solution emerged incorporating 19 of the 30 items with factor loadings >.06 and accounting for 60% of the variance. The items loading most highly on each factor were used to form five subscales: Emotional Empathy; Emotion Recognition; Public Behaviour; Relationship Skills; Anti-social Behaviour.

Pearson's correlation analysis was used to cross validate the total and subscale scores of the Socio-Emotional Questionnaire. The total SEQ score was significantly correlated with all variables ($p < .01$). Four subscales correlated with both the DEX and PCRS total scores ($p < .05$) and overall the five subscales correlated with 63% of the variables.

Comparison of everyday difficulties

When compared to control subjects, the non-orbitofrontal group had significantly higher ratings on the informant-reported cognitive subscale of the DEX ($p < .05$). There were no other significant differences between the two patient groups in comparison to controls or each other on the PCRS and DEX total scores or subscales.

Comparison of social and emotional difficulties

Orbitofrontal patients had significantly more informant-rated difficulties than non-orbitofrontal patients with relationship skills ($p < .05$) and tended to have more self-rated difficulties on the public behaviour subscale. In comparison with controls, the orbitofrontal patient group tended to rate themselves as having less difficulties with public behaviour but their informants tended to rate their difficulties as greater than controls for both the public behaviour and anti-social behaviour subscales. Conversely, the non-orbitofrontal group's informants tended to rate them as having fewer difficulties on the relationship skills subscale than controls. For all other variables, differences between groups were non-significant.

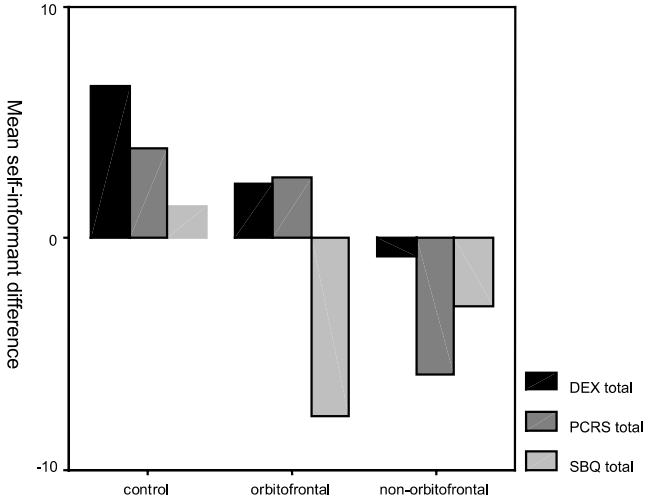

Fig. 1. Mean differences in self-informant ratings for the DEX, PCRS, and SEQ total scores for control, orbitofrontal, and non-orbitofrontal groups.

Comparison of insight into everyday difficulties

Fig. 1 shows differences between self- and informant-rated scores for total scores of the three scales.

Within-subject comparisons showed that control subjects rated their difficulties as greater than the informant-ratings on the dex and pcrs consistently. This discrepancy was significant for both dex and pcrs emotion subscales ($p < .01$), dex total, behaviour, and cognitive subscale scores ($p < .05$). The patient groups did not show this pattern of overestimation as there were no within-subject significant differences.

Between-subject group comparisons revealed that the non-orbitofrontal group showed significantly less insight than controls on the PCRS Interpersonal subscale ($p < .05$) and the DEX Cognitive subscale ($p < .05$).

Comparison of insight into social and emotional difficulties

In contrast with the dex and pcrs measures, within-subject comparisons showed that the control group rated their difficulties in line with their informants on the seq, except for the relationship skills subscale where informants rated significantly more difficulties than control subjects themselves ($p < .01$). For the orbitofrontal group, the within-subject difference between self- and informant-ratings was significant for the relationship skills subscale ($p < .05$) in line with controls, but was approaching significance also for the anti-social behaviour subscale. In addition, the non-orbitofrontal group's self-rating of difficulties were significantly lower than their informant's ratings for emotion recognition ($p < .05$) and approaching significance for emotional empathy.

Between-subject group comparisons revealed a strong trend for the orbitofrontal group to show less insight into socio-emotional difficulties overall as measured by the seq total score and less insight into their anti-social behaviour than controls.

Discussion

This study aimed to compare everyday difficulties of patients with lesions to the prefrontal cortex in the social, emotional, behavioural, and cognitive domains using standardised and a newly devised socio-

emotional measure. Patients with non-orbitofrontal (i.e., Medial and/or dorsolateral) damage were found to have increased informant-rated cognitive difficulties in comparison with control subjects. In addition, they tended to have less difficulty with relationship skills than controls. In contrast, orbitofrontal (with or without medial and dorsolateral damage) patients were found to have more difficulties with relationship skills than patients without orbitofrontal damage and tended to have more anti-social and inappropriate public behaviour than control subjects. These findings are consistent with previous research indicating a dissociation of socio-emotional and cognitive functioning.

An exploration of capacity for insight into difficulties revealed interesting patterns. In general, control subjects significantly over-estimated their everyday difficulties in comparison with their informants' ratings, whereas patients tended to rate themselves in line with or below their informants' ratings. In particular, orbitofrontal patients tended to underestimate their socio-emotional difficulties, especially anti-social behaviours in comparison with controls. In contrast, non-orbitofrontal patients had less insight than controls into everyday difficulties in the cognitive domain. Of note, the non-orbitofrontal patients also tended to underestimate difficulties in recognising emotion and empathising with others and had a diminished capacity for insight in the interpersonal domain. Therefore it seems likely that although the orbitofrontal cortex mediates some socio-emotional functioning and insight, it does not do so in isolation from other prefrontal cortex areas.

Further work will involve analysis of the influence of extent and lateralisation of lesion site. In particular, given that most traumatic brain injuries involve both hemispheres, the question of whether bilateral damage results in greater dysfunction than right or left-sided unilateral lesions is to be addressed. Also, the relationship between reported everyday difficulties and experimental work investigating the dissociation of cognitive and emotional functions will be considered.

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44. The neurophysiology of decision-making in obsessive-compulsive disorder

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Obsessive-compulsive disorder (OCD) patients show executive functioning deficits and insufficient cognitive-behavioral flexibility. Their decision-making, assessed by Bechara's Gambling Task (BGT), seems to be compromised as well. The ventromedial prefrontal cortex, involved in decision-making functioning, is crucial for some etiopathogenetic theories of OCD. The Somatic Marker Hypothesis of Damasio, suggests that decision-making deficiency could be related to an abnormal activation of the somatic state. Starting from these considerations, we try to highlight some abnormalities in neurophysiological parameters of OCD patients, compared to healthy controls, before and during the BGT. Healthy controls and OCD patients show different neurophysiological profiles both at rest and during the task. The arousal of OCD patients is not related to subjective level of somatic anxiety, measured by administered scales.

Report

Patients with Obsessive-Compulsive Disorder (OCD) show a pattern of behavior similar to that of patients with orbital frontal damage who develop severe impairments in the real life decision-making. This similarity suggests that as they are encouraged only by the prospect of immediate reward, OCD patients seem to be insensitive to the future consequences of their choices. These findings reflect the psychopathological aspect of obsessive-compulsive syndrome. In fact, compulsions represent an immediate reward and a relief from anxiety due to obsessions, but this reward has as a negative consequence malfunctioning in daily life.

Studies from bechara's group suggest that the "gambling task" (Bechara et al., 1999) may be suitable to detect and measure in the laboratory the decision-making impairment of patients with neurological damage to the ventromedial prefrontal cortex (vm). Using this task, our group demonstrated a similar decision-making impairment in ocd (Cavedini et al., 2002a) and obsessive-compulsive spectrum disorders (i.e., Pathological gambling) (Cavedini et al., 2002b) in comparison with healthy normal subjects and patients with other anxiety disorders (i.e., Panic disorder). These data sustain a large number of converging evidences which indicate an important involvement of the frontal areas in the psychophysiology of the obsessive-compulsive disorder. In particular, neuroradiological, metabolic, and neuropsychological studies do sustain the hypothesis of a relationship between ocd and brain circuits that are posited to connect the frontal cortex to basal ganglia structures (Cavedini et al., 2001).

Until now, several behavioral paradigms have been developed to investigate neural mechanisms of decision-making in patients with lesion in the prefrontal cortex. The damasio "somatic marker hypothesis" (Damasio, 1996) proposes that the body state evoked by the experience of reward or punishment influences human behaviour in an advantageous way in the long term. According to this hypothesis, previous reports stressed that the absence of anticipatory skin conductance response in patients with prefrontal damage is correlated with their insensitivity to future outcomes, suggesting that these patients fail to generate somatic signals that would serve as a marker in the distinction between advantageous and disadvantageous choices (Bechara et al., 1999). Similarly to patients with vm lesions, also obsessive-compulsive patients show some clinical aspects of a dysregulation of their somatic states (i.e., Anxiety). However, differently from neurological patients, in the obsessive-compulsive patients anxiety seems to be a specific trait of their psychopathological profile. This fact, a long with specific evidences of the prefrontal cortex involvement in the pathophysiology of this disorder, may play a specific role in the expression of decision-making deficit of these patients.

Starting from these considerations, the aim of this work is to assess the somatic state in obsessive-compulsive patients. To do this we compared the somatic state differences between ocd and control subjects in a rest condition and during a decision-making task.

For this study, we recruited 20 subjects from the department of neuropsychiatric sciences at San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy. Ten of these subjects met the

dsm-iv criteria for obsessive-compulsive disorder (OCD). They were all medication free and without other axis *i* diagnosis or somatic illness ($n = 10$, 60% women, age 34.6 ± 11.6 yrs); the other 10 subjects were recruited as healthy control (hc, $n = 10\%$, 50% women, age 33.2 ± 8.4 yrs.).

Somatic state activation at rest condition and during decision-making performance was recorded for all subjects. To test decision-making ability we used the ''gambling task'' (gt) developed by bechara on vm patients. Briefly, the game requires making a long series of card selections (100 selections from four decks of cards identical in appearance) and the subjects are told that the goal of the task is to maximise profit and are given a 2000 loan of play money; after turning over several cards, subjects are either given money or asked to pay a penalty according to a programmed schedule of reward and punishment. Gains and losses are distributed in different ways in the four decks: decks a and b are high-paying but ''disadvantageous'' because the total gains are lower than the losses (they pay out 100 but the penalties are higher) that means that they cost more in the long run. On the contrary, decks c and d, are low-paying but ''advantageous'' because, although they pay out only 50, the penalties are lower, resulting in an overall gain in the long run.

To test the somatic state activation we monitored the respiration effort (using a resistive transducer placed around the body of the subject at the level of maximum respiratory expansion), the heart frequency (using a pulse transducer placed around the finger), and the muscle tension (using a transducer placed around the head at the level of frontal muscles). Sensitivity settings were made and the input signal was calibrated for each channel. Psychophysiological data were collected using a data acquisition system (Myoexpand 200/400, Modulab 800, by Satem) and stored on an IBM computer. Data were elaborated using Panda software and then analysed with Statistica package for Windows.

All subjects were conducted in a quiet room where they seated in front of a table. The acquisition of neurophysiological data and the GT administration was carried out by two trained neuropsychologists in a single session. Before starting the task, the subject was asked to be quiet and relaxed him/herself. For 10 min the somatic state was recorded and the obtained values were considered the baseline. Following this first step, the four decks of cards were placed on the table in front of the subject. While the first neuropsychologist carried out the GT, the second one monitored the psychophysiological parameters. The complete testing session required about 45 min. All subjects completed the test without problems of cooperation or stress.

Analysis of neuropsychological data shows that performance at the GT is different between OCD and HC. In fact, HC subjects make significantly more selections from the ''advantageous'' decks, whereas OCD significantly prefer the ''disadvantageous'' decks. Moreover, OCD select more cards from the ''disadvantageous'' decks than HC. These data further confirm the involvement of the frontal regions in the pathophysiology of the OCD patients and the role of the GT in discriminating decision-making impairments in these subjects.

Analysis of neurophysiological parameters shows that in the rest condition, all neurophysiological mean values in OCD are significantly higher than that ones recorded in HC and do not change during the task. On the contrary, all neurophysiological mean values in HC start from a lower level at rest condition and increase during the decision-making task. This seems to highlight a modulatory function of the somatic state in HC, that is absent in OCD patients.

The preliminary results of this study suggest the presence of abnormalities in neurophysiological parameters during neuropsychological performances in OCD when compared to healthy control subjects. Probably, the inability of OCD subjects to modulate the somatic state plays a crucial role in the involvement of decision-making performances. As for neurological subjects in which damage to VM cortex precludes the ability to use somatic signals, OCD patients are enable to use the somatic state that are necessary for guiding decision in the advantageous direction. However, even if the VM is a critical region in the activation of the somatic state, the neural network involved in this process include other numerous regions as the amygdala and the somatosensory cortices (SI, SII, and insula). In particular, previous reports suggest that the role played by the amygdala and VM in decision-making are different (Bechara et al., 1999).

These results encourage to test the ''Somatic Marker Hypothesis'' in OCD in order to explore the complex function of decision-making in these subjects.

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45. Sensation-seeking and impulsivity in young and older adults' decision making

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The somatic marker hypothesis asserts that decision-making processes involve emotion. Using a gambling task that models real-life decisions, studies showed that old adults perform less efficiently than younger adults, by adopting a strategy that is disadvantageous on the long term. This study aimed at re-examining the age effect on decision-making with the same paradigm, and to explore whether differences are related to sensation-seeking and impulsivity traits of personality. Young and older adults were compared on the gambling task (Bechara, Damasio, & Damasio, 2000a), and on questionnaires of sensation-seeking and impulsivity. Results confirmed an age effect on the gambling task performance. Moreover, performance in both young and older adults on this task was correlated to scores on the sensation-seeking scale, but not to the rating of impulsivity.

Report

The somatic marker hypothesis posits that decision-making is a process that depends on emotion and that deficits in emotional signalling will lead to poor decision-making (see Bechara et al., 2000a). In fact, this hypothesis proposes that individuals make judgements not only by assessing the severity and the probability of outcomes, but also in terms of their emotional quality. In order to explore this hypothesis, Bechara et al., 2000a developed a card task (known as 'gambling task') that

simulates real-life decisions. This task requires the participant to choose cards from four decks. Two decks have high immediate gain but larger future loss, and two other decks have lower immediate gain but lower future loss. During the task, anticipatory somatosensory responses are progressively generated before choosing from a risky deck, which leads normal adults to choose advantageous decks more and more frequently.

Using this paradigm, Bechara et al. observed decision-making impairments in different populations (e.g., patients with damage to the ventromedial sector of prefrontal cortices, or substance-dependent individuals). Normal old subjects also performed less efficiently than younger adults (see Bechara et al., 2000a; Reavis & Overman, 2001). Bechara et al. noted that performance on the gambling task was dichotomous, i.e., some old subjects obtained very bad results while others performed very well. Therefore, a question is, why do some normal adults, sometimes young but more often older ones, adopt a disadvantageous strategy?

This study aimed at re-examining the age effect on decision-making with the same paradigm and to explore whether age differences or strategy differences are related to sensation-seeking and impulsivity trait of personality.

Sensation-seeking is a trait defined by the need for novel sensations and experiences and the willingness to take physical and social risks. Risk-taking also refers to the notion of impulsivity that is usually understood as a lack of response inhibition. The main difference between these dimensions (sensation-seeking and impulsivity) lies in the awareness of the risk taken: the sensation-seeker is aware of risk, while impulsivity refers to a lack of planning and risk-awareness.

Method and materials

Participants

A total of 122 volunteers participated in the study. This included 62 undergraduate students between 18 and 30 years of age (31 females and 31 males; mean age = 24.8 years; mean years of education = 14.7) and 60 older adults between 60 and 70 years of age (30 females and 30 males; mean age = 64.9; mean years of education = 14.2). Young and older adults did not differ in terms of years of education ($P > .05$).

An age difference was observed on a vocabulary test in favour of elderly subjects: Ms = 26.3 versus 23.2 for older and younger adults, respectively ($P < .05$). For both groups, selection criterion was the absence of a factor potentially affecting the CNS (e.g., history of major neurological disorder, drug or alcohol abuse), and defective eyesight that was not corrected.

Behavioural testing

Questionnaires

Two questionnaires were administered: Zuckerman's Sensation-Seeking Scale (SSS) and of the Eysenk Impulsiveness Scale (EIS).

- The SSS was a list of 40 paired statements, and each participant was asked to choose the item with which he agreed the most. Four factors were assessed: Adventure Seeking, Experience Seeking, Disinhibition, and Boredom Susceptibility.
- The EIS assessed self-reported impulsivity. This scale contained 54 yes-no items, divided into 19 impulsivity items, 16 'aventuresomeness' items, and 19 empathy items used for catching subjects' attention.

Decision-making task

A computer version of the Iowa Card Task was administered with 100 trials as described in Bechara et al. (2000b). In summary, the task involved 4 decks of card called A′, B′, C′, D′. Subjects had to pick up one card at the time from one of the 4 decks. In two decks (A′ and B′), picking up a card resulted in high gain of play money (100), but also in unpredictable high money loss in some trials. In the two other decks (C′ and D′), the immediate gain was smaller (50) but the penalty was smaller too. Every 10 cards, the subject encountered a total loss of 1250 in decks A′ and B′ and a total benefit of 250 in decks C′ and D′. Thus, decks C′ and D′ were more advantageous in the long term.

Fig. 1. The figure shows net scores $[(C' + D') - (A' + B')]$ of cards selected by old subjects (filled triangles) and younger subjects (open squares) across different blocks expressed as mean. Positive net scores reflect advantageous performance whereas negative net scores reflect disadvantageous performance.

Results

Card task

As in previous studies (e.g., Bechara et al., 2000b), we subdivided the 100 card selections into 5 blocks of 20 trials each. Then, we calculated a net score for each block (total of cards selected from advantageous minus disadvantageous decks): negative scores indicated a disadvantageous selection strategy and positive scores indicated an advantageous strategy.

Globally, results showed that 35% of young and 45% of older subjects adopted a disadvantageous strategy, but the difference was not significant ($\chi^2 = 2.1$, $p = .15$).

Secondly, results showed that young subjects selected an average of 55 cards from the good decks versus 45 cards from the bad decks. Older subjects selected an average of 51 cards from the good decks versus 49 cards from the bad decks. Note that, following Bechara et al. (1998), the selection of more than 50 cards from bad decks was defined as a cut-off point to determine a disadvantageous strategy.

In addition, we observed that young subjects gradually shifted their preference towards the good decks. Indeed, an ANOVA carried out with the five blocks as a repeated measure raised an effect of blocks on scores ($F(4, 484) = 5.3$, $p < .001$). With the same analysis, we observed that this response shift was not observed in older participants ($F(4, 256) = 1.1$, $p = .37$). See Fig. 1.

Questionnaires

Sensation-seeking

First, young subjects scored significantly higher than older adults on all factors (Ps $< .001$).

Second, across all participants, the global score on the SSS positively correlated with scores in the card task ($R(121) = .26$, $p = .04$). This positive correlation was observed both in young ($R(61) = .20$, $p < .05$) and older ($R(59) = .30$, $P = .03$) adults. Regarding the factors assessed by this scale, only adventure seeking and disinhibition correlated positively with scores ($R(121) = .25$; $p = .05$, $R(121) = .28$, $p = .02$, respectively), both in old and younger subjects.

Third, in comparing older subjects with advantageous and disadvantageous strategy, a 4×2 (SSS factors $\times$ strategy groups) ANOVA showed a factors effect ($F(3,171) = 246.7$, $p < .001$) and a significant interaction ($F(3,171) = 3.1$, $p = .016$). More precisely, older adults using an advantageous strategy had higher scores in adventure seeking ($F(1,58) = 6.01$, $p = .02$) and disinhibition ($F(1,58) = 6.01$, $p = .02$) factors than the old subjects with disadvantageous strategy. On the contrary, a similar analysis carried out in young subjects revealed no difference between subjects with advantageous and disadvantageous strategy ($p > .01$).

Impulsivity

First, young subjects scored significantly higher than older subjects on all factors (Ps $< .001$).

Second, total scores on the EIS were not significantly correlated with scores in the card task in young or older subjects ($p > .10$). Regarding factors assessed by this scale, only the aventuresomeness factor was positively correlated with net scores ($R(121) = .17$, $P = .05$).

Finally, there was no difference between subjects using advantageous or disadvantageous strategy on this scale (all Ps $> .10$).

Discussion

First, there was evidence of an age effect on the decision-making task performance. In fact, older adults showed an initial typical selection from the bad decks a and b, but contrary to younger adults, they did not switched to more and more selections from the good decks c and d. These results confirm previous observations (see Bechara et al., 2000a; Reavis & Overman, 2001).

Second, self-reported impulsivity was not correlated with card task performance. These data might show that disadvantageous decision-making in card task is not the consequence of simple impulsivity. In contrast, and surprisingly, we observed that, on the one hand, the adventure seeking and disinhibition factors in the Sensation-Seeking Scale, and on the other hand, the aventuresomeness factor in the Impulsivity Scale both correlated positively with decision-making performance in young and older adults. Using the same paradigm for exploring potential sex effects on decision-making, Reavis and Overman (2001) recently observed similar results.

Third, young subjects scored higher than older subjects on sensation-seeking scale and impulsivity scales, and this was true for all factors correlated with decision-making performance (deshinibition and adventure seeking).

Fourth, like Bechara et al. before, we noted that young and older adults' performance on card task was dichotomous, i.e., some subjects adopted advantageous strategy while others followed very disadvantageous options. This was more clearly the case in older adults. In addition, older adults who chose favorable card decks at a high rate were also subjects with the highest SSS scores.

To conclude, this study replicated the previously observed age effect in the gambling task. Nevertheless, our findings raise an important question, namely why older high sensation-seeker perform better in the gambling task than other older adults. More studies are obviously needed to clarify the relationships between sensation-seeking and performance on the gambling task.

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46. Brain-stimulation reward shifts circadian rhythms in hamsters

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Circadian rhythms can be phase-shifted in hamsters by rewarding stimuli, such as exercise or food, presented several hours before waking. These phase shifts are mediated through the intergeniculate leaflet (IGL) of the thalamus, which connects with the suprachiasmatic nucleus. Carbachol into the IGL shifted the circadian phase by over 1 h, and this was blocked by atropine pretreatments in IGL. We hypothesized that cholinergic neurons of the pedunculopontine nucleus provide the arousing stimulus to the IGL. We delivered brain-stimulation reward for 1 h at circadian time 8, since pedunculopontine neurons are important for brain-stimulation reward in rats. Brain-stimulation reward shifted the circadian phase by almost 4 h. This supports the idea that cholinergic input from the PPT to the IGL mediates reward-induced phase shifts.

Report

Circadian rhythms can be phase-shifted in hamsters by presenting lights during the dark phase, or by presenting intensely arousing stimuli during the light phase, several hours before normal waking time for hamsters. The latter is called "non-photic phase shifts." The non-photic stimuli that are most often studied are exercise (wheel running) or food, both of which are intensely rewarding to hamsters. This suggests that the circadian rhythm can be altered by intensely rewarding stimuli, and that the phase shift might function to allow the subject to be awake when biologically significant events with a circadian periodicity occur.

Non-photic phase shifts are blocked by lesions of the intergeniculate leaflet (IGL) of the thalamus. The IGL provides the only direct projection from the thalamus to the suprachiasmatic nucleus, which controls circadian activity rhythms in mammals. Recently, we found that the cholinergic agonist carbachol (1–4 μg) into the IGL shifted the circadian phase by over 1 h (Cain, Edelstein, Karatsoreos, Yeomans, & Ralph, 2001). This phase shift was blocked by pretreatment of the muscarinic antagonist atropine (30 μg) in IGL.

The main cholinergic input to the IGL comes from cholinergic neurons of the pedunculopontine nucleus. These neurons are activated by arousing and emotion-provoking stimuli, and are important for brain-stimulation reward in rats (Yeomans, Mathur, & Tampakeras, 1993). We trained hamsters to bar-press for lateral hypothalamic rewarding stimulation, then placed the animals in activity chambers to establish stable circadian activity patterns for at least 4 days. We then delivered brain-stimulation reward for 1 h at circadian time 8 (4 h before their normal waking time). Brain-stimulation reward shifted the circadian phase by almost 4 h. This supports the idea that cholinergic input from the PPT to the IGL mediates reward-induced phase shifts. This study further suggests how reward systems are linked to the circadian clock to allow activity patterns to respond to emotional stimuli.

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47. Emotion-related circuits and transmitters mediating prepulse inhibition of startle in rat

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Prepulse inhibition occurs when nonstartling stimuli are presented 20–500 ms before the startling stimulus. Fendt, Li, and Yeomans (2001), Fendt, Koch, and Schnitzler (1994) proposed that prepulse inhibition is mediated via the inferior colliculus, superior colliculus, and pedunculopontine tegmental nucleus to inhibit pontine reticular formation neurons mediating startle. We found here that prepulse inhibition, evoked by stimulation of the inferior colliculus, is reduced by scopolamine, a muscarinic blocker, or phaclofen, a GABA-B blocker in the pons. Therefore, muscarinic and GABA-B receptors mediate prepulse inhibition by long-lasting, metabotropic inhibition of the startle circuit. Prepulse inhibition was also reduced by carbachol in the pedunculopontine nucleus. Since cholinergic neurons of the pedunculopontine tegmental nucleus also mediate thalamocortical arousal and reward, prepulse inhibition allows processing during approach responses to emotional stimuli.

Report

Prepulse inhibition occurs when brief, nonstartling stimuli are presented 20–500 ms before the startling stimulus. Fendt et al. (1994) proposed that prepulse inhibition is mediated via the inferior colliculus, superior colliculus, and pedunculopontine tegmental nucleus to inhibit caudal pontine reticular formation neurons mediating startle. That idea has been tested by electrically stimulating each nucleus in the circuit and showing that the time course of prepulse inhibition shifts as the electrode advances through the circuit (Li & Yeomans, 2000). This circuit is important in sensory-motor gating of stimuli important to survival, and prepulse inhibition is reduced in several psychiatric disorders including schizophrenia (reviewed by Fendt et al., 2001).

To study the transmitters mediating prepulse inhibition, Koch, Fendt, and Kretschmer (2000) injected blockers, such as scopolamine, into the pontine reticular formation in awake rats. We tested this idea further in anesthetized rats, by electrically stimulating the trigeminal nucleus to evoke startle, and stimulating the inferior colliculus to provide prepulses. This method results in sharper prepulse inhibition curves, and more rapid testing of the effects of drugs on a single day. We found here that prepulse inhibition was reduced 47% by scopolamine (100 μg), a muscarinic blocker, or 29% by phaclofen (4.2 ng), a GABA-B blocker in the pons. The time course of PPI was similar before and after each of the injections, but was reduced in amplitude. Therefore, muscarinic and GABA-B receptors both mediate prepulse inhibition by long-lasting, metabotropic inhibition of the pontine systems mediating startle. These strongly support and extend the results of Koch et al. (2000).

To test whether cholinergic neurons in the pedunculopontine nucleus are the source of the cholinergic input to prepulse inhibition, carbachol (1 μg), a cholinergic agonist that inhibits mesopontine cholinergic neurons was injected into the pedunculopontine nucleus. Prepulse inhibition was also reduced 44% by carbachol. This supports the idea that cholinergic neurons of the pedunculopontine nucleus mediate most of the prepulse inhibition, and provide most of the direct inhibitory input to the startle circuit.

These cholinergic neurons of the pedunculopontine tegmental nucleus also mediate thalamocortical arousal, exploration, and rewarding brain stimulation (Fendt et al., 2001). This suggests that during the rapid processing of emotional or novel stimuli, prepulse inhibition prevents startle responses (eye closure, strong and widespread muscle contractions) from disrupting this processing. This idea is an anatomical elaboration of the proposal of Graham (1979) that prepulse inhibition protects processing of the prepulse. The present theory specifies why this processing is critical for emotions, by showing that prepulse inhibition systems are important in processing during approach responses to emotional stimuli.

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48. Differential impact of emotional status on four cognitive factors

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Factor analysis of 14 Wechsler Memory Scale-III and Wechsler Adult Intelligence Scale-Revised subtests on 124 neuropsychological examinees resulted in four Varimax factors: I—Visual Attention, II—Contextual Memory, III—Long Term Memory, and IV—Facial Recognition. Factor I was correlated with Anxiety and Depression, leading to the hypothesis that visual perception may be related to self-perception. Factor II was related to Distractibility, suggesting that preoccupation with one's inattentiveness may adversely affect memory of prose passages. Factor III was correlated with Pain, age and education, suggesting that pain may block access to well-established knowledge. Factor IV had no emotional correlates.

Report

The purpose of this study was to determine if the emotional state of patients affects their neuropsychological test performance. Factor

analysis was used to combine neurometric data to reflect salient underlying abilities and these factors were correlated with emotional status, demographic features, and patient type.

Method

Subjects

The subjects were 124 consecutive referrals for outpatient neuropsychological evaluation who had completed eight of the Wechsler Memory Scale-III (WMS-III) subtests (Logical Memory I and II, Faces I and II, Visual Reproduction I and II, Spatial Span Total Score, and Digit Span Total Score) and at least seven subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). These were Information, Digit Span, Arithmetic, Similarities, Picture Completion, Block Design, and Digit Symbol.

Subjects, who ranged in age from 17 to 80 years old (mean age = 46.58, $SD = 15.55$), were seen in a metropolitan hospital. They had received an average of 14.73 ($SD = 3.24$) years of education and achieved a mean Verbal IQ score of 100.10 ($SD = 11.16$), mean Performance IQ of 97.86 ($SD = 11.45$) and mean Full Scale IQ of 98.65 ($SD = 10.39$), estimated from averaged age-corrected subtests of the WAIS-R. There were 59 female, 107 right-handed and 112 Caucasian subjects in the study with a variety of neurological problems identified at the bottom of Table 1. English was the first language for 97 of the 124 subjects.

Materials and procedure

Emotional functioning was assessed with the Depression, Anxiety, and Cognitions Status (DACS) instrument, using the Anxiety, Pain,

Table 1
Factor composition and correlates of factor scores

Variable	Factors							
	I		II		III		IV	
Variables in Factor Analysis								
Logical Memory I		.17		**.90**		.22		.13
Logical Memory II		.12		**.89**		.16		.21
Faces I	.02		.30		.01		**.81**	
Faces II		.18		.08		.17		**.86**
Visual Reproduction I	**.66**		**.48**		.01		.19	
Visual Reproduction II		.58		.56		**.06**		**.23**
Spatial Span	**.81**		.13		.13		.01	
Digit Span		**.66**		.01		.24		−.07
Information		.17		.29		**.84**		.05
Arithmetic		**.49**		.34		**.50**		−.14
Similarities		.23		.08		**.83**		.15
Picture Completion	**.49**		−.06		**.53**		.35	
Block Design	**.72**		.13		.32		.25	
Digit Symbol		**.65**		.21		.24		.29
Percent of Variance	43.5		11.7		9.0		8.0	
Demographic Correlates Age		.11		−.21*		.55 ****		.09
Education		.23**		.17		.38****		−.01
English as First Language		−.02		−.12		.24**		.02
Emotional Correlates								
Sadness		−.25**		−.12		−.10		−.06
Pessimism		−.28		−.01		−.07		−.05
Suicidal Thought		−.22*		.01		−.06		−.04
Social Isolation		−.28 ***		−.04		−.21*		−.07
Irritability		−.22*		.05		−.16		−.05
Depression		−.27***		−.09		−.15		.02
Anxiety		−.26***		.02		−.22*		−.03
Distractibility		−.11		−.27***		−.10		.11
Pain		−.05		−.12		−.32****		.11
Coping	−.01		.02		−.19*		−.05	
Correlates with Patient Type								
Memory Concerns ($n = 19$)	.15		.14		.07		.12	
Multiple Sclerosis ($n = 29$)		−.33****		.06		.01		−.15
Dementia Suspected ($n = 11$)	−.04		−.25**		.26**		−.05	
Mild Head Injury ($n = 31$)		.14		−.07		−.21		.07
Mixed Etiology ($n = 34$)		.08		.05		−.02		.01

* $p < .05$.
** $p < .01$.
*** $p < .005$.
**** $p < .001$.

and Depression Scales. Subtests of Depression (Sadness, Pessimism, Suicidal Thought, Distractibility, Insomnia, Fatigue, Social Isolation, and Irritability) were also scored. Each Depression subtest is of established validity with alpha reliability coefficients between .73 and .88. The remaining DACS scales, also with useful concurrent validity, have reported reliability coefficients of .89 for Anxiety, .82 for Pain, and .95 for the summary Depression Scale. Normed DACS T-scores, based on education, were used.

The age-normed scales for the eight wms-iii and six wais-r variables were factor analyzed. (Digit span was used from only the wms-iii.) These were intercorrelated and a principal components analysis conducted. The number of factors was determined by the number of principal components extracted with latent roots greater than unity. The factor matrix was then transformed by kaiser's varimax solution.

A factor score for each subject was generated and product moment correlations were computed between these scores and demographic features, emotional status and patient type.

Results and discussion

The analysis resulted in a four-factor solution, which accounted for 72% of the variance. The factors, shown in Table 1 with their correlates, were designated as i—visual attention, ii—contextual memory, iii—long term memory, and iv—facial recognition. The author of the wms-iii manual (The Psychological Corporation, 1997) emphasized factor analytic solutions with separate immediate and delayed dimensions. However, in the present study both the initial encoding and delayed recall of the memory tests were well correlated and joined together in the same factor, as also found by Millis, Malina, Bowers, and Ricker (1999) for the wms-iii. Taylor and Heaton (2001), using the standardization sample, rotated six factors for the wms-iii and wais-iii and, as in the present study, found immediate and delayed recall scores for the same subtests to combine on the same factor. Bowden, Carstairs, and Shores (1999) reported five factors for the wais-r and the earlier wechsler memory scale-revised with slightly different factor structure.

In the current study, significant relationships were not found between factor scores and gender or handedness.

Factor I

The first factor demonstrated an aggregation of several variables of interest—reproduction of diagrams immediately and after a 30 min delay, spatial and auditory attention, construction of models with blocks, perceptual speed and accuracy with a paper-and-pencil encoding task, mental computation, and ability to scan pictures to identify missing components. These variables make sense in terms of likely components needed to perform the visual reproduction tasks in which geometric diagrams are drawn from memory.

This factor was inversely correlated with the depression and anxiety scales and with four of the depression subtests-sadness, suicidal thought, social isolation, and irritability. With the exception of digit span, variables composing the factor with coefficients greater than .40 were all correlated ($p < .05$) with the depression scale. Some specific items from the dacs which correlated inversely with the visual attention factor reflected the respondents' endorsements of recent irritability, shaking/trembling, tearfulness, and feeling afraid, gloomy, hopeless, like "a loser" and as a failure ($p < .01$).

Multiple sclerosis subjects scored significantly lower on this visuospatial cluster than the other patients ($p < .001$). Studies differ in finding depression among ms subjects and, although the present ms group was no more depressed than the other neuropsychological patients, the severity and nature of the ms was not evaluated. The present results, however, indicated the ms patients to have difficulty with visuospatial processing, independent of their emotional state.

Factor II

Factor II, contextual memory, was constituted primarily of story recall (both immediate and delayed) and had secondary contributions from the visual reproduction subtests. This factor was unrelated to depression, anxiety or pain scales but correlated with the distractibility scale. Items inversely related to contextual memory included endorsement of forgetting what people say, having difficulty remembering sequences of events and forgetting what one was talking about ($p < .005$). It is of interest that distractibility correlated with prose memory (but not with visual reproduction). The operative issue here is the respondent's sense of his or her inability to concentrate rather than poor scores on attention variables. This self-perception appears to contribute to poor retention of contextual information.

The suspected early dementia subjects performed more poorly than the others on this factor did. This is more likely to be due to developing memory difficulties than self-perception of distractibility, which is often denied by this patient group. (Distractibility scale scores were uncorrelated with membership in the suspected dementia group.)

Factor III

Factor III, typically known as the verbal (comprehension) factor, was designated here as long term memory. It reflected access to general knowledge and ability to apply what is known to similarities reasoning/recognition. There were secondary contributions from mental arithmetic reasoning and picture completion, the latter requiring relating the information in stimulus diagrams to images available in long term storage. Despite the use of age-normed subtests, subjects did well on this factor if they were older, better educated and spoke english as their first language. The dacs scale most related to long term memory was pain ($p < .001$). Specific items of the pain scale inversely correlated with factor iii were the presence of headache, neck/shoulder pain, chest pain, and stomach distress ($p < .005$).

It was the suspected early dementia subjects who performed better on factor iii than the others, possibly due to retention of a fund of remote memories, typically preserved in the initial stages of the illness.

Factor IV

Factor IV, facial recognition, was unrelated to any of the emotional or demographic variables. This suggests facial recognition to be a distinctive visual memory task, as others have found.

Conclusions

Performance on the subtests of the first factor, visual attention, was hindered by the presence of depression and anxiety. A traditional explanation might be that both visual organization and negative emotions are typically considered right cerebral hemisphere functions. Also, depression is known to be affected by visuomotor slowing and perceptual speed was an element in this factor. A metaphorical relationship could be stated in the inference, "persons who view themselves negatively are at risk for processing the world outside themselves inaccurately. Physical perception is related to self-perception."

The contextual memory factor was inversely related to a sense of distractibility. The finding raises the question of whether preoccupation with one's inattentiveness may adversely affect the learning of prose passages.

Persons scored better on the long term memory factor (usually labeled the verbal factor), in the absence of physical pain complaints. This result suggests it may be worthwhile exploring the extent to which pain blocks ready access to well-established knowledge.

Finally, the facial recognition factor was unique. It had no correlates among the emotional measures administered.

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49. Humor appreciation in normal aging

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Humor may contribute to healthy aging. Elderly and young participants were compared on verbal and nonverbal humor tests. Measures of working memory, cognitive flexibility, verbal abstraction, and visual scanning were investigated in relation to humor. A relative deficit was found in the elderly in the cognitive comprehension of humor—selecting punch lines to jokes and in choosing funny cartoons from an array. However, the elderly were not impaired compared to patients with focal frontal damage. In contrast to this deficit in comprehension, the elderly showed intact affective appreciation and emotional reactiveness. Measures of cognitive function correlated with humor comprehension. Task complexity and a possible decline in frontal functions with aging may underlie the difficulty in cognitive comprehension of humor with aging.

Report

There is a growing interest in the positive contributions of humor to the aging process. Humor is a unique and complex human ability which reflects the integration of high level cognitive processes and affective responsiveness, which may depend maximally on the integrity of the right frontal lobe. Some recent evidence suggests that normal aging may be accompanied by adverse neurochemical, anatomical, and functional changes that disproportionately affect the frontal lobes. The study of the effects of aging on humor comprehension and appreciation provides a means of investigating one aspect of frontal lobe function in the elderly.

In this study, 20 physically and cognitively healthy elderly (mean age = 73) were compared with 17 young (mean age = 28.8) participants. Two tests assessing verbal humor were administered Funniness Rating Scale, where participants had to assign funniness ratings to humorous and neutral verbal statements, and a Joke Completion Test, where participants had to complete joke stems by selecting punch lines from among four choices. A nonverbal Cartoon Appreciation test was also administered and required participants to choose the funny cartoon from among an array of 4×4 cartoons, only one of which had a relevant visual detail that provided the 'humor twist.' Funniness ratings and mirth responses displayed while performing the tests were measures of affective responding. The number of errors made in selecting the punch lines and cartoons were indicators of cognitive comprehension.

Performances on these humor tests were correlated with that on tests assessing cognitive processes hypothesized to be related to humor appreciation working memory (α span test), mental shifting (Trail Making test—Part B), abstract reasoning (proverb interpretation), visual search and scanning (Trail Making test and Embedded Figures test).

Results indicated that the elderly did not differ significantly compared to the young in their ability to differentiate between truly humorous versus neutral verbal statements, as well as in the number of mirth responses displayed while reading humorous statements on the funniness rating scale. In contrast, the older participants made a significantly greater number of errors while choosing punch lines to complete joke stems but had no difficulty with straightforward narrative language, i.e., completing logical stories. The older participants also made significantly more errors in choosing the humorous cartoon from among the cartoon array where they had to focus on a relevant visual detail to 'get' the humor. Although the elderly made more errors on the humor tests compared to the young, they were not impaired compared to a group of patients with right anterior polar frontal damage (Fig. 1).

When performance on the humor tests was correlated with that on the cognitive tasks, there was a significant correlation between the verbal Joke Completion test and measures of working memory and abstract reasoning. There were significant correlations between the nonverbal Cartoon Appreciation test and measures of working memory, speeded visual scanning, and perceptual ability. Thus, working memory appears to be associated with both verbal and nonverbal humor. In addition, abstract reasoning was related to verbal humor and visual search and scanning was related to nonverbal humor.

To summarize the results, the elderly had no difficulty in differentiating between funny versus neutral verbal statements and demonstrated adequate mirth responses while performing this task. However,

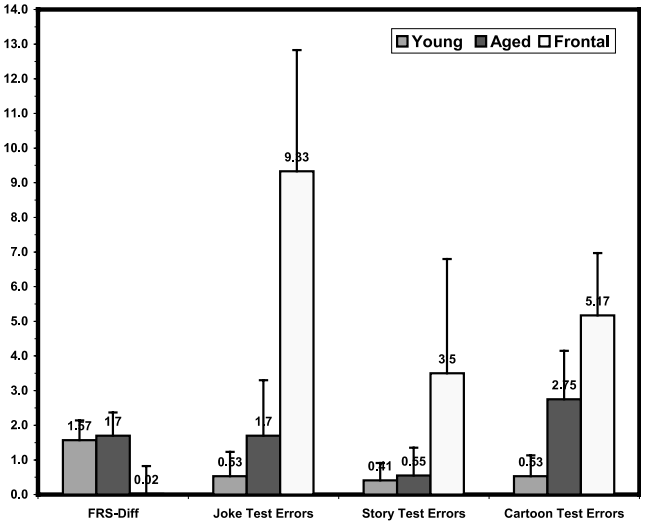

Fig. 1. Performance on the humor tests. (▩) young; (■) aged; (□) frontal.

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they exhibited an impairment compared to the young in their ability to complete joke stems by selecting funny punch lines and also displayed fewer mirth responses during this test. The elderly made more errors in selecting the original funny cartoon depicting a humorous visual detail from among an array of similar cartoons.

The results indicate that the elderly have a relative deficit in the cognitive comprehension of both verbal and nonverbal humor compared to the young as evidenced by the greater number of errors in selecting punch lines and humorous cartoons. In contrast, their affective appreciation of humor appears to be preserved as evidenced by their intact ability to differentiate between humorous and neutral statements and in displaying appropriate mirth responses. That is, aging may be accompanied by difficulties in the cognitive comprehension of humor but does not affect emotional responsiveness to humor.

One hypothesis why cognitive comprehension of humor may be affected in the elderly may be a decline in frontal lobe functions with aging. That is, a relative deficit in "frontal" abilities, such as, working memory, abstract reasoning, and visual search and scanning may underlie a difficulty in the cognitive comprehension of humor. A second hypothesis is that this deficit may be a function of task complexity, i.e., the elderly may demonstrate a difficulty as the task becomes cognitively more demanding (selecting punch lines being more demanding than the relatively straightforward task of assigning funniness ratings to verbal statements).

The study is a preliminary attempt to examine changes in humor and the interaction between cognitive and affective processing with aging. The elderly participants were high-functioning, cognitively intact, independent community-dwelling individuals, yet demonstrated subtle difficulties with cognitive processing of humor, perhaps as task complexity is increased. However, the elderly did not differ from the young in terms of their emotional responding, while patients with right frontal lobe lesions show an impairment in their ability to integrate cognitive and emotional processing of humor. This preserved affective responsiveness of the elderly to humor suggests that they may be able to use humor as a coping mechanism to adapt to stressful life situations and provide a mechanism for healthy aging.

50. Impact of depression and AIDS on phonemic fluency components in adults with HIV-infection

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This study examined the impact of depression and AIDS diagnosis on phonemic fluency components in 211 adults with HIV-infection (45% depressed, 64% AIDS; sample mean age and education: **41.5 ± 8.5** and **14.2 ± 2.8**, respectively). Phonemic fluency (FAS) protocols were analyzed for clustering, related to temporal lobe functioning, and switching, related to frontal functioning. Total FAS score for the sample was **38.5 ± 12.6** and did not differ with AIDS ($p = .083$) or depression ($p = .137$). As expected, switching was worse with AIDS ($p = .049$) but not with depression ($p = .142$). There was no effect of AIDS or depression status on clustering performance ($p = .358$). Advanced HIV disease, but not depression, appears to disrupt frontal–subcortical systems involved in switching. Intact clustering performance suggests sparing of temporal lobe systems.

Background

HIV-infection frequently causes dysfunction in frontal–subcortical brain systems, especially as the disease progresses to AIDS (Kalichman, 1998). Individuals with frontal lobe lesions or subcortical disorders have been found to be differentially impaired on switching tasks, such as the ability to switch between phonemic clusters when generating words beginning with a specific letter (Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998). Individuals suffering from depression have also been found to show poorer switching performance on a semantic fluency task (Lafont et al., 1998). Clustering performance, the ability to produce words within a phonemic category (e.g., words beginning with "st") is reduced in disorders affecting temporal lobe functioning but not frontal-lobe functioning (Troyer et al., 1998). To date, there appear to be no studies that have examined switching and clustering performance in individuals with HIV-infection.

Clinically, detailed examination of verbal fluency performance in individuals with HIV-infection is important since subjective word-finding complaints are common. Complaints of word finding difficulty tend to increase with the presence of depressed mood.

The present study sought to examine the impact of depression and AIDS diagnosis on two phonemic fluency components, switching and clustering, in adults with HIV-infection. We hypothesized that (1) participants with AIDS would perform worse on switching than participants with asymptomatic and mildly symptomatic HIV-infection, (2) clustering performance would not be affected by AIDS diagnosis or depression, and (3) participants with both AIDS and depressed mood would show greater impairments in switching, than participants with AIDS alone.

Methods

The participants were 211 HIV-positive individuals (predominantly caucasian, gay, and bisexual men) recruited as part of a research ethics board approved study of neuropsychiatric complications of HIV-infection. A measure of phonemic fluency (FAS) was completed during a three to four hour comprehensive neuropsychological examination. On average, participants were 41.5 years old ($SD = 8.4$, range = 19–64) and had 14.1 years of education ($SD = 2.8$, range 7–20) years of education. The majority (80.4%) was receiving highly active antiretroviral therapy (HAART) and approximately half (48.2%) had an undetectable viral load (less than 500 copies/mL).

Participants were classified as having AIDS if they had a current or past CD4 lymphocyte count of less than 200 (CDC classification: A3 or B3), an AIDS-defining illness (CDC classification: C1 or C2), or both (CDC classification: C3). One hundred and thirty five (135, 64%) participants met criteria for AIDS, while 76 (36%) did not. Presence of depression was defined as scores >10 on the first 13 items (cognitive/affective subscale) of the Beck Depression Inventory (BDI). Ninety-five (95, 45%) participants were classified as depressed (DEP+) while 116 (55%) were not depressed (DEP−). Four groups were created: AIDS−/DEP− ($n = 37$), AIDS−/DEP+ ($n = 39$), AIDS+/DEP− ($n = 79$), and AIDS+/DEP+ ($n = 56$). The average cluster size (CLUSTER) and total number of switches between clusters (SWITCH) were calculated from participants' phonemic fluency protocols using previously established methodology (Troyer, 2000).

Average sample scores for SWITCH, CLUSTER, and FASTOT were compared to published normative data (Troyer, 2000). A 2 × 2 analysis of variance (ANOVA) was used to compare phonemic fluency performance in participants with AIDS (AIDS+) vs. non-AIDS (AIDS−) and depressed (DEP+) versus non-depressed (DEP−). Separate ANOVAs were performed for total words (FASTOT), average cluster size (CLUSTER), and total number of switches (SWITCH). Correlations between SWITCH, CLUSTER, and FASTOT were also examined.

Results

Demographic and fluency data for the four AIDS and depression groups are shown in Table 1. The total FAS score for the sample was 38.5 ± 12.6, corresponding to the 25–50th percentile in normal control data presented elsewhere (Troyer, 2000). Average cluster size on FAS for our sample was .33 ± .20 and total switching on FAS was

Table 1
Demographic characteristics and phonemic fluency scores of patients by AIDS and depression status

Characteristics	Group 1 (AIDS−/DEP−) ($n = 37$)	Group 2 (AIDS-/DEP+) ($n = 39$)	Group 3 (AIDS+/DEP−) ($n = 79$)	Group 4 (AIDS+/DEP+) ($n = 56$)
Age[a]	41.0 (9.2)	40.2 (8.6)	42.0 (8.4)	42.1 (8.0)
Education (years)[a]	14.1 (3.0)	13.2 (2.9)	14.6 (2.7)	14.3 (2.7)
Recent CD4 lymphocyte counts[b]	482.5 (199.4)	446.7 (195.8)	193.6 (128.7)	348.0 (288.3)
Percentage of participants with undetectable viral load	56%	47%	46%	47%
Percentage of participants receiving HAART[c]	70%	59%	91%	87%
Word finding complaints score (×/10) from patient's assessment of own functioning (PAOF)[d]	3.8 (2.2)	5.8 (2.2)	4.2 (2.2)	5.3 (2.1)
Total FAS raw score[a]	41.7 (13.2)	39.1 (12.7)	38.6 (13.9)	35.8 (9.6)
Total switching score for FAS[e]	30.5 (9.2)	27.9 (9.5)	27.2 (10.2)	26.0 (7.0)
Average cluster size for FAS[a]	.31 (.17)	.38 (.21)	.32 (.22)	.31 (.20)

[a] All differences between groups not significant.
[b] Group 3 < Groups 1, 2, and 4; Group 4 < Group 1 ($p < .05$).
[c] Groups 3 and 4 > Group 2 ($p < .05$).
[d] Groups 2 and 4 > Groups 1 and 3.
[e] Group 1 > Group 4 ($p < .01$).

27.6 ± 9.2. These scores correspond to the 25–50th and 50–75th percentiles in normative data, respectively. This indicates that our sample performs within normal limits on all phonemic fluency measures. Nonetheless, as expected, participants from the DEP+ groups reported significantly more word-finding difficulties than the DEP− groups.

Analysis of the total words produced (FASTOT) showed no differences as a function of AIDS diagnosis ($p = .083$) or depression status ($p = .137$). The interaction between AIDS status and depression was not significant ($p = .981$).

Analysis of switching performance (SWITCH) revealed a main effect of AIDS status, with the AIDS+ group showing fewer switches ($F(1, 207) = 3.91,\ p = .049$). There was no main effect of depression ($p = .142$) and no interaction between AIDS status and depression ($p = .584$).

Clustering performance (CLUSTER) did not differ as a function of AIDS ($p = .278$), depression ($p = .361$), or the interaction of AIDS and depression ($p = .193$).

Both switching and clustering were significantly correlated with total word generation, but switching was more highly correlated with total words ($r = .835,\ p = .01$ for SWITCH, $r = .328,\ p = .01$ for CLUSTER). Correlations between switching and clustering and other neuropsychological measures of switching and/or speed of processing (i.e., Trail Making Test-Part B and Digit Symbol) were examined. As expected, there were significant correlations between FAS total switching and the time to complete Trail Making Test-Part B ($r = -.253,\ p = .01$). There were significant correlations between FAS total switching and the total number of symbols completed on Digit Symbol ($r = .369,\ p = .01$). Average cluster size did not correlate significantly with these other neuropsychological measures.

Discussion

As predicted, individuals with AIDS demonstrated reduced switching on a phonemic fluency task. This is consistent with research documenting decreased switching in disorders affecting frontal–subcortical brain systems. Individuals with AIDS are at higher risk of frontal–subcortical dysfunction than HIV-infected individuals who do not meet criteria for AIDS (Heaton et al., 1995).

Contrary to our expectations, participants with both AIDS and depressed mood did not show greater impairments in switching. Lafont and colleagues (Lafont et al., 1998) observed decreased switching on a semantic fluency task in a group of individuals with depression. The participants in their study were inpatients, met criteria for DSM-IV major episode of depression, and were assessed using the Montgomery and Asberg Depression Rating Scale. All participants in the present study were outpatients. Presence of depression was defined by a cutoff score >10 on the Beck Depression Inventory. The participants in our sample may be less severely depressed than those in the latter study (Lafont et al., 1998). Our depressed group also had significantly more education than their depressed group (13.8 vs. 9.9 years). Given that the total FAS score as well as total switching is significantly correlated with years of education, this may also be explaining the difference in the findings. Further research is underway in our laboratory to examine semantic fluency performance in this sample.

Advanced HIV disease, but not depression, appears to disrupt frontal–subcortical systems involved in switching. Intact clustering performance suggests sparing of temporal lobe systems. Further research should examine these fluency components in individuals with HIV-Associated Dementia Complex (HAD-C) and minor cognitive-motor disorder (MCMD).

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51. The Rey complex figure test: Retrieval deficits related to depression levels following TBI

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The effect of depression on performance of the Rey Complex Figure Test (RCFT) was examined in 48 subjects who had sustained a traumatic brain injury. Depression elevations on the Personality Assessment Inventory (PAI) were not related to scores on any trial of the RCFT. However, the difference score between the Recognition trial and the Delayed Recall trial was correlated with depression elevations. Specifically, improved recognition, relative to delayed free recall, was related to elevated depression levels on the PAI. The difference score, which reflects retrieval processes, was sensitive to depression levels but insensitive to overall impairment. It was suggested that the retrieval score may serve as a marker of memory deficits that can be attributed to depression in individuals who have sustained a TBI.

Report

Memory difficulties are frequently reported by individuals who have sustained a traumatic brain injury (TBI). A substantial proportion of these individuals concomitantly experience depression, which has also been associated with memory difficulties. The individual with comorbid TBI and depression presents a unique challenge to the assessing neuropsychologist. The question arises whether memory deficits should be attributed to the injury per se or the concomitant depression. This determination is crucial for the accurate formulation of a diagnosis, prognosis and treatment plan. The differentiation also has important implications in the medicolegal assessment/treatment of individuals who have sustained a TBI.

Memory difficulties following TBI have been attributed to decreased capacity for initial encoding. For example, DeLuca, Schulteis, Madigan, and Christodoulou (2000) reported that individuals who had sustained a TBI required a greater number of trials to reach criterion on a list learning task. However, once they learned the list to criterion, their recall and recognition scores were equivalent to those of controls. Although there is a relative paucity of analogous studies on visual learning processes following TBI, Shum, Harris, and O'Gorman (2000) reported similar findings with regards to performance on the Shum Visual Learning Test. Individuals who had sustained a TBI recognized fewer of the targets and their learning slope across five trials was reduced, relative to controls. In contrast, their levels of retention were not significantly different from those of the controls. These findings suggest that, following TBI, the quantity of information that is encoded is reduced, although information that is encoded is adequately stored, maintained and accessed.

In contrast, memory deficits in depression are thought to reflect deficits in the active retrieval of information which has been adequately encoded. Ilsley, Moffoot, and O'Carroll (1995) reported that their depressed individuals manifested reduced free recall, but adequate recognition, on the story and message subtests of the Rivermead behavioural memory test. Similarly, Fossati, Deweer, Raoux, and Allilaire (1995) reported that the memory deficits of their inpatient depressed subjects on the CVLT were best characterized as retrieval deficits. The depressed subjects recalled fewer words across the learning trials, relative to controls, although the slopes were equivalent. In addition, depressed subjects exhibited greater inconsistency in their recall. Recognition performance did not differ in depressed subjects and controls.

The current study utilized a sample of 48 subjects who had sustained TBI of varying severities in order to determine the effect of self-reported depression symptoms on performance of the Rey Complex Figure Test (RCFT). The Personality Assessment Inventory (PAI) was utilized to assess the level of self-reported symptoms of depression. It was hypothesized that severity of depressive symptoms would be related to deficits in the free recall trials, whereas recognition would be preserved with increasing levels of depression.

Methods

A sample of 48 subjects was drawn from individuals who had completed a neuropsychological assessment at a private practice in Ontario. All individuals had sustained a head injury, although the sample was not restricted to a particular severity. The individuals were assessed at a mean of 15.4 months ($SD = 18.8$) post-injury. The subjects had a mean age of 37.9 years ($SD = 13.8$) and a mean education of 13.2 years ($SD = 3.0$). There were 24 males and 24 females.

The subjects completed a neuropsychological battery which included the Wechsler Adult Intelligence Scale-3 (WAIS-3), Wechsler Memory Scale-3 (WMS-3), verbal fluency (FAS), the Trail-Making Test, Sentence Repetition, the RCFT, and PAI. A performance rating was derived by calculating the average z-score of each individual on the following tests: FAS, Trails B, Sentence Memory, Digit Symbol of the WAIS-3, and Delayed Logical Memory of the WMS-3. Four subjects were lacking one of the above scores. As a result, the four remaining subtest *z*-scores were utilized to calculate an average performance rating.

Results

As predicted, more severely impaired individuals performed significantly worse on all RCFT measures including the Copy ($r = .324$, $p = .025$), Immediate Recall ($r = .410$, $p = .004$), Delayed Recall ($r = .431$, $p = .002$) and Recognition ($r = .408$, $p = .004$) scores. In contrast, level of depression was not significantly correlated with any RCFT score. Nonetheless, the Recognition score was positively correlated with depression ($r = .131$, $p = .375$), whereas the Delayed Recall score was negatively correlated with depression and approached significance ($r = -.261$, $p = .073$).

Hierarchical regression analyses suggested that the combination of Delayed Recall and Recognition provided the most accurate linear regression equation. As a result, difference scores between the Delayed Recall score and the Recognition score (i.e., Recognition T score–Delayed Recall T score) were calculated. This difference score presumably reflects the retrieval process, with increasing values demonstrating inefficient retrieval in the free recall condition. The retrieval difference score was significantly correlated with level of depression ($r = .354$, $p = .014$), but not with the average performance rating ($r = -.101$, $p = .496$). The correlation between the retrieval score and depression level is unlikely to have been related to constructional skills because the correlation was negligibly reduced by controlling for the Copy score ($r = .3385$, $p = .020$). The relationship between the retrieval score and the depression score remained significant after controlling for age, education, time since injury and average performance rating ($r = .3497$, $p = .027$).

Discussion

The current analyses indicated that greater overall impairment, which presumably reflects severity of the TBI to a substantial degree, was associated with reduced performance on all trials of the RCFT. Conversely, increased levels of depression were not related to performance on any of the RCFT trials. However, improved recognition, relative to delayed free recall, was related to elevated depression levels on the PAI. This relationship was not accounted for by difficulties in reproducing the figure. In addition, the relationship remained significant after controlling for age, education, time since injury and average performance rating.

The retrieval difference score was unrelated to the average performance rating, whereas the scores on all RCFT trials were related to the average performance rating. This suggests that the retrieval difference score is sensitive to levels of depression, but relatively insensitive to the severity of the TBI sequelae. As a result, it is suggested that significant improvement in the Recognition condition, relative to the Recall condition, may serve as a marker of memory deficits that can be attributed to depression in individuals who have sustained TBI.

The current findings provide further support for the suggestion that depression contributes to impaired retrieval of information. The incidental nature of the RCFT reduces the likelihood that the observed findings are due to deficits in applying effortful strategies during the course of initial encoding. Nonetheless, failure to deploy effortful encoding strategies may exacerbate the memory deficits of depressed individuals with TBI, when performing memory tasks in which they have been forewarned. Furthermore, it should be noted that the deficits observed in the current study do not necessarily rule out inefficient encoding in depression.

The current study also illustrates an important point which should be considered in the design and analyses of future studies. In this study, depression was related to the difference between recognition and free recall performance, although neither score alone was related to depression. Configural analyses of test performance may more accurately tap the effects of depression than performance on a single trial.

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52. Assessment of apathy in dementia and mild cognitive impairment with the apathy inventory

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The apathy Inventory (IA) was designed to assess separately three dimensions; emotional blunting, lack of initiative and lack of interest with three subscores (0–12) and a total score. The same set of questionnaire can be used with caregiver and patients. Ninety subjects were evaluated using the IA; 17 healthy elderly subjects, 22 patients with mild cognitive impairment (MCI), 51 subjects with Alzheimer's disease. Only when using the caregiver evaluation AD subjects showed a significantly greater score than controls and MCI for the lack of initiative, lack of interest dimensions and for the total score. When the AD patients where divided according the diagnostic criteria for apathy proposed by Marin, analysis of the caregiver/patient discrepancy score indicated that AD apathetic subjects had poorer awareness of their behavioral changes.

Report

Apathy was defined as a syndrome of diminished motivation and includes symptoms such as reduction or lack of interest, productivity, will, initiative and affective responses towards positive or negative events, leading to decreased goal-directed activities.

Apathy is one of the most frequent behavioral symptoms in Alzheimer's disease (Benoit et al., 1999). Quantitative evaluation of apathy was usually done using either a (by) specific scale such as the Marin's apathy scale (1991) or the derived 14 items scale designed by Starkstein et al. (1992). Alternatively, apathy was also assessed in clinical research and in the majority of the pharmacological intervention studies with the neuropsychiatric inventory (NPI) (Cummings, Mega, Gray, Rosemberg-Thompson, & Gornbein, 1994). In fact, (the) NPI is the only general behavioral inventory which specifically included an apathy item. Limitation of NPI apathy item interest is mainly due to the fact that this leads to a global evaluation of the apathetic phenomenology without possible dissociation of the subcomponent included in the definition.

In order to have such an evaluation, we designed the apathy inventory (IA) which allows the specific assessment of emotional, behavioral and cognitive domains with three different items (1) emotional blunting (lack of emotional response); (2) lack of initiative (diminished goal directed behavior); and (3) lack of interest (diminished goal directed cognition).

The IA was designed on the model of NPI. Information may be obtained from the spouse or another person intimately familiar with the patient's behavior. Information may be gathered by direct observation and by questioning the patient. Each domain had screening questions, which provide a comprehensive overview of abnormal behavior manifested by the patient. If the caregiver indicates that the disturbances have been present during the past month or another specific period, he/she is asked to rate the frequency (1–4) and the severity (1–3) of the disturbances yielding to a frequency $\times$ severity score. The same set of questions can be used with the patient. For scoring, the subject is required to evaluate the importance of the disturbance on a Likert-style scale ranging from 0 to 12.

Population and method

Ninety subjects were evaluated using the IA at the Nice University Memory Center; 17 healthy elderly subjects (7 males/10 females), 22 patients with mild cognitive impairment (6 males/16 females) (MCI), and 51 subjects with Alzheimer's disease (26 males/25 females) according to the icd 10 diagnostic criteria.

In a second step, the AD patients were allocated to an AD apathetic subgroup (AD/A; $n = 20$) if they fulfilled the diagnostic criteria for apathy (Starkstein et al., 2001). AD without these apathetic characteristics were allocated to the nonapathetic subgroup (AD/NA; $n = 31$). Global cognitive performance was assessed in all (the) subjects with the mini mental score evaluation (MMSE).

The following scores were analyzed both for the caregiver and the subject IA version: emotional blunting, lack of initiative, lack of interest and the total score. finally the ratio caregiver/subject evaluation was calculated for each of these dimensions. Statistical analysis was carried out by using means and standard deviations, one-way analysis of variance (ANOVA) and the bonferroni significant difference post hoc tests.

Results

Table 1 summarizes the clinical and IA scores for each groups. there were no differences for any of these scores between the control and the MCI groups. MMSE score indicated that ognitive perfor-

Table 1
Demographic data and IA scores of the control, MCI, and AD subjects with and without apathy

	Control $n = 17$	MCI $n = 22$	AD $n = 51$	AD/apathetic $n = 20$	AD/nonapathetic $n = 31$
Age	71.1 (8.5)	71.7(6.1)	74.3 (6.8)	73.8 (6.6)	74.6 (7.1)
MMSE	28.9 (1.1)	28.2(1.1)	22.8 (3.9)**	22.8 (4.1)	22.8 (3.9)
IA caregiver					
Emotion	0	.4 (1.3)	1.6 (3.2)*	3.7 (4.2)	.2 (.7)
Initiative	.2 (.5)	2.2 (4.2)	3.5 (4.2)*	7.3 (4.2)	1.1 (1.7)
Interest	.3 (1)	2 (4)	3.6 (4.7)*	8.4 (3.5)	.5 (2.2)
Total score	.5 (1.1)	4.6 (8.9)	8.7 (10)*	19.4 (9.2)	1.8 (2.7)
IA subject					
Emotion	.6 (2.3)	.4 (1.3)	.6 (1.7)	.9 (2.2)	.4 (1.2)
Initiative	0	1.2 (2.4)	1.4 (2.6)	1.4 (2.7)	1.4 (2.5)
Interest	.7 (2.1)	1.6 (2.5)	1.6 (2.8)	2.3 (3.2)	1.1 (2.3)
Total score	1.3 (3.3)	2.7 (3.8)	3.6 (5.7)	4.6 (7.3)	3 (4.3)

* $p > .01$ AD vs Controls and MCI.
** $p > .001$ AD vs Controls and MCI.

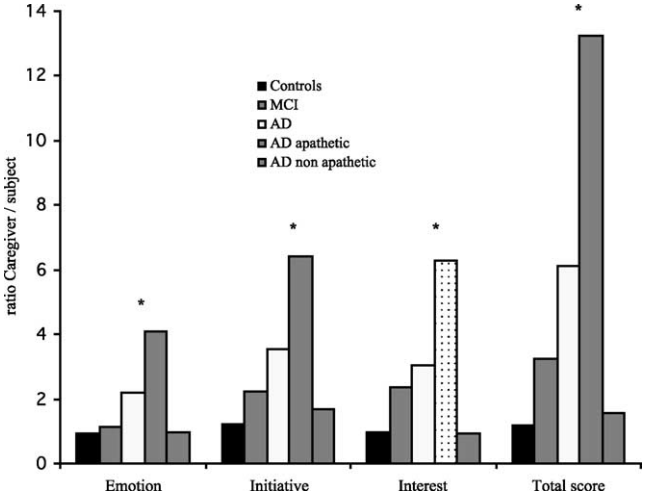

Fig. 1. Awareness of apathy in the different subgroups using the ratio Caregiver/subject evaluation. *, $p > .01$ AD vs. controls; **, $p > .001$ AD/A vs. AD/NA.

mance of the AD group were significantly poorer than the control group and the MCI groups ($p < .0001$).

Regarding to the IA scores only when using the caregiver evaluation, AD subjects showed a significantly greater score than controls and MCI for lack of initiative, lack of interest dimensions and for the total score.

When AD patients were divided in apathetic (AD/A) and nonapathetic (AD/NA) according to the diagnostic criteria for apathy proposed by Marin, the analysis of the caregiver/subject evaluation score indicated that AD/A patients had higher ratios than the AD/NA. This indicated that AD apathetic subjects had a poor awareness of their behavioral changes (see Fig. 1).

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