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Hemispheric Dominance for Emotions, Empathy and Social Behaviour: Evidence from Right and Left Handers with Frontotemporal Dementia

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Abstract

Although evidence from primates suggests an important role for the anterior temporal cortex in social behaviour, human research has to date concentrated almost solely on the orbitofrontal cortex and amygdala. By describing four cases of the temporal variant of frontotemporal dementia we show how this degenerative condition provides an excellent model for investigating the role of the anterior temporal lobe, especially the right, in emotions, empathy and social behaviour. Assessments of semantic memory, processing of emotional facial expression and emotional prosody were made, empathy was measured, and facial expressions of emotion were coded. Of the two right handers described, one subject with predominantly left temporal lobe atrophy had severe semantic impairment but normal performance on all emotional tasks. In contrast, the subject with right temporal lobe atrophy showed severely impaired recognition of emotion from faces and voices that was not due to semantic or perceptual difficulties. Empathy was lost, interpersonal skills were severely affected and facial expression of emotion was characterized by a fixed expression that was unresponsive to situations. Additionally, two left handers with right temporal lobe atrophy are described. One demonstrated the same pattern of hemispheric lateralization as the right handers and had emotional impairment. The other left hander showed the opposite pattern of deficits, suggesting a novel presentation of anomalous dominance with reversed hemispheric specialization of semantic memory and emotional processing.

Introduction

Towards the end of the last century there was a renewed interest in the neural basis of emotions and social behaviour, concentrating primarily on the limbic system. Phylogenetic studies, supported by anatomical evidence, suggest that the limbic system can be divided into two paralimbic divisions (Mega *et al.*, 1997). One of these, the paleocortical division, appears to have begun its development in the orbitofrontal region of the olfactory paleocortex and spread, in both phylogenetic and anatomical terms, through the insula, the temporal pole and amygdala. Through mammalian evolution this paleocortical system has become specialized for appetite drives, social awareness, mood, visceral integration, and implicit processing.

To date, studies of abnormal human social behaviour have concentrated predominantly on the role of the orbitofrontal cortex (Eslinger and Damasio, 1985; Damasio *et al.*, 1994; Damasio, 1996; Cicerone and Tanenbaum, 1997; Sarazin *et al.*, 1998; Blair and Cipolotti, 2000) with recognition of the amygdala's involvement in the processing of emotions (Adolphs *et al.*, 1994, 1995; Young *et al.*, 1995; Calder *et al.*, 1996; Scott *et al.*, 1997). Despite several lesion studies of primates suggesting that the anterior temporal cortex is important in modulating social behaviour (Plotnik, 1968; Franzen and Myers, 1973; Raleigh and Steklis, 1981), work with humans has tended to neglect the role of this region, possibly because discrete lesions of the anterior temporal pole are rarely due to tumours and almost never strokes.

As shown by its use in elucidating the neural representations of semantic memory, the temporal variant of frontotemporal dementia provides a powerful model for investigating the functions of the anterior temporal lobe (Hodges and Patterson, 1997; Mummery *et al.*, 2000). In this article we present evidence that the anterior temporal lobe, especially the right, is involved in aspects of emotional processing and empathy and that temporal variant frontotemporal dementia offers a hitherto unrealized opportunity to study systematically these aspects of social behaviour in humans.

Several studies have suggested that emotional processing is mediated primarily by the right cerebral hemisphere in humans (Ley and Bryden, 1979; DeKosky *et al.*, 1980;

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Blonder *et al.*, 1991; Bowers *et al.*, 1991a; Adolphs *et al.*, 1996; Borod *et al.*, 1998). Consensus on which parts of the right hemisphere are involved in specific emotional processes has been harder to delineate, although the majority of studies have concentrated on the right posterior temporal and parietal lobes. In addition to the right hemisphere hypothesis is the valence hypothesis which states that the right hemisphere is dominant for negative/unpleasant emotions and that the left hemisphere is dominant for positive/pleasant emotions (Sackeim *et al.*, 1982). The emotional system may be investigated in many ways and it is useful to distinguish between tasks that assess a subject's ability to recognize, name, or match emotional stimuli, and tasks that assess the emotional production or reactivity of a subject. In this article we use a task, the Florida Affect Battery, to measure the ability to name and match emotional faces and voices, and assess emotional production by examining facial expression of emotion.

Effective social communication and the formation and maintenance of interpersonal relationships are fundamental to the success of an individual in a social group and to the success of the social group itself. A primary requirement for this is the ability to empathize, that is, to be able to share the emotional states of others. The neural underpinnings of empathy are virtually unexplored (Brothers, 1989) and what attempts have been made to measure empathy have concentrated on patients with static lesions of the orbitofrontal cortex (Eslinger, 1998). Although formal definitions of empathy have remained elusive, research recognizes two distinct aspects of empathy. In one, a cognitive approach, empathy relies upon the ability to take another's viewpoint and may be seen as role taking or perspective taking. The other more emotional approach requires the ability to experience the feelings of another. This multidimensional approach to empathy led to the development of the Interpersonal Reactivity Index (IRI), a four subscale measure used in the present study, that assesses perspective taking, fantasy, empathic concern, and personal distress (Davis, 1983).

Four cases of the temporal variant of frontotemporal dementia are described. First, two right-handed subjects, one with right temporal atrophy and one with left temporal atrophy, suggest the lateralization of semantic memory to the left hemisphere and emotional processing and empathy to the right hemisphere. Additional evidence that emotional processing and empathy are lateralized not only to the right hemisphere, but more specifically to the non-language dominant hemisphere, comes from the subsequent description of two left-handed subjects, both with right temporal atrophy. One of the left handers demonstrated the same cerebral lateralization of functions as seen in the right handers, while the other appeared to have crossed functions of semantic memory and emotions.

Whereas the literature contains cases of reversed hemispheric organization in left handers (Delis *et al.*, 1983; Dronkers and Knight, 1988; Padovani *et al.*, 1992), the lesions involved have invariably been posterior temporal or parietal and the crossed functions have been language, visuospatial function, neglect, prosodic interpretation, and praxis. To our knowledge cases of reversed hemispheric organization of semantic memory, emotional processing, and empathy have not been described.

Methods

Four male patients with frontotemporal dementia were selected from those undergoing longitudinal evaluation at the Memory and Aging Center, University of California, San Francisco, USA. All patients were assessed by a neurologist and neuropsychologist and had magnetic resonance imaging (MRI). Subjects were excluded if they had a history of known or suspected cerebral ischaemic event, alcohol abuse, other major medical illness or if there was a past history of depressive illness.

All patients met current consensus criteria for the diagnosis of frontotemporal dementia (Neary *et al.*, 1998). The subjects and their spouses or siblings gave written consent to participate in the research and to have their photographs used for scientific publications.

Structural MRI analysis

MRI images were analysed to obtain measurements of regions of interest. MRI images were acquired using a Siemens Vision scanner and the standard Siemens head coil. Coronal views through the anterior temporal region of each subject are shown in Fig. 1. Structural MRI sequences included: (1) two-dimensional FLASH MRI along three orthogonal directions, 3-mm thick slices, 15 slices in each direction to obtain scout views of the brain for positioning; (2) a double spin echo sequence was performed to obtain proton density and T2-weighted MRIs, $TR/TE_1/TE_2 = 5000/20/85$ ms, 51 contiguous axial slices (3 mm) covering the entire brain and angulated $-10°$ from the anterior commissure-posterior commissure line; 1.0×1.25 mm^2 in-plane resolution; and (3) volumetric T1-weighted gradient echo MRI (MPRAGE) of the entire brain, $TR/TE/TI = 10/4/300$ ms, 15° flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0×1.0 mm^2 in-plane resolution and 1.5 mm slab thickness.

The subjects' brains were first segmented into grey and white matter and cerebrospinal fluid (CSF) using locally developed software that uses proton density, T2-weighted, and T1-weighted MRI to classify tissues automatically into the three major tissue types (Di Sclafani *et al.*, 1995; MacKay *et al.*, 1996a, b; Tanabe *et al.*, 1997). Further manual editing was performed to separate cortical from subcortical grey matter, ventricular CSF from sulcal CSF, and to delineate subcortical white matter lesions.

Regions of interest included the frontal lobe cortex, amygdala and cortex of the anterior temporal pole.

The frontal lobes were delineated in the axial plane directly on segmented images, using co-registered T1-weighted

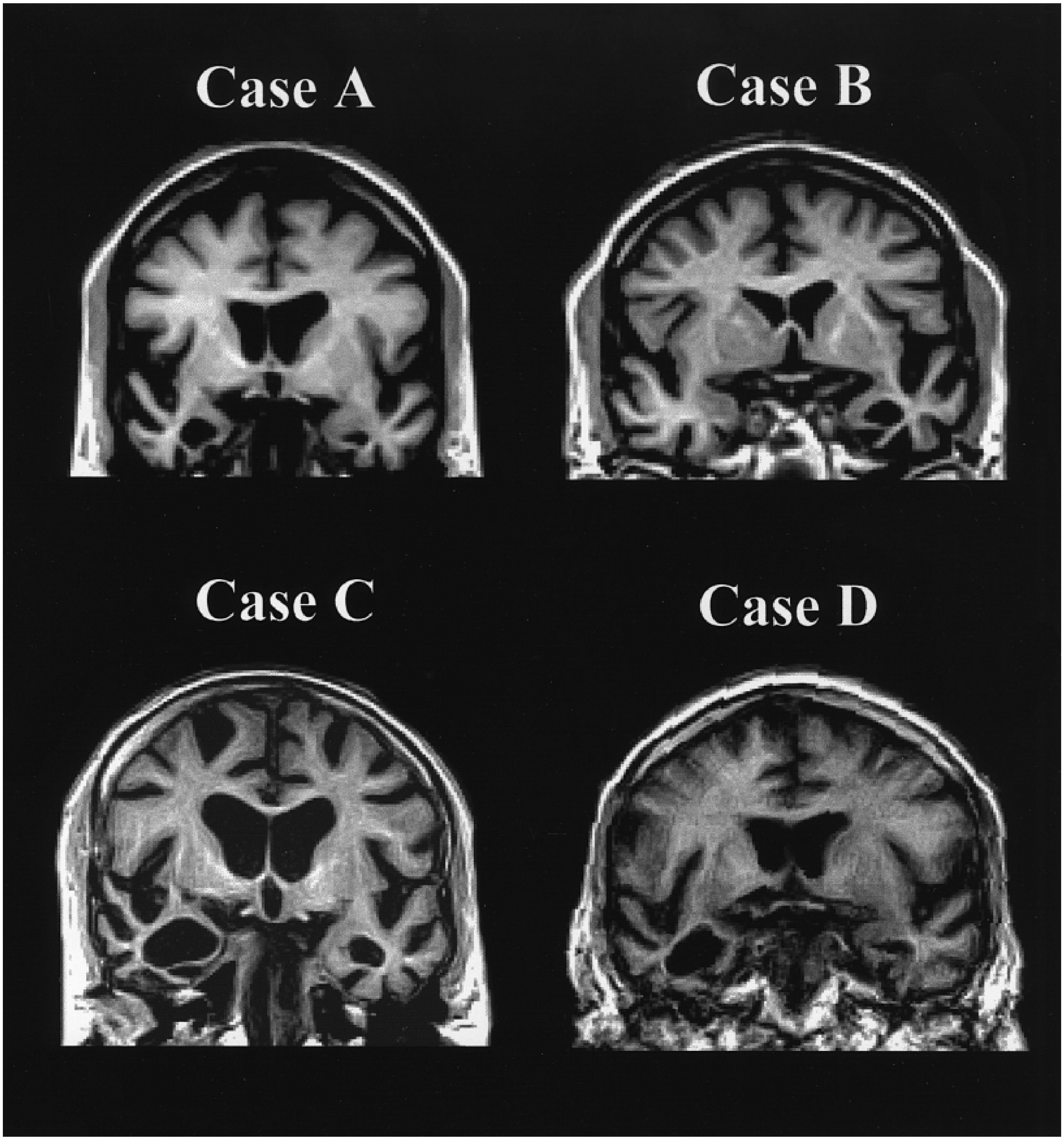

Fig. 1. MRI scans showing coronal views through the anterior temporal lobe at the level of the amygdala.

images as a guide. The central sulci and sylvian fissures were used as landmarks for the posterior border, while the lateral, medial, superior and inferior borders were easily identifiable by grey matter/CSF boundaries.

The temporal lobe was delineated in the coronal plane on the T1-weighted images. The anterior temporal pole was defined as those regions of the temporal lobe anterior to the closure of the sylvian fissure, where the uncinate fasciculus passes between the frontal and temporal lobes (posterior border). Lateral and anterior borders for the anterior temporal lobes were easily identifiable and marked by CSF.

The amygdala was also identified in the coronal plane on T1-weighted images. The anterior boundary of the amygdala was defined posterior to the closure of the entorhinal sulcus. The medial and superior boundaries were the CSF medial to the temporal lobe. The lateral boundary was defined by the grey/white border in the white matter of the temporal lobe with the extra requirement that no tissue be included superior to the entorhinal sulcus. This approach is essentially the same as the one used by Watson *et al.* (1992) to obtain amygdala volumes. While the use of the CSF margin as the medial boundary includes portions of entorhinal cortex in the amygdala measurement, the separation between amygdala and entorhinal cortex medially can be very difficult, even at 1 mm resolution. The approach including all structures lateral to the CSF boundary ensured the reproducibility of the measurements. Likewise, the superior/lateral border of the amygdala can be difficult to separate from the adjacent caudate nucleus and claustrum. The approach of making the entorhinal sulcus the arbitrary superior border was used to increase reliability.

Masks were obtained for each structure outlined in the coronal plane and combined with the segmented images to obtain a grey matter volume for each structure (not required for amygdala as it is essentially all grey matter). All regions of interest were corrected for differences in head size by normalizing the regional volume using the total intracranial volume, which is the sum of tissue and fluid volumes measured inside the skull.

Region of interest measurements were made as outlined above for the four patients discussed in this analysis, as well as for 12 control subjects, approximately matched in age to the patient group. All control subjects had no history of neurological or psychiatric disorders, and had no evidence of focal disease or subcortical white matter ischaemic changes on their MRI. The mean age for the 12 control subjects was 66.8 years [standard deviation (SD) = 8.19, range 56–81]. The degree of abnormality for each region of interest in each patient was expressed as a *z*-score (patient value – control mean/control SD). A *z*-score of less than –2.33 ($P = 0.01$) was selected as a cut-off for a significant degree of abnormality.

Cognitive and behavioural assessment

Each subject was given a brief background neuropsychological evaluation to assess general cognitive abilities, executive function, and visuospatial function before a more detailed examination of semantic memory and emotional processing. For the background neuropsychological evaluation and semantic memory assessment, the subjects were compared with 10 age-matched controls (see Table 1).

Background neuropsychological evaluation

Each subject completed the Mini Mental State Examination (Folstein *et al.*, 1975) and verbal and performance IQ scores were calculated from the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1981). Executive function was assessed by verbal fluency and the California Card Sorting Test. For verbal fluency, the subjects were asked to generate as many words as possible beginning with the letters F, A and S (excluding proper nouns) each within 1 min and the score was taken as the total number of correct responses. The California Card Sorting Test (Dimitrov *et al.*, 1999; Delis *et al.*, 2000) is a measure of concept recognition and categorization, where six variously coloured, sized, and shaped cards bear the names of six items. The subjects were asked to 'sort' the cards into two piles according to self-generated concepts. The cards can be sorted by size, shape, colour, semantic categories (e.g. animals), semantic attributes (e.g. can fly), etc. The maximum number of sorts is 8. Visuospatial function was briefly assessed using the modified Rey Figure, a simplified version of the Rey–Osterrieth Figure, scored out of a total of 17.

Semantic memory

Naming

A 64-item naming test was given to each subject. The naming test consisted of line drawings selected from the Snodgrass and Vanderwart corpus to comprise a test of 32 living and 32 man-made items.

Pyramids and Palm Trees Test

This 52-item test assesses semantic knowledge and both the picture and word versions were given (Howard and Patterson, 1992). Subjects are required to match conceptually related items. For instance, in the picture version, a picture of an Egyptian pyramid is placed above a picture of a pine tree and a palm tree, and the subject is asked to judge which one goes with the pyramid. In the word version, the word 'pyramid' is placed above the words 'pine tree' and 'palm tree'.

Emotional processing

All subjects were given tasks of facial and prosodic emotional processing. Selected subtests of the Florida Affect Battery were used (Bowers *et al.*, 1991b). All subtests consisted of 20 trials.

(i) Facial affect discrimination. The subjects were presented with cards bearing two photographs of different women. In half the trials, the two women displayed the same emotional expression, and in the remaining trials the expressions were different. The subjects were asked whether the two faces showed the same or different emotional expressions.

(ii) Facial affect naming. The words 'happy', 'sad', 'angry', 'frightened' and 'neutral' were placed beside the face of one of four women each displaying one of the five emotions. The subjects were asked to name the affect of individual faces shown sequentially.

(iii) Emotional prosody discrimination. Semantically neutral pairs of sentences that may be spoken in the same or different emotional tone of voice were played. The subjects judged whether the emotional prosody was the same or different in both sentences.

(iv) Prosodic affect naming. The subjects listened to semantically neutral sentences spoken with one of five emotional prosodies (happy, sad, angry, frightened, or neutral). The

Table 1. Performance of four subjects on background neuropsychological assessment and assessment of semantic memory

	Case A	Case B	Case C	Case D	Controls (*n* = 10)
Handedness	R	R	L	L	
Side of atrophy	R	L	R	R	
Mini Mental State Examination (30)	30	24	24	23	29.1 (0.9)
Verbal IQ	90	82	90	84	
Performance IQ	83	109	68	–[a]	
Naming: living (32)	24	5	21	5	31.2 (0.8)
Naming: man-made (32)	32	16	29	15	30.9 (1.7)
Naming (total) (64)	56	21	50	20	62 (2.05)
Pyramids and Palm Trees: pictures (52)	41	43	31	43	50.8 (0.63)
Pyramids and Palm Trees: words (52)	46	39	42	38	50.8 (1.32)
FAS fluency	33	43	23	–[a]	33.2 (12.2)
California Card Sorting Test	5	5	1	3	4.1 (1.4)
Rey Figure copy	17	17	12	17	16.2 (1.0)
Design fluency	6	9	2	9	8.0 (3.1)

[a]Testing not completed due to time constraints.

subjects were asked to name the emotional prosody for each sentence from a list of the five emotions.

(v) Match emotional face to emotional prosody. Semantically neutral sentences were played to the subjects. Each sentence was spoken with one of five emotional prosodies. In front of each subject was a card with three photographs of the same woman expressing three different facial emotions. The subjects were asked to point to the emotional face that corresponded to the emotional tone of voice of the speaker.

Empathy

The spouses of the subjects completed an assessment of empathy, the IRI (Davis, 1983). The IRI consists of 28 statements, seven for each of four subscales, which are rated on a Likert scale from A to E according to how well each statement describes the subject. The maximum score on each scale is 28. The perspective taking scale (e.g. the patient believes there are two sides to every question and tries to look at them both) assesses the ability to adopt spontaneously another's point of view and is associated with higher self-esteem but little emotionality. The personal distress scale (e.g. being in a tense emotional situation scares the patient) measures levels of personal anxiety and unease. The fantasy scale (e.g. the patient is likely to daydream and fantasize, with some regularity, about things that might happen to them) gives an indication of how easily someone can transpose themselves into the feelings of imaginary characters in books, movies and plays. The empathic concern scale (e.g. if the patient saw someone being taken advantage of, they would feel protective towards them), which shows a relationship to emotional reactivity, assesses feelings of sympathy and concern for unfortunate others and is related to prosocial behaviour. The IRI was adapted to be completed by observers in rating empathy both currently and before disease onset. Control subjects were age matched and spouses completed the IRI questionnaire judging the subjects for both the current time and 10 years previously.

Facial expression

Videotapes of all four subjects were coded using the Facial Action Coding System (FACS; Ekman and Friesen, 1978). This coding system identifies specific muscle movements involved in facial expression of emotion. Two aspects of emotional expression were of particular concern: duration of emotional expression and genuine versus unfelt smiles (Ekman *et al.*, 1990).

Results: right handers

First we describe the pattern of semantic memory and emotional impairment seen in right and left temporal lobe atrophy in right handers.

Case A

Case A, a 52-year-old right-handed male, presented with the chief complaint of 'my wife thinks that I may benefit from seeing a doctor'. He saw nothing to be gained from the evaluation, as he believed that he was perfectly normal and came only because his wife had recommended it. He went on to report that for the last 3–4 years his wife had complained about his angry outbursts, memory problems and behavioural changes. He denied any angry outbursts and described his memory problems as forgetting peoples' names. He denied behavioural changes but admitted to diminishing his interactions with his wife to prevent upsetting her. The patient had stopped working several months previously. He explained that his employers had told him to take a few weeks off and denied any difficulties in the workplace. He reported no problems with driving, reading, writing, handling money, or finding his way around. His wife, who gave a contrasting history, accompanied the patient to the clinic.

Case A had a normal social life at school and at college and was described as a warm and empathic personality who used to write love letters to his young wife when he was on his military service. Early photographs also show him enjoying a costume party and playing affectionately with his children. From about 8 years prior to presentation this bright, light-hearted and energetic person became progressively more serious, tired and sombre. A subtle emotional blunting began 8 years previously. More dramatic problems began 4 years prior to evaluation. Following an incident when the couples' daughter had been unfairly slandered by a teacher at school, case A's family were shocked at his lack of concern for their distraught daughter. Later, when his wife cut off the tip of her finger with a borrowed power tool, the patient responded by ensuring that the tool was returned to their neighbours before searching for his driving licence. Also he accused his wife of screaming too much while they drove to hospital. Along with a loss of empathy, the patient lost his sense of humour and developed an increasing interest in religion. He became a voracious reader of the Bible, stopped drinking for religious reasons, and 2 years ago chastised his friends at a Super Bowl party for betting on the game. He lost his sense of dress, self-care, and played solitaire on his computer for hours at a time. Rigidity was noted in his dressing and driving habits where he would insist on changing lanes, even if the lane change was dangerous. His appetite changed with an increase in weight and loss of libido. Cognitive deficits started about 2 years ago.

The patient had graduated from university and previously worked as a logic circuit designer for a computer company until inefficiencies and unresponsiveness at work led to his dismissal. There were progressive naming problems and the patient was unable to remember the names of neighbours and family friends that he had known for many years. On examination, social interaction was strikingly abnormal. Case A showed a normal range of voluntary facial movements but a severely restricted range of spontaneous expression in social interaction. Owing to the lack of reassuring facial signals that we usually expect in social interaction, those meeting case A for the first time often felt uneasy and interpreted his facial expressions and behaviour as hostile. Speech was fluent, quiet, with loss of prosodic variation but normal syntax. There were deficits in speech pragmatics with a seeming unawareness of socially accepted rules of conversation. Case A was prone to verbosity, related over-detailed personal memories that were often tangential to the preceding conversation, and he seemed unaware and unconcerned about whether those listening to him were interested. Neuropsychological testing showed a perfect score of 30/30 on the Mini Mental State Examination and above average episodic memory on a nine-item version of a list-learning task. After a 10 min delay, case A was able to remember eight out of nine items and could recall seven of these items when tested 2 weeks later. Memory for visual information was also normal and visuospatial function was intact in copying a complex figure. IQ scores were below expectations given his level of education (verbal IQ = 90; performance IQ = 83), although performance IQ was felt to be the more affected of the two measures (see Table 1).

Case B

A 65-year-old male was brought for assessment of a progressive language disorder. His language problems were first noted on a boating trip with his brother when he was unable to remember the names of places that they had often visited on previous vacations. Despite being unable to name places, he showed excellent navigational skills in steering the boat to these places after their radar had broken down. On 4 July he described fireworks as 'those things that shot up in the sky' and when he visited the hospital clinic he had difficulty in filling out questionnaires that contained words such as 'diarrhoea'. Day-to-day memory was preserved and he had no difficulty in recalling details of previous visits to the hospital, even where they had stopped off for gas on the way. His navigation and spatial skills remained excellent and he still flew a glider solo. Seven years previously he lost most of his money when deceived by an unscrupulous business partner. After this he was never able to work successfully and became highly disorganized. His wife noted that there was a tendency for him to be obsessive and on visiting the clinic he made a point of collecting and filing photocopies of all forms that he had been given. He asked all members of staff for their business cards and insisted on giving each person one of his own. He brought photographs of his gliding trips and his dog to the clinic and showed them to everyone several times, giving out photographs for the staff to keep.

On examination speech was fluent but empty of content words with frequent semantic paraphasias but normal syntax and phonology. Social interaction was normal, humour was intact and facial expressions of emotion were considered to be normal. Neuropsychological evaluation demonstrated a Mini Mental State Examination of 24/30. Insight was preserved and he was keenly aware of his shortcomings on neuropsychological tests. Episodic memory was normal on interview but formal testing showed impairment in verbal list learning and recall, with only one of nine words recalled after a 10 min delay; recognition was only 5/9 words with seven false-positive errors. Visuospatial function skills were intact, with above average scores obtained on WAIS-3 Block Design and Matrix Reasoning. He earned a performance IQ of 109 but a verbal IQ of only 82. Executive function was unimpaired on the California Card Sorting Test where he identified an average number of novel sorts (5/8).

Semantic memory

Case B (left temporal lobe atrophy) showed a severe semantic deficit on all tests of semantic memory (see Table 1). Confrontational naming was profoundly impaired and errors were semantic in nature with superordinate and cross-category responses (e.g. all kinds of birds were called birds with no discrimination, most of the animals were called dog), typical of reported cases of semantic dementia (Hodges *et al.*, 1995). That his semantic deficit is not solely a language deficit is

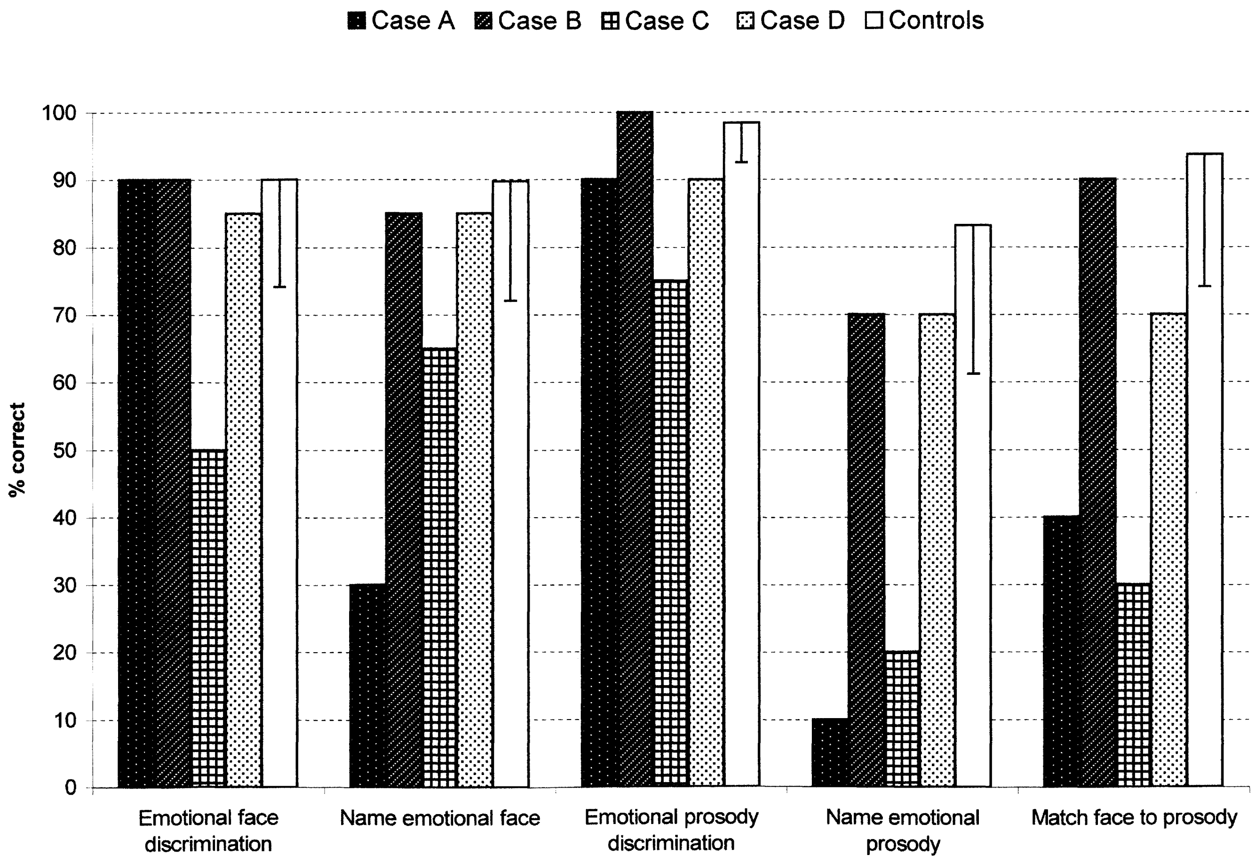

Fig. 2. Performance on tests of emotional face and prosody processing from the Florida Affect Battery. Error bars for controls represent a score of 2 SD below control mean.

evidenced by his performance on the Pyramid and Palm Trees Test where he showed impairment on both the word and picture versions. In summary, his pattern of deficits is consistent with semantic dementia, in which semantic memory loss has been shown to correlate with volume loss in the left temporal pole (Mummery *et al.*, 2000).

Case A (right temporal lobe atrophy) showed mild semantic deficit in comparison with case B (see Table 1). Although significantly impaired on the naming test overall, he was able to name all 32 of the man-made items. It is of note that although case A was impaired on both versions of the Pyramid and Palm Trees Test, in contrast to case B, he showed superior performance on the word version in comparison with the picture version. This is consistent with previous reports of patients with semantic dementia where those with predominant right temporal lobe atrophy tend to have worse performance on the picture version and those with left temporal lobe atrophy have worse performance on the word version (Lambon Ralph *et al.*, 1999).

Emotional processing

Performance on the subtests of the Florida Affect Battery is shown in Fig. 2. Case B performed normally across all emotional processing tasks. In contrast to case B who showed severe loss of semantic memory but normal emotional processing, case A demonstrated marked impairment in naming both facial emotional expressions and in naming emotional prosody. That this deficit is not solely due to a semantic impairment for emotional terms is evidenced by his poor performance on matching emotional prosody to emotional faces, a task that can theoretically be completed without verbal mediation. Neither is this likely to be due to subtle perceptual problems, as case A was performing normally on a task in which he had to distinguish perceptually whether two emotional faces or two emotional voices were the same or different.

Empathy

The most significant changes in empathy were seen in the empathic concern and perspective taking subscales, commonly associated with the emotional and cognitive aspects of empathy. In the fantasy and personal distress subscales, changes in all subjects were within 2 SD of control means. Consistent with his history, case A showed a marked loss of empathy when assessed by his spouse (see Fig. 3). His score on the empathic concern subscale dropped from 21/28, to 3/28, and from 20 to 0 on the perspective taking subscale. Case B showed no significant change in empathic concern or perspective taking.

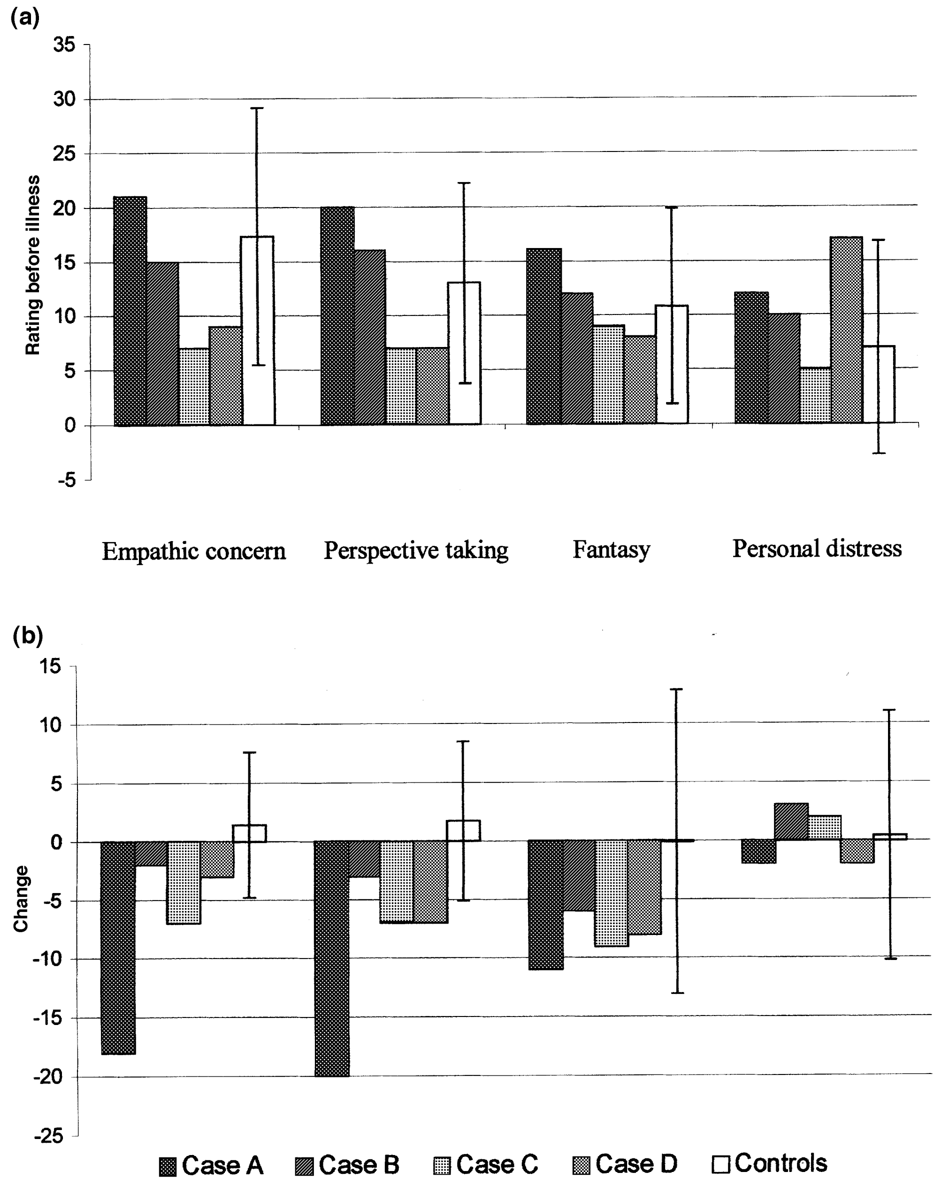

Fig. 3. Assessment of empathy as measured with the IRI: (a) rating before disease onset; (b) rating now.

Facial coding for felt and unfelt smiles

First, the duration of emotional expression was compared between the subjects. A hallmark of normal emotional expression is the brief display of emotion on the face in response to a particular stimulus. Case B showed dynamic facial expression of emotion in response to interactions, whereas in contrast case A had a frozen facial expression. Specifically, case A showed slight movement of the zygomatic major muscle resulting in a fixed smile.

In addition to duration, these two cases showed a difference between genuine and unfelt emotion. Research has demonstrated that Duchenne smiles reflecting genuine positive emotion involve a different pattern of facial movements than smiles that are unfelt or do not reflect positive emotion (Ekman *et al.*, 1990; Frank and Ekman, 1993). Specifically, Duchenne smiles involve synchronous movement of the zygomatic major and the orbicularis oculi (and not other movements), whereas unfelt smiles only involve zygomatic major movement. Figure 4 shows example smiles from all four subjects. The smile of case A reflects an unfelt smile. All the facial movement is concentrated around the mouth and there is no involvement of orbicularis oculi. In addition to zygomatic major there is also involvement of caninus around the mouth which gives rise to the slightly pinched look of the upper lip drawn back across the teeth. Of interest are earlier family photographs of case A. In 1980 he is seen with a broad and intense Duchenne smile, but by 1993 his smile is clearly abnormal (Fig. 5).

In comparison, case B shows a relatively low-intensity Duchenne smile with synchronous movement of the zygomatic major and orbicularis oculi reflecting a 'felt' smile.

Fig. 4. Facial expressions of the four subjects. From top left, clockwise, case A, case B, case D, case C.

In summary, the subject with left temporal lobe atrophy demonstrated the profound semantic impairment typical of semantic dementia. Performance on emotional tasks was preserved with normal processing of facial and prosodic expressions of emotion, no change in empathy, and normal facial movements in expressing positive emotion. Social interaction remained intact with good insight, humour and warmth in personal relationships.

In contrast, the subject who had right temporal lobe atrophy showed severe impairment on all tasks of the emotional

Fig. 5. Facial expression of case A seen in 1980 (left) and 1993 (right).

assessment. He was unable to name emotional expressions from face or voice cues, unable to match emotional faces to voices, showed a dramatic loss of empathy, and had abnormal facial expression of emotion. Social interaction was highly abnormal and relationships within family, friends and workplace had deteriorated.

Results: left handers

Having described the semantic and emotional lateralization in right handers we looked for further supportive evidence from the investigation of two left handers. Both left handers had predominant atrophy of the right temporal lobe (see Fig. 1).

Case C

A 74-year-old left-handed man was brought to the clinic by his wife. There was no family history of sinistrality in first-degree relatives. He opened the consultation by claiming that he had sleep difficulties. He went on to report that he had seen a doctor who had told him he had Alzheimer's disease. Case C emphatically denied this and claimed 'I don't have Alzheimer's, never have had it, never will have it'. Before arriving at his clinic appointment, case C had telephoned our staff several times. He repeatedly claimed that the consultation was too expensive and should not cost more than $100. His previous personality was described as generally unempathic, hot-tempered and inflexible.

He had graduated from university and worked as an economist for the foreign service and was able to give an accurate account of the countries that he and his wife had lived in while attached to the diplomatic corps. In the last 3–4 years he had become obsessive. He would constantly explain that his zip code was wrong and write an amendment to this effect on every envelope that he posted. He started to write repetitive letters to an ambassador in Sydney, Australia about a contentious issue that dated back to the 1970s and wrote over 10 letters to our own clinic over a 6-month period. Each letter was virtually identical and explained that the patient did not have any behavioural or cognitive problems but merely had sleep difficulties. After his initial diagnosis he was advised not to drive and became obsessed with regaining his licence. He became unaware and unconcerned about the feelings of others. When his wife had to undergo surgery, case C did not seem to register her worries. He was asked whether he considered his wife's surgery or his regaining his driving licence to be of greater importance and explained at length how good a driver he was and how he had never had an accident. His facial expressions of emotion changed and he developed a fixed expression that was often incongruent with the moment. There was evidence of disinhibition. For example, case C threw a tantrum audible throughout a theatre auditorium after ushers refused to let him into the concert late. New habits developed in addition to his hypergraphia. He played scrabble and solitaire on the computer for many hours at a time. A decline in organizational abilities was shown when he was unable to organize speakers for a yearly lecture series that he had run. When introducing speakers he neglected to concentrate on the quality of the speakers or their past achievements but instead spoke only about himself. Social interaction was abnormal. Case C lost the art of conversation and would ramble on themes of his own. He would interrupt others and showed no interest in those around him. Speech was fluent with some mild evidence of word-finding difficulties. Autobiographical memory was intact and he was still able to write a coherent, if inappropriate, letter. Episodic memory was intact on interview and he was able to recall details of recent events. Increasingly he had difficulty in recalling people's names. Mini Mental State Examination was 24/30. He was fully oriented to time and place. Verbal IQ was 90 and performance IQ was only 68. He had some difficulty with visuospatial tasks, making several mistakes on a copy of the modified Rey Figure. Executive function was impaired on the California Card Sorting Test, but he was within normal limits on verbal fluency.

Case D

A 73-year-old left-handed man presented to the memory clinic with the claim that he never remembered anything. He described particular trouble with names and was no longer able to remember the name of his best man. He had developed difficulties in remembering the names of colleagues that he had worked with for over 30 years. He was no longer able to remember the names of his grandchildren and would write them down before visiting them. Although case D reported that his memory problems started 3 years ago, his wife believed that he may have had problems with peoples' names for as long as 8–10 years. Until 2 years prior to being seen he had run his own business. He still kept a bank account, used an automated cash machine, and wrote cheques without difficulty. Case D reported no difficulty in finding his way around and had never been lost. He was able to give a detailed account of his journey to the clinic, including the airline he travelled on, the time of the flight, where they sat, and what they ate. He was, however, unable to recall the name of the city he had come from. When describing what he had for breakfast he said he had 'eggs and that brown stuff that you fry and it's long like this'. When he was given the word 'bacon' he went on to say 'Yeah, and I like that stuff that comes from that country north of us', but was unable to remember the name 'Canada'. Behavioural symptoms had started 3–4 years previously. Case D became disinhibited in public and prone to theatrical and hypochondriacal behaviour. He approached strangers and openly discussed grandiose tales about his business deals. He became obsessed about taking his medicines and would take them at exactly the same time wherever he happened to be or whatever he or those around him were engaged in. He also became obsessive about pains in his legs and constantly rubbed cream into them, getting up several times a night to do this. Breakfast had to consist of three pieces of Canadian bacon and he would not tolerate two or four pieces. His weight had increased due to a newly developed liking for 'In and Out Burgers' and 'Taco Bell'. Self-care had declined. Case D used to be a particularly sharp dresser, but would leave the house with stained clothing and wear the same clothes every day. Case D had a life-long talent for art and sculpture and continued to exhibit excellent spatial skills. On examination, social skills were intact and he was charming to the staff in our clinic. Facial emotional reactions were intact. In conversation he was somewhat verbose and occasionally broke the rules of turn-taking by interrupting others. Speech was fluent, had normal syntax and prosody, but was empty with significant word-finding difficulty and circumlocution. General neuropsychological evaluation showed a Mini Mental State Examination of 23/30. Verbal IQ was 84. Although a performance IQ could not be generated because of time constraints, he scored at the 91st percentile on WAIS-3 Matrix Reasoning. He was well oriented to time but could not remember the name of the hospital. On an episodic memory task of word list learning he showed impaired encoding but no evidence of rapid forgetting as he could recall the same number of items after a 10-min delay as after the four learning trials. Calculations were normal and he scored three novel sorts on the California Card Sorting Test which was low but within normal limits. Further testing of executive functioning showed that he was able to complete a modified Trails test within the normal time and performed normally on the Stroop Interference Test, despite some difficulty with basic colour naming. The intersecting pentagons from the Mini Mental State Examination and a modified Rey Figure were copied without mistake.

Semantic memory

Case C demonstrated semantic deficits of similar severity to case A (see Table 1) with a mild impairment in naming. Both the pictures and words versions of the Pyramids and Palm Trees Test were below normal and the discrepancy between pictures and words was even greater for case C than for case A. It has previously been suggested that such a difference may represent poor perceptual processing in the right temporal cases (Lambon Ralph *et al.*, 1999). Although no evidence of visuospatial disorder was apparent from the copying of a complex figure in case A, case C certainly made errors, suggesting that perceptual problems may account for some of the discrepancy between scores on the word and picture versions in his case.

Case D showed semantic deficits highly comparable with those of case B with left temporal lobe atrophy. Naming to confrontation was equivalent in severity, and errors were semantic in nature with the broad superordinate and cross-category errors seen in case B. On the Pyramids and Palm Trees Test, case D showed the same pattern as case B and the opposite pattern to cases A and C. That is, the performance on words was worse than the performance on pictures.

In summary, in tests of semantic memory, case D, a left hander with right temporal atrophy, showed a similar quantitative and qualitative pattern of deficits as case B, a right hander with left temporal lobe atrophy. In contrast, the other left hander with right temporal lobe atrophy, case C, showed a similar quantitative and qualitative pattern of semantic deficits as case A. This suggests that for the left handers, case D showed evidence of a reversal in cerebral lateralization of function, and case C showed similar lateralization to right handers.

Emotional processing

As with the performance on semantic tasks, case C showed the pattern seen in right temporal atrophy and case D showed a reversed pattern more similar to that of case B with left temporal lobe atrophy.

Perceptual difficulties in case C hinder interpretation of his performance on the facial and prosodic processing tasks as he scored in the impaired range (greater than 2 SD from control mean) on all tasks. As can be seen from Fig. 2, both cases C and D fell below the cut-off score on matching emotional prosody but case C showed a disproportionately greater impairment on naming emotional prosody and matching emotional faces to emotional prosody. Case D, despite having similarly predominant right temporal lobe atrophy seen in case A, showed a profile or performance more similar to case B with left temporal lobe atrophy.

Empathy

A significant change in empathic concern was seen in case C but not case D. Although the change in empathy seen in case C was not as large as that seen in case A, it is worth noting that his score represents the maximum change possible as he was described as an unempathic personality before disease onset. After the onset of the disease, case C also scored a minimum score of zero on the perspective taking scale, again representing a significant change when compared with controls.

Facial coding for felt and unfelt smiles

Case C demonstrated abnormal facial expression of emotion in terms of both the duration of expression and in the facial muscles involved. His facial expression was fixed and not responsive to external stimuli. He showed only slight movement of the zygomatic major muscle, orbicularis oculi was not involved and he also chronically lifted the inner and outer portions of his eyebrows (see Fig. 4).

Case D's smile is an example of a high-intensity Duchenne smile and demonstrates the normal facial expression of emotion seen in the left temporal case B.

In summary, the two left handers showed contrasting patterns of semantic and emotional processing impairments. Case C had a similar semantic profile to case A suggesting similar lateralization despite being left handed. Although the results of his performance on emotional tasks were not as clear cut as in case A, his abnormal facial expression of emotion and his poor social interaction were strikingly similar.

Case D had a similar pattern seen in left temporal atrophy suggesting reversed hemispheric localization. His semantic deficits were as severe as case B and his performance on emotional tasks, facial expressions, and social interactions were normal.

Results of MRI analysis

While visual inspection of MRI scans showed evidence of some bilateral anterior temporal atrophy in all cases, there was marked asymmetry in all four subjects. All subjects except case B had predominant atrophy in the right temporal lobe.

Volumetric analysis

Reliability

The amygdalas, anterior temporal lobes, and frontal lobes were measured twice by the same rater in five of the control subjects, yielding 10 amygdalas, 10 temporal and 10 frontal cortical volumes for inter-rater reliability estimates. The intrarater correlation coefficients (r) were 0.899 ($P < 0.001$) for the amygdala, 0.967 ($P < 0.001$) for anterior temporal lobe and 0.988 ($P < 0.001$) for frontal lobe.

Region of interest results

The z-scores for each of the regions of interest when each region was compared with the control group are presented in Table 2. In all cases, significant temporal atrophy was evident, with anterior temporal lobe z-scores being the highest (most negative) in every patient in the group. Atrophy in the amygdala passed our statistical threshold in three of the patients, although the fourth patient also had a substantial degree of amygdala atrophy. In every case, amygdala atrophy was most profound on the side where temporal cortex atrophy was largest. Only one of the cases showed a degree of frontal lobe atrophy that surpassed our threshold. Of note, the two patients with the most significant problems with emotional processing (cases A and C) showed relatively little frontal volume loss. These results suggest that the emotional processing problems seen in this group are more closely associated with volume loss in the anterior temporal lobe and amygdala, particularly on the right, than with volume loss in the frontal lobes.

Discussion

The four cases described provide evidence for the hemispheric lateralization of semantic memory, emotional processing, insight, and empathy. Studies describing the behavioural symptomatology of left temporal versus right temporal frontotemporal dementia have shown a greater prevalence for behavioural disturbance in those with right temporal atrophy (Miller *et al.*, 1993; Edwards-Lee *et al.*, 1997). In the same way that the left temporal lobe variant of frontotemporal dementia has been used to understand how semantic memory is represented in the brain, we suggest that those with right temporal atrophy may provide a useful model with which to investigate systematically the neural substrates of emotional processing, empathy, and social behaviour.

Over the last decade, much progress has been made in understanding the neuropsychological construct of semantic

Table 2. *z*-scores for the volumes of selected regions of interest in patients with frontotemporal dementia. Significant results are shown in bold type

Case	Right amygdala	Left amygdala	Right anterior temporal cortex	Left anterior temporal cortex	Right frontal cortex	Left frontal cortex
A	**–2.90**	–1.51	**–4.44**	**–3.25**	–0.19	1.84
B	–1.03	–1.86	**–4.16**	**–4.41**	–0.97	–1.73
C	**–3.19**	–1.28	**–4.58**	**–2.46**	–0.92	–1.01
D	**–2.94**	–1.48	**–5.35**	**–3.78**	**–3.24**	**–2.56**

memory, how it relates to other cognitive functions, and the brain areas most critical for it (Hodges and Patterson, 1997). The majority of cases of semantic dementia described have had predominant left anterior temporal lobe atrophy (Hodges *et al.*, 1992, 1995; Lambon Ralph *et al.*, 1999). Some early and asymmetrical cases have been described without significant right temporal lobe atrophy and this, combined with strong correlations shown between semantic memory loss and atrophy of the left temporal pole, have provided increasing evidence that this region is a critical neural substrate of semantic memory (Mummery *et al.*, 2000).

Case B is a typical case of semantic dementia with a profound and progressive loss of semantic memory but otherwise intact neuropsychological performance. Speech was fluent but empty of content, day-to-day memory was preserved on interview, and visuospatial and executive functions appeared intact. As with other cases of semantic dementia, behavioural changes became apparent as the disease progressed. Insight into his cognitive deficits was well preserved. His social skills were preserved and he never failed to leave an agreeable impression on clinic staff. In contrast to his severe deficits on semantic tasks, he performed normally on all tasks of emotional processing, showed little change in empathy and exhibited appropriate and genuine emotion in his facial expressions.

Case B contrasts markedly with case A, who having predominant atrophy of the right anterior temporal lobe, presented with a progressive deterioration in social behaviour.

As noted in the introduction, despite evidence supporting the hypothesis that the anterior temporal cortex, amygdala, and orbitofrontal cortex all play an important role in mediating social behaviour in humans, researchers have to date concentrated almost exclusively on the orbitofrontal lobe and amygdala.

Interest in the orbitofrontal cortex dates back to the 19th century and the famous case of Phineas Gage (Harlow, 1868; Damasio *et al.*, 1994). Subsequent reports of alterations in social behaviour following orbitofrontal damage (Eslinger and Damasio, 1985; Cicerone and Tanenbaum, 1997; Sarazin *et al.*, 1998) have been extended to attributing a central role of this brain region in emotional recognition (Hornak *et al.*, 1996), the anticipation of the future consequences of actions (Bechara *et al.*, 1996), and theory of mind (Stone *et al.*, 1998).

Rather than in the complexities of social behaviour and the meeting of cognition and emotion, it is in the processing of discreet emotions themselves that the amygdala is primarily involved. Initial studies in animals showed that the amygdala is a critical structure in the recognition of, and response to, fear (LeDoux, 1992). Subsequent investigations of single cases with bilateral amygdala damage have confirmed a similar role in humans in the processing of facial expressions of fear (Adolphs *et al.*, 1994, 1995; Young *et al.*, 1995; Calder *et al.*, 1996; Morris *et al.*, 1996). The advent of functional neuroimaging has supported these findings for fear (Morris *et al.*, 1996) and also linked the anterior insula to the emotion of disgust (Phillips *et al.*, 1998; Sprengelmeyer *et al.*, 1998). Attempts to localize other discrete emotions such as sadness have met with less conclusive results, but recent functional neuroimaging has suggested that the processing of sad facial expressions, sad films, or recall of sad events may involve the right anterior temporal cortex (Lane *et al.*, 1997; Blair *et al.*, 1999).

In non-human primates, the role of the anterior temporal cortex in social behaviour has been well recognized. In the 1970s Franzen and Myers studied monkey social groups where selected individuals were subjected to bilateral ablation of either the cingulate cortex, the pre-frontal cortex, or the anterior one-third of the temporal lobe, sparing the amygdala (Franzen and Myers, 1973). When studied over the year following surgery, those monkeys who had undergone bilateral cingulate removals showed no signs of social behavioural or emotional abnormalities. Both those that had undergone surgery to the orbitofrontal cortex and those with anterior temporal removals exhibited profound losses in the patterns of their social behaviour. The lesioned animals had a reduction in those activities that maintain social bonds, such as grooming, huddling, near-body contact, and lost signals of social communication, such as facial and vocal expressions, and body postures. They failed to re-establish relationships with their family members, and a loss of social awareness was seen when inappropriately approaching other group members irrespective of that animal's dominance status.

Despite showing normal scores on the Mini Mental State Examination and conventional neuropsychological tests of episodic memory, executive function, and visuospatial function, case A became unable to maintain his role in his family and workplace. Some of the changes in social behaviour paralleled those observed in monkeys with anterior temporal ablation. His relationships with his close family and others changed dramatically and he appeared totally indifferent to the feelings and lives of those around him. Social interaction was highly abnormal, his frozen facial expression caused unease in others, and he no longer seemed to be aware of the normal rules of social communication. He had no insight into the changes in his behaviour and was unaware of the effect that his behaviour had on others around him. Examination of his emotional system showed deficits in both input and production. Performance on tasks of emotional face and emotional prosody processing were severely impaired without any evidence to suggest that this may be due to either a semantic or perceptual deficit. Facial expressions of emotion were lost and he had a fixed, almost grimacing, facial expression. There were marked changes in empathy, particularly in empathic concern and perspective taking.

Volumetric analysis of the MRI images in case A failed to demonstrate volume loss in his frontal lobes. Although the results of the volumetric analysis offer no support for linking his changes in social behaviour to frontal lobe damage, they do not help to differentiate between the roles of the amygdala and anterior temporal cortex in these behavioural phenomena.

Significant atrophy was seen in the right amygdala but it was the anterior temporal cortex that showed the greatest degree of volume loss. Case B also had significant atrophy in both anterior temporal cortices but showed the reverse pattern to case A, with greater atrophy on the left side. As noted above, a number of lesion and functional imaging studies have confirmed the amygdala's role in the processing of facial expressions of fear, but the majority of these studies have examined subjects with bilateral amygdala damage. A more recent study by Adolphs and Tranel (1999) included seven subjects with unilateral amygdala damage, two of whom had right-sided damage, and demonstrated normal processing of facial emotions in all subjects. Furthermore, case A showed deficits not only in processing facial expressions, but also in processing emotional prosody where the role of the amygdala is in question. Despite an initial report of impairment in recognizing emotional prosody in a patient with bilateral amygdala damage (Scott *et al.*, 1997), it is possible that damage outside the amygdala region may have contributed to this, as subsequent studies of unilateral and bilateral amygdala damage have shown intact emotional prosody recognition (Anderson and Phelps, 1998; Adolphs and Tranel, 1999).

The profiles of cases A and B support the theory that the recognition of both emotional prosody and emotional facial expression is lateralized to the right hemisphere. The results of facial action coding of felt and unfelt smiles do not support the valence hypothesis, as expression of a positive emotion was impaired in a case with right temporal lobe atrophy. These two cases also suggest that empathy is lateralized to the right hemisphere and that the anterior temporal cortex may be a critical neural substrate for this ability.

The left-handed cases C and D add to the evidence supporting the lateralization of emotions and empathy. Case C showed a similar semantic profile to case A, and the comparability of his cerebral lateralization with the majority of right handers is further supported by his visuospatial deficits. Case C had severe emotional and behavioural deficits. Like case A, his social skills were dramatically affected. He showed little interest in others, had lost empathy, the art of social conversation and lacked proper non-verbal communication of his emotions.

The lateralization of semantic and emotional function was reversed in case D. This left-handed man with predominant right temporal lobe atrophy showed the same pattern of semantic and emotional processing as the right hander with left temporal lobe atrophy. His severely impaired semantic memory was comparable with that of case B and suggests that like 15–30% of left handers he was right hemisphere dominant for language with this 'anomalous dominance' further supported by his intact visuospatial skills. Of greater interest to the present discussion was his relatively intact emotional function. His social behaviour was appropriate and he was outgoing, warm and cheerful. He showed normal performance on the tasks of emotional face and prosody processing and his facial expressions of emotion remained normal. Although there had been some loss of empathy it was to a far lesser degree than found in cases A and C.

In conclusion, the four cases presented provide evidence for the lateralization of emotional processing to the non-language dominant hemisphere. Our data support previous work suggesting right hemisphere dominance for emotions and produce new evidence that empathy is also mediated by the right hemisphere. In addition, the left handers suggest that such 'emotional dominance' may shift as previously described with other non-dominant hemisphere functions. With the right hemisphere damage being relatively circumscribed to the anterior temporal lobe, our investigations suggest that the temporal variant of frontotemporal dementia provides an excellent model for further investigation of the neural representation of emotions, empathy and human social behaviour.

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Hemispheric dominance for emotions, empathy and social behaviour: evidence from right and left handers with frontotemporal dementia

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Abstract

Although evidence from primates suggests an important role for the anterior temporal cortex in social behaviour, human research has to date concentrated almost solely on the orbitofrontal cortex and amygdala. By describing four cases of the temporal variant of frontotemporal dementia we show how this degenerative condition provides an excellent model for investigating the role of the anterior temporal lobe, especially the right, in emotions, empathy and social behaviour. Assessments of semantic memory, processing of emotional facial expression and emotional prosody were made, empathy was measured, and facial expressions of emotion were coded. Of the two right handers described, one subject with predominantly left temporal lobe atrophy had severe semantic impairment but normal performance on all emotional tasks. In contrast, the subject with right temporal lobe atrophy showed severely impaired recognition of emotion from faces and voices that was not due to semantic or perceptual difficulties. Empathy was lost, interpersonal skills were severely affected and facial expression of emotion was characterized by a fixed expression that was unresponsive to situations. Additionally, two left handers with right temporal lobe atrophy are described. One demonstrated the same pattern of hemispheric lateralization as the right handers and had emotional impairment. The other left hander showed the opposite pattern of deficits, suggesting a novel presentation of anomalous dominance with reversed hemispheric specialization of semantic memory and emotional processing.

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Primary diagnosis of interest

Frontotemporal dementia

Author's designation of case

Cases A, B, C, D

Key theoretical issue

- Hemispheric lateralization of emotion and empathy

Key words: frontotemporal dementia; emotion; empathy; anterior temporal lobe

Scan, EEG and related measures

MRI volumetrics

Standardized assessment

WAIS IQ, verbal fluency, Pyramids and Palm Trees

Other assessment

Florida Affect Battery, Interpersonal Reactivity Index

Lesion location

- Anterior temporal lobe

Lesion type

Degenerative

Language

English