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The impact of early and late damage to the human amygdala on 'theory of mind' reasoning

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Summary

There is a burgeoning interest in the neural basis of the ability to attribute mental states to others; a capacity referred to as 'theory of mind' (ToM). We examined the effects of lesions of the amygdala which arise at different stages of development on this key aspect of social cognition. Tests of ToM, executive and general neuropsychological function were given to subjects with lesions of the amygdala arising congenitally or in early childhood ('early damage', *n* = 15), subjects who acquired damage to the amygdala in adulthood ('late damage' *n* = 11) and matched clinical (*n* = 14) and healthy comparison groups (*n* = 38). Subjects with early damage to the amygdala, particularly if the lesion was associated with childhood onset of seizures, were impaired relative to all other groups on more advanced tests of ToM reasoning, such as detecting tactless or ironic comments or interpreting non-literal utterances. These deficits held for subjects with either left or right early amygdala damage and encompassed the understanding of both the beliefs and emotional states of others. In contrast, subjects who acquired damage to the amygdala in adulthood (usually as part of an anterior temporal lobectomy) were not impaired in ToM reasoning relative to both clinical and healthy controls, supporting the position that the amygdala is not part of the neural circuitry mediating the 'on-line' performance of ToM reasoning. In line with theories which claim that ToM is an independent faculty of cognition, we found that the pattern of results held after co-varying for measures of executive function, memory and general intellectual functioning. We discuss the results in the light of recent theories which link early developmental insults to the amygdala with the ToM impairments which are thought to be a core neurocognitive deficit found in disorders such as autism. We conclude that the amygdala may play an important role in the neural systems supporting the normal development of ToM reasoning.

Keywords: amygdala; theory of mind; autism; executive function

Abbreviations: DNET = dysembryoblastic neuroepithelial tumour; fMRI = functional MRI; IQ = intelligence quotient; ToM = theory of mind

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Introduction

The term 'theory of mind' (ToM) has been applied to the capacity to attribute mental states to others in order to understand and predict their behaviour (Premack and Woodruff, 1978). Several models of the neural circuitry mediating this key aspect of social cognition have already been developed on the basis of functional neuroimaging, human lesions and primate studies. The amygdala has been included in most models of ToM reasoning as part of a distributed network which includes other regions of the temporal lobe (particularly the polar cortex and superior temporal gyrus) and frontal lobes (the orbitofrontal cortex and anterior cingulate cortex) (Brothers, 1989; Stone *et al*., 1998; Tager-Flusberg *et al*., 1998; Abu-Akel and Bailey, 2000; Baron-Cohen *et al*., 2000; Tager-Flusberg and Sullivan, 2000; Adolphs 2003; Frith and Frith, 2003).

Several positions have emerged concerning the exact role of the amygdala in the mediation of reasoning about the mental states of others. First, some theorists place the amygdala at the very core of the neural circuitry which supports ToM reasoning and argue that it is both necessary for the development of the ability to reason about others and a component of the 'on-line' circuitry recruited during per-

formance of ToM tasks (Brothers, 1989; Abu-Akel and Bailey, 2000; Baron-Cohen *et al*., 2000; Stone *et al*., 2003). In support of the necessity of the amygdala in the development of ToM abilities, there are case reports of subjects with lesions of either one or both amygdalae which arise early in development who show impairments on a range of tasks requiring ToM reasoning (Adolphs *et al*., 1998; Heberlein, 1998; Fine *et al*., 2001). People who have autism consistently have been found to exhibit deficits in ToM reasoning, which are thought to underpin many of the anomalies in social behaviour typical of autism (Baron-Cohen *et al*., 1985). This has been linked explicitly to structural and, by implication, functional developmental abnormalities of the amygdala, with reports of both macroscopic and microscopic abnormalities (Bailey *et al*., 1998; Aylward *et al*., 1999; Baron-Cohen *et al*., 1999*b*; Howard *et al*., 2000; Salmond *et al*., 2003). Similarly, cortical tubers which develop within the temporal lobes during fetal life have been associated with autistic comorbidity among people who have tuberose sclerosis (Bolton and Griffiths, 1997).

Evidence for the necessity of the amygdala in the adult 'on-line' performance of ToM tasks comes from human lesion and functional neuroimaging studies. Stone *et al*. (2003) describe two such subjects who acquired damage to the amygdalae in adult life who are impaired in the attribution of mental states to others on the basis of the appearance of the eye region and also in the ability to detect when a character in a story had unintentionally hurt the feelings of another. Larger group studies have demonstrated acquired deficits in ToM tasks among adult subjects with both left and right hemisphere cerebrovascular insults, which may have compromised the blood supply to the amygdala from the deep perforating branches of the middle cerebral artery (Happe *et al*., 1999; Channon and Crawford, 2000). The findings of the lesion studies are corroborated to some extent by findings from functional MRI (fMRI). In healthy subjects, the amygdala is activated when judgements are made about the mental states of others on the basis of their appearance (Baron-Cohen *et al*., 1999*b*; Winston *et al*., 2002) and when mental states are attributed to the movements of abstract shapes, as in the Heider and Simmel paradigm (Castelli *et al*., 2002; Schultz *et al*., 2003).

A second position holds that while the amygdala may support the development of ToM skills, it is not a critical component of the circuitry which supports the 'on-line' performance of ToM reasoning in adulthood. In this vein, Frith and Frith (2003) have highlighted in their synthesis of fMRI studies that although some studies have demonstrated amygdala activation during the performance of ToM reasoning tasks, such studies are the exception rather than the rule. They and other authorities (Tager-Flusberg *et al*., 1998; Tager-Flusberg and Sullivan, 2000) have argued that the amygdala is more likely to support the development (and on-line performance) of basic social perceptual abilities which are taken to be the precursors or 'protoforms' of ToM knowledge. There is consistent evidence for the activation of the amygdala during the 'on-line' adult perception of basic and complex emotional states and for the deleterious effects of early amygdala lesions on emotional perception (for a review of fMRI studies see Zald, 2003; and for a review of lesion studies see Adolphs, 2002). As skills such as the perception of the emotional states of others develop into the ability to reason about these mental states, there is a concomitant shift from a reliance on phylogenetically ancient structures such as the amygdala to frontal cortical regions. It is argued that without these social perceptual skills, the attainment of ToM skills is at the very least delayed and rendered error prone in contrast to the qualitatively effortless and accurate ToM attributions found in healthy subjects. Thus, in these models, the amygdala is not thought to be necessary for the on-line execution of ToM reasoning; however, its role in supporting the precursors of ToM reasoning may make its integrity a necessary but not sufficient condition for the development of normal ToM abilities.

One way of comparing these two positions is to examine ToM reasoning among subjects who acquire lesions to the amygdala early in development (either congenitally or in early childhood) with those who acquire damage to a normally developed amygdala in adulthood. Both positions would predict that subjects with early damage would be impaired in ToM reasoning. If the amygdala additionally supports adult 'on-line' ToM reasoning, then we would predict similar ToM impairments in subjects with damage acquired in adult life. If, however the amygdala has a purely developmental role and is not involved in the adult 'on-line' execution of ToM reasoning, then we would expect relatively intact ToM performance among those with amygdala damage acquired in adulthood.

A third position argues that the amygdala is only part of the substrate of reasoning about the mental states of others in so far as it supports domain-general cognitive functions (Frye, 1999, 2000). Some have argued that there is no need to invoke a domain-specific ToM module and instead emphasized the frequent presence of executive dysfunction among many subjects with ToM impairments (Channon and Crawford, 2000). However, there are already several case reports, including a subject with an amygdala lesion, suggesting that ToM impairment can occur even in the presence of intact executive function—a dissociation in favour of a modular ToM mechanism (Bach, 2000; Fine *et al*., 2001; Rowe *et al*., 2001). Further detailed examination of subjects with focal lesions of the amygdala may shed light on the issue: prominent executive dysfunction, general intellectual and language impairment would not be expected in this group, and thus any deficits in 'ToM' reasoning would not be readily reduced to impairments in other cognitive systems.

Other emergent themes in research on the amygdala include the possible impact of gender and laterality on amygdala function, in domains such as the perception of, and memory for, emotionally salient stimuli (Buchanan *et al*., 2001; Zald, 2003). For example, two fMRI studies have

reported that enhanced recognition memory for emotionally arousing material correlates with left amygdala activation at encoding in women and right amygdala activation in men (Cahill *et al*., 2001; Canli *et al*., 2002). Turning to ToM, there are gender differences, most evident in the acquisition of ToM milestones which are generally attained earlier by girls (Baron-Cohen *et al*., 1999*a*). In addition, several groups have reported laterality differences in ToM reasoning with prominent deficits among subjects with right, but not left, hemisphere damage (Happe *et al*., 1999). Other human lesion studies and one functional imaging study report exactly the opposite pattern (Channon and Crawford, 2000). Stone *et al*. (2003) have speculated that there is an effect of the content of the mental state inference on laterality of function. In their *faux pas* task, subject D.R. who had predominantly right-sided amygdala damage was most impaired in affective state attributions, i.e. realizing that a person would feel hurt or insulted when confronted with a tactless comment. In contrast, subject S.E. who had more prominent left-sided amygdala damage made more errors in appreciating that the tactless comment was made unintentionally, thus showing impairment in epistemic or belief attribution. This is similar to the subject described by Fine *et al*. (2001) who had more selective left-sided amygdala damage and was impaired on a range of ToM tasks which assessed mainly epistemic (belief) mental state attributions. We aimed to explore further this possible dissociation of the ability to reason about the epistemic and affective mental states of others.

Previous research into the neural basis of the development of ToM skills is limited by its reliance on case studies, in which damage to the amygdala arises from a range of aetiologies and typically is accompanied by extensive extra-amygdala damage. We attempted to overcome such limitations by studying a large group of subjects with relatively focal pathology of the amygdala. The lesions were thought, on clinical and neuroradiological grounds, to be compatible with the presence of a dysembryoblastic neuroepithelial tumour (DNET) (Raymond *et al*., 1994, 1995; Honavar *et al*., 1999). DNETs are composed of bundles of axons lined by small oligodendrocyte-like cells and astrocytes (Daumas-Duport *et al*., 1988; Honavar *et al*., 1999). Neurons are relatively sparse and appear to float with random orientation within a mucoid matrix, and have a morphology that occasionally differs from that of normal cortical neurons (Raymond *et al*., 1994; Honavar *et al*., 1999). The tumour thus constitutes a major disruption of normal neuronal architecture and function which is reflected in its association with a childhood onset of focal seizures. The neurophysiological abnormalities are often accompanied by metabolic anomalies with the finding of resting hypometabolism in the region of the DNET on fluordeoxyglucose PET. The tumour is also well characterized in terms of its clinical course and preoperative MRI appearances, which allows for a reliable presumptive diagnosis (Kuroiwa *et al*., 1995).

The exact age at which a DNET arises is not clear, but many authorities argue for a dysembryoblastic origin, supported by the presence of multiple and distinct cell lineages in the tumour, the frequent association of cortical dysplasia and evidence of bone remodelling over more superficial lesions (Daumas-Duport *et al*., 1988; Hirose *et al*., 1994). By this reasoning, the age of onset of damage to the amygdala in patients with a DNET is thus in the embryonal or fetal periods.

A complementary, if more conservative method of establishing the developmental age of an amygdalar lesion is to adopt the age of onset of habitual seizures caused by the lesion. This method has been used in research into the effects of damage to mesial temporal lobe structures on memory and the perception of emotional expressions (Lespinet *et al*., 2002; Meletti *et al*., 2003). This approach has the advantage of reflecting the presence of a lesion that is clinically apparent, acting as an epileptogenic focus with adverse effects on the neurophysiological integrity of local neuronal populations. In this study, both approaches are employed: for the primary analyses, the early amygdala group is defined by the presence of a focal amygdala lesion (regardless of age of onset of seizures). In further exploratory analyses, the developmental age of the amygdalar lesion is taken more conservatively to be the age at which it became clinically apparent, acting as an epileptogenic focus.

Damage in adult life to the amygdala usually occurs as a result of a temporal lobectomy or amygdalo-hippocampectomy as part of surgical treatment of medically intractable epilepsy. In most of these cases, the amygdala will show pathological changes such as sclerosis. However, occasionally, a normal amygdala will have been excised, and such subjects effectively acquire damage to a normal amygdala in adult life. The age of onset of amygdala damage in such subjects is thus the age of the operative excision of the amygdala (and surrounding structures). As all these subjects typically have epilepsy and are on anticonvulsant medication, it is clearly important to have an appropriate clinical comparison group. We chose a group of subjects with epilepsy arising from similar focal pathologies affecting the temporal or parietal lobe which completely spared the amygdala.

We thus aimed to explore systematically the effects of early and late developmental damage to the amygdala on 'ToM.' We predicted that subjects with early amygdala lesions would be impaired on tests of ToM reasoning compared with both healthy and clinical comparison groups. In line with the earlier discussion, we also predicted that subjects who acquired damage to a normal amygdala in adult life would not show such impairments. We also examined the possibility that there may be an interaction between the content of the ToM task and the side of amygdala which mediates its processing. Specifically, on the basis of previous case reports, we predicted that subjects with lesion of the left amygdala would show greater impairment on ToM tasks which involved epistemic attributions and subjects with right-sided lesions would have greater impairment on affective state attributions.

Subjects and methods

Participants

All clinical subjects were recruited from the regional neuroscience centre at King's College Hospital, London. The early amygdala damage group all had lesions which centred on the amygdala with minimal extension. Neuroradiological differential diagnoses of the lesion were made by consultant neuroradiologists, and the clinical histories were reviewed by consultant neurosurgeons and neurologists to ensure they were compatible with the presence of an indolent non-progressive tumour of the amygdala, such as a DNET (Honavar *et al*., 1999). For some analyses, the age of acquisition of the DNET was taken conservatively to be the age of onset of seizures which arise from the lesion. The late amygdala damage group had all received surgical treatment for their epilepsy with either an *en bloc* anterior temporal lobe resection. The normality of the excised amygdala was defined neuroradiologically as a preoperative volume of the amygdala falling within 1 SD of the mean volume of the amygdala measured in 66 neurologically intact subjects. Previous work has found that preoperative volumetric analysis of MRIs of the amygdala is sensitive to the presence of even minimal sclerosis (Hudson *et al*., 1993; Lambert *et al*., 2003). Additionally, the excised amygdala had to display no gross or microscopic abnormality on histological examination. The age of onset of damage to the amygdala in this group is the age at which the normal amygdala was surgically excised. The clinical comparison group had lesions which spared the amygdala (see Table 1 for details of all lesions). These lesions were of a similar nature to those of the subjects with early damage to the amygdala with a preponderance of DNETs. Healthy controls were recruited from a database of volunteers held locally with no history of neurological or psychiatric disorders.

Ethical approval for the study was given by the Research Ethics Committee at the South London Maudsley NHS Trust and King's Healthcare NHS Trust, and subjects gave consent obtained in accordance with the Declaration of Helsinki.

Neuroimaging

For volumetric analyses, a 3D inversion recovery prepared fast spoiled GRASS T1-MRI weighted data set was obtained in the coronal plane with 1.5 mm contiguous sections. The volume of the amygdala was measured using existing protocols (Watson *et al*., 1992; Brierley *et al*., 2002) and adjusted for intracranial volume in the preoperative scans of the subjects in the late acquired damage group. Two independent raters with high inter-rater reliability performed the volumetric analyses (intracranial content for the amygdala 0.95). MRIs from selected patients in each group are shown as Supplementary data available at *Brain* Online.

Tasks

Clinical groups completed the vocabulary, digit span, comprehension and similarities subscales for verbal intelligence quotient (IQ), and the block design and object assembly subscales for performance IQ (Wechsler, 1997*b*). An estimate of IQ was obtained from the National Adult Reading test for the neurologically intact control subjects (Nelson, 1982). Memory was assessed with the immediate and delayed logical memory test from the Wechsler Memory Scale—third version (Wechsler, 1997*a*). Executive function was assessed using the Hayling and Brixton tests (Burgess and Shallice, 1996*a*, *b*). The Hayling test provides a measure of the ability to inhibit a prepotent response as well as task initiation speed. The Brixton test is a rule detection and set shifting task.

Experimental tasks

False belief tasks

Examples of all tasks are given in the Supplementary data. The false belief tasks were adapted from vignettes designed by Baron-Cohen and colleagues with superficial changes made to make the content more suitable for adults (Baron-Cohen *et al*., 1985; Baron-Cohen, 1989). Subjects must predict the actions of a character on the basis of the character's mistaken belief. Both first order ('Peter thinks that….) and second order tasks ('Susan thinks that Peter thinks….') incorporating control questions assessing comprehension and memory were included. Throughout all testing, subjects were read the vignettes and also held their own copies to minimize memory load. Throughout, overall scores are expressed as percentages to allow for comparison across tasks.

Happé's strange stories

In these vignettes, characters typically say something they do not mean literally and the participant is required both to demonstrate comprehension of the statement and explain the possible motivations underlying it. Stories on themes of lying, double bluff, being tactful and persuasion were included (with minor superficial alterations). In line with Happé and collaborators, we coded the responses as including a completely and explicitly correct mental state reference (scoring 2 points), a context-appropriate mental state which only implicitly correctly answered the question or a response which contained no references to mental states but purely physical terms (both scoring 1 point), or an incorrect response (scoring 0 points). These scores were then expressed as percentages. For details see Happé (1994) and Snowden *et al*. (2003).

Metaphor and irony

Several theorists argue that the understanding of metaphor can be achieved by grasping the intentions of the speaker; it thus requires a first order ToM. In contrast, the comprehension of an ironic statement requires the ability to appreciate the thought of the speaker and also the speaker's attitude towards that thought, i.e. have second order meta-representational abilities exemplified by a second order ToM. In each vignette, the chief protagonist makes both a metaphorical and an ironic comment and the participant is asked to interpret the intent of the protagonist. Responses were coded as correct or incorrect and converted to percentage scores. For details see Happé (1993).

Faux pas task

The *faux pas* task explicitly assesses various constituent components of theory of mind. In each of nine vignettes, person A unintentionally says something which will hurt the feelings of person B. Participants were then asked if someone in the story had said something awkward (detection of the *faux pas*), to identify who made the *faux pas* and to explain why s/he should not have made the comment (the epistemic attribution, 'he didn't realize

Table 1 *Details of lesion location and pathology*

Subject	Side	Lesion	Estimated age of amygdala damage (years)*	Pathology
Early amygdala damage group				
EA2§	L	Amygdala only	1	DNET
EA7	R	Amygdala only	21	DNET
EA3§	L	Amygdala only	11	DNET
EA4	L	Amygdala only	1	DNET
EA9	R	Amygdala only	1	DNET
EA10	R	Amygdala only	6	DNET
EA12	L	Amygdala only	18	DNET
EA14	R	Amygdala only	26	DNET
EA15	L	Amygdala only	24	DNET*
EA6	L	Amygdala extending to entorhinal cortex	20	DNET
EA11	L	Amygdala extending to lentiform nucleus	1	DNET
EA13	R	Amygdala extending to uncus	16	DNET
EA1§	L	Amygdala extending to temporal pole	18	DNET*
EA5	L	Amygdala extending to temporal pole	3	DNET*
EA8	R	Amygdala extending to temporal pole	12	DNET*
Late damage to a pre-operatively normal amygdala				
LA9	L	Anterior temporal lobectomy	18	Mild sclerosis of hippocampus*
LA2	R	Radiotherapy damage to ATL including anterior amygdala	35	Previous AVM in ATL
LA1	L	Anterior temporal lobectomy	39	Temporal DNET*
LA3	R	Anterior temporal lobectomy	31	Temporal epidermoid*
LA4	R	Anterior temporal lobectomy	20	None*
LA5	R	Anterior temporal lobectomy	26	Mild sclerosis of hippocampus*
LA6	R	Anterior temporal lobectomy	25	None*
LA7	R	Anterior temporal lobectomy	48	None*
LA8	R	Anterior temporal lobectomy	39	None*
LA10	L	Anterior temporal lobectomy	18	Parahippocampal DNET*
LA11	R	Anterior temporal lobectomy	44	Uncal cavernoma*
Clinical comparison group				
CC1§	L	Temporal pole (antero-inferior portion)	No damage to the amygdala	DNET*
CC2§	L	Parahippocampus	N/A	DNET
CC7	R	Parahippocampus	N/A	Cavernoma*
CC4	R	Parietal lobe	N/A	Cavernoma
CC11§	L	Parieto-occipital junction	N/A	DNET*
CC5	L	Temporo-parietal junction	N/A	DNET*
CC10	R	Insula	N/A	Surgical excision*
CC6	L	Parahippocampus	N/A	DNET*
CC8	L	Hippocampus	N/A	Dysplasia
CC12§	R	Temporal operculum	N/A	DNET
CC9	R	Anterior temporal lobe	N/A	Ganglioglioma
CC14	R	Temporo-parietal junction	N/A	Epidermoid
CC13	R	Occipital cortex	N/A	Cortical dysplasia
CC3	R	Anterior temporal lobe extending to frontal operculum	N/A	DNET*

For the 'early' damage group (DNET), a conservative method of dating the age of damage to the amygdala as the age of onset of seizures is used. For the 'late' amygdala group, the age of damage is the age of surgical excision of the previously normal amygdala. AVM = arteriovenous malformation; ATL = anterior temporal lobectomy; L = left; R = right; N/A = not applicable; *diagnosis confirmed by histology; §MRIs shown in Appendix 1.

he….'). Subjects are also asked about the emotional response of person B (the affective attribution, 'He would feel hurt…'). Finally, a question relating to story comprehension was asked. One point was given for: correct detection of the *faux pas* and the person who had made it, a correct epistemic attribution and a correct affective attribution, giving a maximum score of 27, which was then converted to an overall percentage score. For details see Stone *et al*. (1998)

'Conflicting belief and emotion' task

This is a novel task in which participants are given vignettes which concerned two protagonists A and B and centred on a social scenario, typically on themes of social exclusion or threat. In the vignette, A holds a true first order belief and B holds a false second order belief. Each belief is associated with an emotional state—in each scenario one of the emotional states has a positive valence and the other a negative valence (see Supplementary data). Participants

Table 2 *Demographic and neuropsychological characteristics*

	Early amygdala	Late amygdala	Clinical comparison group	Healthy comparison group	Significance
Sex (M : F)	7 : 8	7 : 4	6 : 8	17 : 21	$\chi^2(3) = 1.39$, $P = 0.71$
Age (years) mean (SD)	35 (13)	32 (12)	27 (7)	36 (11)	$F = 2.46$, $P = 0.07$
Age (years) of onset of epilepsy	12 (10)	17 (9)	17 (9)	–	$F = 0.85$, $P = 0.44$
Verbal IQ	98 (13)	96 (11)	94 (13)	112 (9)	$F = 12.4$, $P = 0.001$; EA***, LA***, CC*** < NCC
Performance IQ	102 (14)	98 (18)	101 (18)	111 (6)	$F = 4.5$, $P = 0.01$; LA* < NCC
Logical memory-scaled scores	7.4 (2.9)	8.3 (3.2)	8.0 (2.6)	11.4 (2.5)	$F = 11.7$, $P < 0.001$; EA***, LA***, CC** < NCC
Brixton	5.6 (1.7)	5.9 (1.6)	6.1 (1.8)	6.9 (1.0)	$F = 2.7$, $P = 0.052$
Hayling	5.6 (1.4)	5.0 (1.3)	5.4 (1.8)	7.1 (1.3)	$F = 9.1$, $P < 0.001$; EA***, LA***, CC** < NCC

EA = early amygdala damage; LA = late acquired amygdala damage; CC = clinical comparison group; NCC = healthy comparison group. Levels of significance: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$. M = male; F = female.

are asked, in a random order, questions designed to assess their understanding of the two conflicting beliefs and conflicting emotional states. Control questions testing memory for the story and inference making are included. Answers given in response to the question concerning second order false belief were coded using the same method as in the Happé strange stories, with responses categorized as containing a full mental state, partial mental state or physical state response.

Effect of side of lesion and content of task.

To explore the hypothesis that left-sided amygdala lesions will more severely impair epistemic, and right-sided lesions affective ToM reasoning, scores on tests requiring epistemic attributions (epistemic components of *faux pas* and conflicting belief and emotion) and tests assessing affective inferences (affective attributions in the *faux pas* and conflicting beliefs and emotions task) were combined. An index of 'content specificity' was calculated by using the equation (total epistemic attributions – total affective attributions)/(total epistemic + total affective attributions). This index thus expressed the difference in performance arising from the content of the task, adjusted for a measure of overall accuracy.

Results

Demographic and neuropsychological measures

There were no significant differences on the basic neuropsychological measures between the clinical groups, who were, however, significantly impaired relative to healthy comparison subjects on most measures. Demographic variables were similar for all the groups. Although the age of onset of habitual seizures was lower in the early amygdala damage than the late amygdala damage group, this did not reach statistical significance (Table 2).

False belief tasks

No subject made errors on the first order false belief questions (Table 3).

Four subjects with early amygdala damage and one late amygdala subject made errors on the second order false belief task, although the group difference in total number of errors did not reach significance.

Happé's strange stories

There was a main effect of group in overall scores, and *post hoc* analyses with Tukey's HSD (honestly SD) test confirmed significant differences between the early amygdala damage group and the late amygdala, clinical and healthy comparison groups and between the clinical and healthy comparison groups (Fig. 1).

This arose largely as there was a group effect in the number of full mental state attributions made [$F(3,74) = 7.79$, $P < 0.001$]. *Post hoc* analyses showed that the early amygdala group made significantly fewer full accurate mental state attributions than the late amygdala group ($P = 0.01$), the clinical comparison ($P = 0.045$) and healthy comparison groups ($P < 0.001$). For results, see Table 3.

Metaphor and irony

The results (Table 3) were highly skewed as subjects in late amygdala damage and comparison groups made no errors. There was no effect of group on comprehension of metaphor. A Kruskal–Wallis test demonstrated a significant group difference in the comprehension of irony, with pairwise comparisons showing the difference to be in the early amygdala relative to healthy comparison group ($Z = –3.1$, $P = 0.001$) and trend for an impairment relative to the late amygdala group ($Z = –1.89$, $P = 0.06$).

Faux pas *task*

There were no group differences in the scores on control questions (with all groups displaying near perfect scores). There was a significant effect of group on the total number of

Table 3 *Results for each group on ToM tests*

	Early amygdala (15)	Late amygdala (11)	Clinical comparison group (14)	Healthy comparison group (38)	ANOVA (and *post hoc* Tukey's HSD) or Kruskal–Wallis (and pairwise Mann–Whitney)
False belief					
Number of subjects making errors	4	1	1	2	χ^2 =5.7, P = 0.13
Happé strange stories, metaphor and irony					
Strange stories mean (SD); correct/incorrect	78 (13)	90 (7)	90 (12)	96 (6)	$F(3,74)$ = 14.6, P < 0.001, EA <**LA, **CC, ***NCC, CC < *NCC
Metaphor; median (quartiles)	100 (100–100)	100	100	100	$\chi^2(3)$ = 2.21, P = 0.52
Irony; median (quartiles)	100 (70–100)	100 (100–100)	100	100	$\chi^2(3)$ = 10.9, P = 0.012, EA < ***NCC
Faux pas					
Detection; median (quartiles)	100 (87–100)	100 (78–100)	100 (97–100)	100	$\chi^2(3)$ = 10.8, P = 0.01, EA < ***NCC, LA < **NCC
Affective attributions	100 (64–100)	100 (75–100)	100 (97–100)	100 (90–100)	χ^2 = 5.3, P = 0.16
Epistemic attributions	89 (70–100)	100 (65–100)	94 (86–100)	100	χ^2 = 16.9, P = 0.001, EA < *CC, ***NCC, LA < *NCC
Total score	89 (73–100)	100 (74–100)	98 (92–100)	100	χ^2 = 7.39, P = 0.06, EA < CC (P = 0.06), EA < **NCC
Conflicting beliefs and emotions					
Belief; true first order; median (quartiles)	100 (96–100)	100 (95–100)	100 (96–100)	100	$\chi^2(3)$ = 4.2, P = 0.24
Belief; false second order	93 (67–100)	100 (87–100)	93 (86–100)	100	χ^2 = 11.9, P = 0.01, **EA <NCC, *LA < NCC, *CC < NCC
Emotion; first order	87 (75–100)	87 (80–100)	100 (86–100)	100	χ^2 = 9.0, P = 0.03, EA <*CC, **NCC
Emotion; second order	85 (62–87)	85 (74–90)	100 (86–100)	100 (87–100)	χ^2 = 16.4, P = 0.001, EA < **CC, ***NCC

Level of significance of *post hoc* comparisons: *P < 0.05, **P < 0.01, ***P < 0.001. EA = early amygdala damage; LA = late amygdala damage; CC = clinical comparison group; NCC = healthy comparison group.

correct detections and epistemic attributions, but not in affective attributions. Errors in the epistemic attributions all involved assuming that the *faux pas* had been made intentionally with the aim of upsetting the other protagonist in the vignette. There was a significant group difference in overall performance, with pairwise Mann–Whitney comparisons showing that the early amygdala group were significantly impaired relative to the healthy comparison group (Z = –2.7, P = 0.007) and there was a near significant impairment relative to the clinical comparison group (Z = –1.84, P = 0.066).

Conflicting beliefs and emotions' task

One subject in the late amygdala damage and one in the early amygdala group failed to complete the test. There was no significant difference between the groups in the memory and inference questions. Performance on the first order true belief component was nearly at ceiling in all groups, and a Kruskal–Wallis test showed no effect of group (see Table 3). In the attribution of second order false beliefs, there was a significant difference between the groups in overall number of incorrect responses [$F(2,72)$ = 4.3, P = 0.008], with the early amygdala group making more such errors than the healthy comparison group (P = 0.01). There was a significant

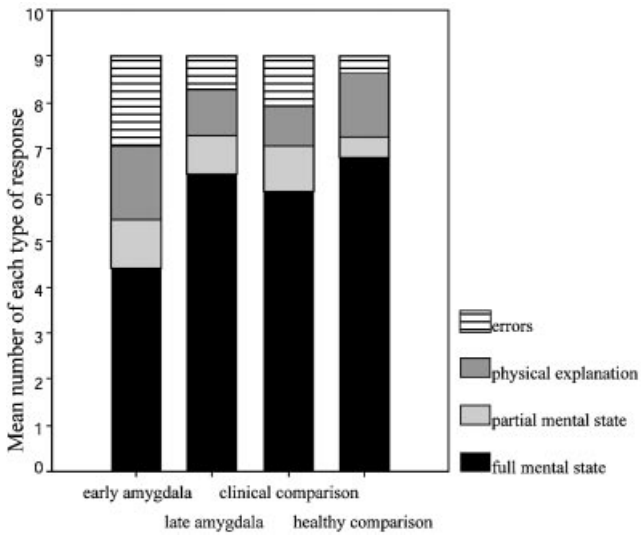

Fig. 1 Type of response in Happé's strange stories (a total of nine stories were used and the diagram illustrates the number of each type of response).

group difference in the number of correct responses which contained a full mental state reference [$F(3,72)$ = 5.4, P = 0.004] and physical state references [$F(93,72)$ = 3.7, P = 0.01]. *Post hoc* Tukey's HSD test showed that the early

Table 4 *Mean (SD) cumulative score on all ToM tests for each group*

	Early amygdala mean 81.4 (10.3)	Late amygdala mean 89.2 (7.9)	Clinical comparison mean 90.4 (8.1)	Healthy comparison mean 95.9 (4.7)
Early amygdala	–	0.79	0.89	1.55
Late amygdala	–	–	0.17	1.09
Clinical comparison	–	–	–	0.87

Effect sizes between each group are expressed as Cohen's d.

Table 5 *Pearson correlations between ToM tests (overall score) and IQ, logical memory and executive function*

Group	VIQ	PIQ	Logical memory	Brixton	Haylings
Early amygdala	0.43	0.21	–0.04	0.35	0.56
Late amygdala	0.35	0.29	0.12	0.57	0.42
Clinical controls	0.17	0.46*	0.50*	0.22	0.19
Healthy controls	0.27	0.28	0.32*	0.16	0.27

PIQ = performance IQ; VIQ = verbal IQ. *Significant at $P < 0.05$.

amygdala group gave fewer mental state responses ($P = 0.004$) and more attributions containing a physical state reference ($P = 0.049$) than the healthy comparison group. There was no effect of group on the number of partially correct mental state attributions [$F(3,72) = 0.01$, $P = 0.96$].

All but four subjects made more errors in emotional than belief attributions. There was a significant group difference in the number of correct emotional attributions associated with both first and second order beliefs. *Post hoc* analyses showed that the early amygdala damage group made more errors in providing an emotion which was congruent with the belief state of the characters relative to both clinical ($Z = –2.7$, $P = 0.006$) and healthy comparison groups ($Z = –3.0$, $P = 0.001$).

Overall performance

A cumulative score reflecting in equal measure the scores on the four tests was calculated (Table 4).

There was a significant group difference [$F(3,74) = 15.4$, $P < 0.001$] with impairment in the early amygdala damage group relative to all the other groups (late amygdala damage group $P = 0.04$, clinical control group $P = 0.006$, and healthy control group $P < 0.001$, Bonferroni corrected contrasts). The late amygdala damage group were significantly impaired relative to the healthy comparison group only ($P = 0.05$). Effect sizes were also calculated, using Cohen's d, a statistical power analysis quantifying the size of the difference between groups (Cohen, 1992). The index is interpreted as indicating a small between-group difference for d = 0.20, medium for d = 0.50 and large for d > 0.8. All clinical groups were substantially impaired relative to the healthy comparison group. The early amygdala group showed a large (d = 0.92), and the late amygdala group showed a small (d = 0.21) difference relative to the clinical comparison group.

The relationship with general intelligence, memory and executive function

There were modest positive correlations within each group between these variables and the overall measure of performance on ToM tests, but no significant interactions between these covariates and the measure of overall performance in each group. We thus reanalysed the data with these measures as covariates

The significant difference between the early amygdala damage group and all other groups held in pairwise comparisons between the individual groups (with a Bonferroni correction and $P < 0.05$) after co-varying for executive function, logical memory and general intelligence. The significant difference between the late amygdala damage and healthy comparison groups similarly survived co-varying for these measures (pairwise comparison with Bonferroni correction, $P < 0.01$). However, the significant difference between the late amygdala damage group and clinical controls in overall performance in ToM tests did not remain after adjustment for differences in executive function, memory and IQ between the groups. For results see Table 5.

The effect side and size of lesion and gender

For the cumulative score, subjects with right-sided lesions had a mean score of 86.7 (SD 11) which did not differ significantly from the mean score of 86.7 (SD 10.4) or the score of the subjects with left-sided lesions [$t(38) = 0.02$, $P = 0.98$]. For the early amygdala damage group, there was also no significant difference [$t(13) = 0.14$, $P = 0.88$] between those with right- (mean score 82, SD 9) and left-sided damage (mean score 81, SD 12). There was no significant difference between the subgroup of early amygdala damage subjects whose lesions were confined to the amygdala (nine subjects) and those with lesions which had some extension into

Table 6 *Results in the overall performance on ToM tests by gender*

	Early amygdala	Late amygdala	Clinical comparison group	Healthy comparison group
Male; median (quartiles)	79 (75–85)	90 (75–96)	94 (83–99)	96 (94–98)
Female; median score (quartiles)	82 (76–91)	91 (85–95)	90 (84–96)	98 (94–99)
Mann–Whitney *U* test	$Z = -0.69$, $P = 0.49$	$Z = -0.37$, $P = 0.71$	$Z = 0.9$, $P = 0.36$	$Z = -1.02$, $P = 0.3$

adjacent structures (six subjects) on any of the ToM measures [Happé $t(13) = 1.08$, $P = 0.27$; *faux pas* $t(13) = 1.66$, $P = 0.12$; belief and emotion $t(13) = 0.76$, $P = 0.46$; false belief and deception $t(13) = 0.15$, $P = 0.87$].

An index of content specificity was calculated to give a measure of the relative performance on epistemic versus affective ToM reasoning. The side and location of damage (24 amygdala damage and 14 non-amygdala damage) were then entered into a 2×2 analysis of variance (ANOVA) with the index as the dependent variable. There was no main effect of side [$F(1,34) = 1.18$, $P = 0.28$] or location of damage [$F(1,34) = 1.4$, $P = 0.23$] and no interaction [$F(1,34) = 1.1$, $P = 0.30$].

As can be seen from Table 6, there were no significant gender differences within each group, although in the early and late amygdala damage group and the healthy control group, females tended to perform slightly better. Collapsing the results for the cumulative index across all groups, females had a marginally higher score than males (female mean 91.7, SD 7.1; male mean 90.7, SD 10; $t = -0.53$, $P = 0.60$).

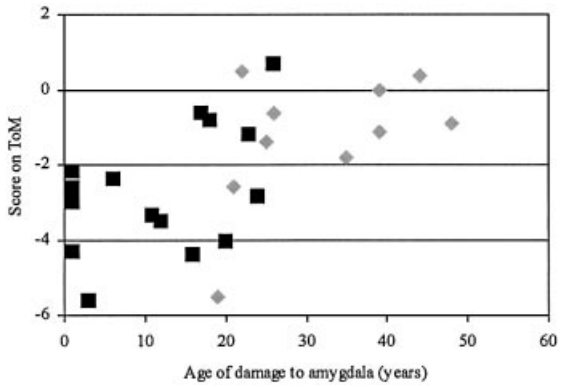

Fig. 2 Relationship between the age of damage to the amygdala and overall score on the ToM battery (scores expressed as standard deviations from mean score of healthy comparison group). Filled black squares = early amygdala damage group (DNETs); filled grey diamonds = late amygdala damage group (surgical excision).

Relationship with the age of onset of damage to the amygdala

As discussed earlier, the age of damage for the early amygdala group can be taken to be the age of onset of seizures which arise from the lesion. The age of damage to the amygdala in the late onset group is the age at which the patient underwent its surgical excision. As would be expected, the age of damage to the amygdala in the 'early damage group' was in childhood (12 ± 9 years; mean $\pm$ SD) and in the late amygdala damage group in adult life (31 ± 10 years). This difference was highly significant ($t = 4.8$, $P < 0.001$). There was a significant positive correlation between the age of onset of amygdala damage and the overall score (Spearman's rho = 0.64, $P < 0.001$). Figure 2 illustrates this correlation, with the overall score expressed as number of standard deviations from the mean of the healthy comparison group.

All patients with a DNET who had an onset of epilepsy in childhood (<16 years) fell at least 2 SDs below the mean of the healthy comparison group. Four of the six patients who had a DNET associated with adult onset of seizures were less impaired (falling within 2 SDs of the healthy comparison group). Turning to the late amygdala damage group, only two of the 11 subjects scored 2 SDs below the healthy comparison group. The age of onset of habitual seizures was not related to the degree of impairment in ToM reasoning in the late amygdala and clinical comparison groups (Spearman's rho = 0.28, $P = 0.39$ for the late amygdala damage group, and Spearman's rho = 0.31, $P = 0.28$ for the clinical controls). Thus it is unlikely that an early age of onset of seizures *per se*, regardless of the location of the epilpetogenic focus, leads to deficits in ToM reasoning.

Discussion

Key findings

The study demonstrated deficits in advanced tests of reasoning about the mental states of others among subjects with lesions of the amygdala arising early in development, particularly if associated with childhood onset of seizures. In contrast, subjects with lesions of the amygdala acquired in adult life showed no significant impairment in ToM tasks relative to a clinical comparison group of subjects with lesions which spared the amygdala. This pattern of deficits held after co-varying measures of general intelligence, executive function and verbal memory. There was no effect of side of damage or gender on overall performance. There was also no evidence of an interaction between the side of amygdala damage and impairment on specific types of mental state attribution (epistemic versus affective).

In the primary analyses, the developmental stage of amygdala damage was defined pathologically; early amygdala damage subjects had a presumed DNET and late amygdala damage subjects had a histologically normal amygdala excised in adulthood. Given the uncertainly about the exact age at which DNETs arise, we include a complementary method of dating the age of the amygdala lesions, i.e. taking the age of onset of the lesion to be the age of onset of associated epilepsy. Adopting this method, all subjects with amygdala lesions associated with a childhood onset of seizures (<16 years) had impaired ToM reasoning compared with healthy subjects. In contrast, only two subjects with damage to the amygdala which arose in adult life due to surgery showed marked ToM impairments. This raises the possibility of a sensitive period in development of ToM reasoning which extends to late childhood, during which damage to the amygdala leads to impairments, particularly if the damage is so severe as to be clinically and neurophysiologically apparent. Research into healthy children suggests that the ability to perform the *faux pas* task is acquired in late childhood (between the ages of 7 and 11 years), several years after children reliably pass first and second order false belief ToM tests (Baron-Cohen *et al*., 1999*a*; Wellman *et al*., 2001). Deficits in the early amygdala damage group are only apparent in the developmentally advanced tests of ToM such as the *faux pas*, implying that such damage is associated with a degree of developmental delay, rather than developmental arrest.

We can speculate about the possible cognitive origins of this delay. The amygdala appears to be a pivotal structure in supporting some of the earliest precursors of ToM reasoning. Lesion and fMRI studies both suggest that it plays a critical role in monitoring the direction of eye gaze necessary to engage in shared attention and detecting the emotional states of others on the basis of their appearance (Baron-Cohen *et al*., 1999*b*; Kawashima *et al*., 1999; Morris *et al*., 2002; Zald, 2003). By disrupting such precursors of ToM reasoning, early damage to the amygdala may thus slow the trajectory of the development of ToM, in many cases preventing subjects reaching the most advanced stages of the skill. This may explain the pattern of deficits found in the early amygdala damage group of generally intact, but not perfect, basic ToM function, and impaired, qualitatively anomalous performance on the more complex tasks of ToM such as the *faux pas* and comprehension of irony. This explanation links the role of the amygdala in emotional perception with a role in ToM reasoning.

Early damage to the amygdala has been linked explicitly to the later development of autism, which arguably has impaired ToM reasoning as its core neurocognitive deficit. It is interesting that the quality of the correct responses given by the subjects with early amygdala damage is reminiscent of those given by people who have autism (Happé, 1994; Jolliffe and Baron-Cohen, 1999). For example, in Happé's strange stories and the novel conflicting belief and emotions tasks, the subjects with early amygdala lesions tended to give fewer correct answers couched in explicitly correct mental state references. This is suggestive of impairment in spontaneously and automatically 'mentalizing' when faced with the task of interpreting the actions of other agents. Similarly, participants with early amygdala damage frequently made inappropriate affective attributions in the conflicting belief and emotion test, even when they made the correct epistemic attributions. This is reminiscent of the finding by Baron-Cohen (1991) that subjects with autism find the comprehension of emotional states particularly difficult when they are associated with belief states (rather than, for example, those evoked by a certain situation). Given the similarities between these responses and those given by subjects with autism and Asperger's syndrome to similar stories, we would interpret such answers as reflecting an inability to reason accurately about the mental states of others. Thus, the impairments in ToM reasoning are qualitatively similar to those often reported in autism and Asperger's, and as such are consistent with the idea that the amygdala plays a role in the aetiology of these neurodevelopmental disorders.

There are several possible interpretations of the lack of deficits in the late amygdala damage group. First, it could be argued that the amygdala may be necessary for the performance of ToM reasoning and that just one intact amygdala is sufficient for this processing. There are several instances of functional reduplication within the brain whereby the loss of one structure is readily compensated for by the presence of its homologue. If this were the case, then deficits in ToM reasoning would be present in subjects with late acquired damage only if both amygdalae were affected, such as that found in subjects described by Stone *et al*. (2003), all of whom have some impairment in ToM reasoning tasks. This position would also explain the functional imaging reports of amygdala activation during putative ToM reasoning tasks. However, these lesion and functional imaging studies are open to criticism. First, two of the bilateral subjects (S.E. and D.R.) in the study of Stone *et al*. (2003) had damage to regions extending beyond the amygdala which may have contributed to the impairments in ToM tasks. One of the subjects (D.R.) had marked impairments in executive function which alone could have led to failure on many of the tasks, and the subject may also have had early developmental damage to one amygdala. Turning to the functional imaging studies, Frith and Frith (2003) have noted that the tasks which report amygdala activation use stimuli such as the human face and eye region, which may recruit the amygdala even in the absence of a clear ToM component. It is debatable the extent to which the simple attribution of a mental state to another person on the basis of their appearance is truly a 'ToM' activity, which some argue must entail a meta-representational component. None of the tasks which we employed which more clearly assess ToM reasoning has demonstrated amygdala activation during fMRI. Although the evidence from our study cannot rule out the possibility of an 'on-line' role for the amygdala, we feel it weakens the plausibility of this position. In other domains of social cognition such as moral reasoning, a similar relationship between impairments

Table 7 *Effect sizes (Cohen's d) of the difference between clinical groups and relevant comparison groups reported in different studies using Happe's strange stories*

Study	Clinical group	Comparison group	Cohen's d
Current study	Early amygdala	Healthy subjects	1.55
	Early amygdala	Clinical comparison	0.89
Happe (1994)	Subjects with high functioning autism*	Age-matched healthy subjects	1.23
	Subjects with autism who failed basic ToM tests	Age-matched healthy subjects	2.25
Jolliffe and Baron-Cohen (1999)	Subjects with high functioning autism	Age-matched healthy subjects	1.41
	Subjects with Asperger's syndrome	Age-matched healthy subjects	1.24
Happe *et al.* (1999)	Right hemisphere cerebrovascular accident	Age-matched healthy subjects	1.35

*High functioning autism refers to the ability to pass first and second order false belief tasks.

and the age of acquisition of a lesion has been reported. A comparison of the effects of early and late acquisition of lesions to the prefrontal cortex found more pervasive impairments in moral reasoning among subjects with early compared with late prefrontal cortex damage (Anderson *et al*., 1999).

Several important cautions must be considered in this study. First, the impairment demonstrated by the early amygdala damage group might not be considered severe: the majority of subjects passed the standard first and second false belief ToM tests and were mostly intact in the detection of irony (which is in essence a test of second order ToM reasoning). Deficits were only apparent in the more advanced tests of ToM, and even in these tests the deficits in absolute terms were not great. It would therefore be important to place these impairments in the context of other groups who are also thought to exhibit ToM deficits. This is limited by the lack of a standardized battery of ToM tests, but some comparisons are possible from several studies which have used Happé's strange stories (Table 7).

On this test of advanced ToM processing, the deficits in the early amygdala group relative to a healthy comparison group are of a similar magnitude (reflected in a similar large effect size) to those shown by subjects with high functioning autism and Asperger's syndrome and subjects with extensive right hemisphere damage due to strokes. In the *faux pas* test, a direct comparison is possible with Stone's original study (Stone *et al*., 1998). Patients with orbitofrontal damage had an estimated median score of 86% (interquartile range 76–96%), compared with performance at or near ceiling for subjects with dorsolateral prefrontal cortex lesions and healthy comparison subjects. These scores are similar to the median score of the early amygdala damage group of 89% (interquartile range 73–100%). Studies with subjects with autism and the frontal variant of fronto-temporal dementia are suggestive that the deficits in these groups on the *faux pas* test are more severe, but direct comparisons are difficult due to methodological differences (Baron-Cohen *et al*., 1999*a*; Gregory *et al*., 2002). These findings suggest that the early amygdala group have impairments in the advanced tests of ToM which are comparable with those of subjects with high functioning autism and Asperger's syndrome and those with lesions of other candidate components of the ToM neural circuitry.

Equally, the impairments in the subjects with early amygdala DNETs are not as severe as those found among most people who have autism, emphasizing the fact that we view early amygdala damage as only one of the contributors to a delay in the development of ToM reasoning.

A second important caveat is the presence of almost entirely normal ToM function in some of the subjects in the early amygdala group. Why were these subjects unimpaired? First, there is the possibility of a type 1 error, although the probability of this is low given the effect sizes reported. Secondly, the presence of intact performance in the face of amygdala damage raises the possibility that the amygdala may not be a core component of the development of ToM reasoning and may provide instead domain general support for ToM reasoning. By this reasoning, compensation for early damage to the amygdala may occur more readily as it is not a core component of ToM reasoning, and thus subjects with amygdala damage may not always demonstrate clear ToM impairments. If this were so, deficits would only be evident in tests which relied on the domain general functions of the amygdala (e.g. its role in memory for emotionally salient material used in some of the stories). While this is not excluded by our study, it is unlikely as the impairment of the early amygdala damage group relative to the other groups held after co-varying for a wide range of measures of general cognitive function. However, the case for a core contribution of the amygdala would be strengthened by the demonstration of deficits on a wider battery of tests, less reliant on verbal processing and comprehension than those used in the current study.

Finally, it is notable that all the unimpaired subjects with amygdala lesions had an adult onset of epilepsy (see Fig. 2). This may reflect the presence of a lesion which is less disruptive to amygdalar neuronal integrity leading both to a later age of onset of epilepsy and less impairment in the development of ToM. This is reminiscent of Jackson's hypothesis that a discharging or epileptogenic focal lesion may inhibit neuronal reorganization and compensation more than focal lesions which are 'non-discharging' (Jackson, 1931). Thus patients who have a clinically silent DNET

throughout early childhood may have been better able to compensate for the presence of an early focal lesion of the amygdala. We would, however, predict that such compensation may often not be complete, which would account for the deficits found in subjects with early amygdala lesions who have an adult onset of seizures. Additionally, we might expect that on more subtle measures of ToM processing such as reaction times or the quality of responses, differences may be apparent. As the age of onset of habitual seizures was not significantly correlated with the degree of impairment in ToM reasoning in the late amygdala and clinical comparison groups (whose epileptogenic lesions lie outside the amygdala), it is unlikely that an early age of onset of seizures *per se*, regardless of the location of the epileptogenic focus, accounts for the deficits in ToM reasoning.

The role of gender and other brain regions in ToM reasoning

Although the focus of the study was on the amygdala, some participants had damage to other structures which are held to mediate ToM reasoning, such as the temporal poles which are activated in fMRI studies tapping this domain (Frith and Frith, 2003). However, as can be seen from the individual results in Table 3, the subjects with early developmental, combined amygdala and temporal pole damage showed a range of scores spanning from the most impaired individual to subjects performing at average levels for the amygdala damage group. Subjects who acquired temporal pole damage as part of a temporal lobectomy were unimpaired compared with clinical controls. The left temporo-parietal junction recently has been isolated as another key region in ToM reasoning (Saxe and Kanwisher, 2003). Only one subject in this study had a lesion in this region (a DNET) and she made relatively few errors on the tasks, performing at the mean level for the clinical control group. Future work will examine more systematically the effects of lesions in these specific areas.

There were no significant gender differences within or across groups. This was a surprising finding as we might have expected males to compensate less readily for amygdala damage given the male predominance in developmental disorders with ToM impairments as a core feature.

Limitations of the study

A major potential drawback of this study is the difference in extent of extra-amygdala damage in the early onset and late onset groups, with the latter group generally having more extensive involvement of other anterior temporal lobe structures. However, if the greater volume of extra-amygdala tissue damage is functionally important, then we would expect those with most damage to be most impaired, which was not the case.

We did not include a control condition of stories which had a non-mental state content, which may help in excluding the possibility that impairment arises from factors unrelated to ToM reasoning such as the ability to form an integrated narrative from each vignette. However, the lack of a significant correlation between measures of general intellectual ability, executive function and ToM performance and the intact performance on the comprehension and inference conditions in the tests makes an explanation in these terms unlikely. Additionally, the vignettes for assessing the comprehension of irony and metaphor were structurally identical, yet deficits were only present in the interpretation of irony, which relies on intact ToM reasoning.

Conclusion

In conclusion, we found that lesions of the amygdala which arise early in development and act as epileptogenic foci in childhood were associated with deficits in ToM reasoning. Subjects who sustained surgical damage to a previously normal amygdala in adult life were intact in most tests of ToM relative to a clinical comparison group. These impairments cannot be reduced to executive dysfunction, which was not marked in the subjects with amygdala lesions and which did correlate strongly with overall performance. Although the findings were statistically robust and large effect sizes were observed, a minority of subjects had essentially normal ToM reasoning in the face of an amygdala DNET. All such subjects had an adult onset of epilepsy, perhaps reflecting a less aggressive amygdala lesion which may have also been less disruptive to the development of ToM reasoning. However, the presence of these intact subjects emphasizes the need for replication of these findings using complementary measures of ToM reasoning. The study provides initial evidence compatible with the postulation of the amygdala as part of the neural system which supports the development of ToM reasoning.

Supplementary data

Supplementary data are available at *Brain* Online.

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