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Acquired theory of mind impairments in individuals with bilateral amygdala lesions

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Abstract

Studies in humans suggest that the amygdala plays a role in processing social information. A key component of social information processing is what developmental psychologists call "theory of mind": the ability to infer others' mental states. Recent studies have raised the possibility that the amygdala is involved in theory of mind, showing amygdala activation during a theory of mind task, or showing impairment on theory of mind tasks in a patient with amygdala damage acquired in childhood. Here, we present the first evidence of theory of mind deficits following amygdala damage acquired in adulthood. Two participants, D.R. and S.E., with acquired bilateral amygdala damage showed difficulties with two theory of mind tasks, "Recognition of Faux Pas" (for D.R., $z = -5.17$; for S.E., $z = -1.83$) and "Reading the Mind in the Eyes" (for S.E., $z = -1.91$; for D.R., $z = -1.4$). The items on which D.R. and S.E. made errors on these tasks were uncorrelated with the items that control participants found most difficult, indicating that these deficits cannot be attributed solely to the cognitive difficulty of the tasks. These results indicate that the amygdala's critical role in theory of mind may not be just in development, but also in "on-line" theory of mind processing in the adult brain.
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1. Introduction

A large body of research demonstrates that the amygdala is a critical structure for normal social development and social behavior. Primates with amygdala lesions become socially withdrawn or disinhibited, depending on which species is studied, and display inappropriate social behavior [29,30,44–46,52]. Humans with bilateral amygdala damage have difficulty reading emotional expressions and making other social judgments [2–5,20,25,62,72]. Anatomically, the amygdala is well positioned to process social information, as well as many other types of complex information. The amygdala receives highly processed input from polysensory association areas in several regions of cortex, projects to the hypothalamus, ventrostriatal areas, temporal and insular cortex, and is highly interconnected with orbitofrontal cortex [21,31,36,54,60]. Thus, it can receive information about complex, polysensory stimuli and can affect autonomic, motor and cognitive responses. Social stimuli are one category of complex and polysensory stimuli (e.g. one often sees faces and hears voices together), and they also elicit emotional, behavioral and cognitive responses. Thus, one might expect the amygdala to play a role in social intelligence. One important aspect of social intelligence is what developmental psychologists call "theory of mind": the ability to make inferences about others' mental states, such as intentions, feelings, beliefs, or focus of attention. This ability has often been discussed in the developmental psychology literature as a specific faculty, separable from more general cognitive abilities such as executive function and general intelligence [9,10,16,27,28,34,56,61,64,68,70].

A wide variety of tasks have been used to measure theory of mind, and these tasks tap into a range of mental state attribution abilities. These can roughly be divided into three types: (1) attribution of epistemic mental states, i.e. mental states that refer to something in the world, such as knowledge, attention or belief; (2) attribution of intention, e.g. the understanding of whether an act was intentional or accidental; and (3) attribution of more affective mental states, such as desire, or fear or anger. Some tasks use verbal material, such as stories, others use pictures and require participants to process perceptual input, and others use both. Some tasks, such as Happé's "Strange Stories" task [37], or Stone et al.'s

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[66] and Baron-Cohen et al.'s [15] "Faux Pas Recognition" task, measure more than one type of mental state attribution.

The most commonly used tasks are "false belief tasks", which are based on verbal stories, often acted out with puppets, in the case of children, or accompanied by pictures. Such tasks measure the ability to infer another's mistaken knowledge or belief, and thus measure the ability to infer *epistemic mental states* [11–34,55,56]. One methodological difficulty with false belief tasks is that they often make other cognitive demands as well, such as inhibition of a prepotent response, an executive function ability. Other theory of mind tasks use visual displays to measure the ability to infer epistemic mental states from eye gaze direction, such as knowledge about, reference to, or attention to something [12,13,17,59]. These more visual tasks do not place as many demands on executive function, i.e. working memory, planning, sequencing, set-shifting, and inhibition of a prepotent response.

Other studies focus on *intentions* as mental states, measuring the ability to infer deceptive intention [8,37], or the ability to infer whether something is intentional or accidental [15,26,64,66].

Other theory of mind tasks measure young children's ability to understand more *affective mental states* such as desire, by comprehension of words such as "want" or inferring desire from eye gaze direction [12,69]. Other tasks, used on older children or adults, measure the ability to infer affective mental states either from stories or from pictures of eyes [13,15,17,37,64,66]. Affective mental states differ from epistemic mental states in that they do not represent or refer to something in the world, and some have argued that the term "theory of mind" should only be applied to inferences about intentionality and about epistemic mental states [19,47–49].

To what extent all these mental state attribution tasks share common processes or neural structures is currently debated. However, populations that are thought to be impaired in theory of mind, such as individuals with autism or patients with frontotemporal dementia, do show impairment across many of these tasks without showing corresponding impairment in more general cognitive abilities [9,10,16,35,50,57,61], indicating that these are not completely disparate abilities, but share something in common.

Individuals with autism are known to have theory of mind impairments on a variety of tasks. Several studies indicate amygdala abnormalities in autism [1,7,18], opening up the possibility that the amygdala may play a role in theory of mind. There is also some recent direct evidence for the amygdala's role in theory of mind: a patient with bilateral amygdala damage interpreted Heider and Simmel [40] displays geometrically rather than as intentional agents [39], and one study has demonstrated theory of mind deficits in a patient with early unilateral amygdala damage and a diagnosis of Asperger's syndrome and schizophrenia [32]. Using functional imaging, Baron-Cohen et al. [14] found amygdala activation in normal participants during a task requiring participants to infer mental states from pictures of people's eyes. Here we extend these results by demonstrating theory of mind deficits in two individuals with bilateral amygdala damage acquired in adulthood.

1.1. The amygdala's role in processing social information

In non-human primates, the amygdala appears to be important in processing social information. Brothers and co-workers [22,23] have reported cells in the macaque amygdala that respond specifically to visual displays of socially significant conspecific gestures, such as approaching, touching, or making a bid for food. There are also cells in the amygdala that respond specifically to separation distress calls or predator warning calls [44]. Dicks et al. [29] and Kling et al. [46] gave adult macaques and vervet monkeys amygdala lesions and released the monkeys into their social groups in the wild. The monkeys became socially withdrawn, fearful of others and isolated when released, and either were attacked by other group members, or withdrew from the group and were taken by predators. (In these primates' natural social environment, there was a complete absence of Klüver-Bucy syndrome.) Bilateral lesions of the amygdala in rhesus macaques produced disinhibition and decreased fear when monkeys were tested in pairs in the laboratory, quite a different pattern from that seen in the wild [30]. Neurotoxic lesions of the amygdala, which affect amygdala tissue but not connecting fibers to adjacent areas, produced increased submission, and decreased fear and aggression in laboratory monkeys [52]. The exact nature of the social behavior changes seen depends on the species studied, e.g. vervets, stumptail macaques, rhesus macaques, and on the context of the testing [21,45]. Amygdala lesions can produce different effects on rhesus macaques in the wild than those in the laboratory (social withdrawal versus disinhibition), but it is clear that amygdala lesions impair normal social behavior in several primate species.

Recent studies of humans with bilateral amygdala damage have shown that such individuals have deficits in processing social information. Several groups have found that individuals with bilateral damage to the amygdala have difficulty recognizing facial or vocal expressions of emotion, and that this difficulty is most pronounced for expressions of negative emotions ([3,5,20,25,62], but see [6] for intact prosody recognition of some emotions in one person with bilateral amygdala damage). That the impairment is not specific to one sensory modality suggests that the amygdala is involved in polysensory representation of emotional and social stimuli. Adolphs et al. [2] found that individuals with unilateral or bilateral amygdala damage were more impaired in the recognition of social emotions than in the recognition of basic emotions. Studies using PET and fMRI in normal participants have also found that the amygdala is active when facial or vocal expressions of fear are presented [53,58].

However, the human amygdala may be involved in more than just the processing of emotional displays. Young et al. [72] found that one individual with bilateral amygdala damage was impaired in judging from photographs whether someone was making direct eye contact, and Kawashima et al. [43] found amygdala activation during a task measuring discrimination of eye contact. Other imaging studies have found activation during tasks requiring discrimination of eye gaze direction in the banks of the superior temporal sulcus and medial prefrontal cortex, also areas thought to be involved in theory of mind [24]. Adolphs et al. [4] found that three patients with bilateral amygdala damage had difficulty judging from photographs whether people appear trustworthy or approachable. This deficit was evident only for judgments made from photographs, not for judgments made from verbal descriptions. Winston et al. [71] found bilateral amygdala activation to faces judged untrustworthy in an fMRI experiment asking participants to judge trustworthiness and age of faces. Stone et al. [67] found that a patient with bilateral disconnection of the amygdala and orbitofrontal damage who was impaired on a variety of theory of mind tasks was also significantly impaired on a verbal reasoning task requiring detecting cheaters in a social exchange, but performed well on a non-social reasoning task closely matched for difficulty and task demands. Patients with orbitofrontal damage did not show this dissociation. The amygdala could process more kinds of social information than just judgments of others' emotional states.

Thus, the amygdala may be involved in a variety of processes that could underlie or partially overlap with theory of mind abilities. Assessing trustworthiness or detecting cheaters could involve inferring another person's likely intentions, though it is also possible it could involve other processes. As discussed above, detecting eye gaze direction, in which the amygdala appears to be involved [43,69], is a key component in inferring someone else's epistemic mental states. The discovery of deficits on these tasks point to the possibility that the amygdala participates in some of the processes which underlie our theory of mind abilities. However, direct tests of the amygdala's involvement in theory of mind tasks are scarce.

1.2. The amygdala and theory of mind

A few recent studies have explicitly pointed to a role for the amygdala in theory of mind. Baron-Cohen et al. [14] found amygdala activation in normal participants during a task requiring participants to infer mental states from pictures of people's eyes, but not during a task requiring a judgment of gender. No corresponding amygdala activation was found in participants with Asperger's syndrome who could perform the task. However, this task required judgments of the depicted person's emotional state, and did not probe participants' ability to judge epistemic mental states, such as focus of attention. Adolphs et al. [2] found that patients with unilateral or bilateral amygdala damage were impaired on a similar task requiring the judgment of social emotions from the eye region of the face. One patient with bilateral amygdala damage that had occurred sometime in childhood or adolescence from Urbach-Wiethe disease was tested on the Heider and Simmel paradigm [40], in which geometric figures move around in a way that most neurologically normal participants interpret as social agents pursuing goals and having feelings. S.M. did not interpret the displays in terms of intentional behavior or agents having mental states, but described them as geometrical forms moving on the screen, a striking difference from normals [39].

Fine et al. [32] report a patient with early left amygdala damage and a diagnosis of Asperger's syndrome and schizophrenia who was impaired on second-order false belief tasks (which can usually be passed by children aged 6–7 years), comprehension of mental state cartoons, and advanced theory of mind stories requiring participants to understand non-literal utterances such as white lies, bluffing or sarcasm. His impairment on these tasks relative to controls ranged from moderate ($z = -1.25$) to severe ($z = -4.1$). In contrast to his theory of mind performance, the patient's IQ was in the average range, and his executive function, as measured by a variety of tests, was intact.

Fine et al.'s [32] and Heberlein et al.'s [39] results raise the possibility that early damage to the amygdala may impair theory of mind or theory-of-mind-related abilities later in life. However, this leaves open three possible interpretations. First, these patients may have been impaired on these tasks because their early amygdala damage prevented theory of mind abilities from developing properly. Second, these patients may have been impaired on these theory of mind tasks because the amygdala plays a critical role during theory of mind processing in the adult brain, which could be called "on-line" theory of mind processing. Third, these patients may have been impaired on these tasks for both reasons, i.e. the amygdala may be crucial for both the normal development of theory of mind and for "on-line" theory of mind processing in adults. Baron-Cohen et al.'s [14] functional imaging results point to a possible "on-line" role for the amygdala in theory of mind in the adult brain.

We addressed these questions by investigating whether amygdala damage acquired later in life can also affect theory of mind functioning. A failure to find impairment on theory of mind tasks in individuals with amygdala damage acquired in adulthood would be inconsistent with both the hypothesis that the amygdala has an "on-line" role in theory of mind in adults and with the hypothesis that the amygdala is involved in both theory of mind development and in normal "on-line" theory of mind processing in the adult brain. In contrast, results showing impairment on theory of mind tasks in individuals with amygdala damage acquired in adulthood would be inconsistent with the hypothesis that the amygdala's role in theory of mind is only in the development of theory of mind abilities.

1.3. Testing theory of mind in adults

Measuring acquired theory of mind deficits in adult neurological patients with acquired lesions requires using different methods than measuring theory of mind deficits in young children or in individuals with autism in order to avoid ceiling effects. Adults with acquired neurological damage have presumably had intact, developmentally normal theory of mind abilities until the time of their damage. Thus, one would expect that rather than the severe theory of mind deficits exhibited by individuals with autism who have never fully developed the theory of mind capacity, adult neurological patients might have more subtle deficits in theory of mind, not evident on the simplest theory of mind tasks. Many standard tests of theory of mind, such as false belief tasks, can easily be passed by children aged 4–6 years and are trivially easy for adults. To be able to measure more subtle deficits, more developmentally advanced tasks, at which normal adults are not at ceiling, are needed.

Stone et al. [66] have developed a theory of mind task for use with adults. The "Recognition of Faux Pas" task tests whether participants can recognize when a person unintentionally says something that would hurt or insult another person. It measures inferences about affective mental states, by testing the ability to recognize that something awkward or hurtful has been said, inferences about epistemic mental states, by assessing whether a participant understands that a story character has a false belief, and inferences about intentionality, by assessing whether a participant understands that the faux pas was said unintentionally (see detailed description of task below). This task has been used to measure deficits in theory of mind in adult patients with orbitofrontal damage from head trauma [66] and in patients with orbitofrontal damage from frontotemporal dementia [35]. The ability to recognize faux pas develops later than the ability to solve standard theory of mind tasks. Children do not perform well on the task until age 11 years [15]. Twelve-year-old children with Asperger's syndrome were significantly impaired on this task relative to age-matched controls [15]. IQ was not correlated with performance on the Faux Pas task in either participants with Asperger's syndrome or controls [15]. Further evidence for the Faux Pas task being a theory of mind task is that Faux Pas task performance was highly correlated with first and second-order false belief task performance in a sample of 19 patients with frontotemporal dementia [35].

Baron-Cohen et al. [14] found amygdala activation during a task designed to measure theory of mind in adults, "Reading the Mind in the Eyes". It requires participants to make inferences about subtle mental states based only on viewing pictures of someone's eyes. Since the amygdala appears to be active during this task, we chose this task to measure theory of mind as well. However, whereas the version of the task used by Baron-Cohen et al. [14] measured the ability to judge subtle affective states from pictures of the eyes [17], we used an older version of the task [13] that includes both items that ask about affective mental states and items that ask about epistemic mental states such as attending to or noticing. It is a difficult task even for adults—normal adults do not perform at ceiling [13,35]. To validate that this task does measure theory of mind, the authors demonstrated that performance on this task is correlated with another theory of mind task, Happé's "Strange Stories", and that high-functioning adults with autism or Asperger's syndrome are significantly impaired on this task [13,37].

2. Methods

2.1. Participants

2.1.1. Individuals with amygdala damage

We tested two individuals, D.R. and S.E., with bilateral damage to the amygdala acquired in adulthood. D.R. was a 53-year-old woman who had had neurosurgery targeted at the left and right amygdala to address intractable epilepsy [25,72]. MRI scans revealed an extensive lesion of the left medial amygdala, which destroyed much of the basal nuclei but largely spared the lateral nucleus. The area of damage extended throughout the rostrocaudal limits of the left amygdala, just reaching the anterior horn of the left hippocampus. Associated damage extended dorsally beyond the amygdala to involve part of the anterior commissure, lateral putamen and external capsule. In the right hemisphere, there was a small posteriorly placed lesion at the caudal limit of the amygdala, and a second small lesion in the right anterior amygdaloid area. See [25,72] for scan images.

There was also some additional extra-amygdalar subcortical damage in the right hemisphere, probably as a result of bleeding noted on CT after one surgery; this involved a discrete lesion in the pallidal region at the level of the anterior commissure, extending more dorsally within the striatum at a level rostral to the anterior commissure, with possible damage to adjacent parts of the internal capsule and caudate nucleus. In addition, very small areas of cortical abnormality (high signal on T2 and low signal on T1) were noted in the left occipitoparietal region adjacent to the falx and in the anterior right frontal lobe; these were also considered to result from surgery.

A striking aspect of D.R.'s character is her upbeat mood. She rarely becomes upset, a fact noted by both her husband and herself, and does not always respond appropriately when other people are upset or distressed. That said, she happily engages in conversation, although she does have some difficulties in finding the exact words to use. Her communication skills are not unduly hindered by this problem, however, as she is able to use effective circumlocutions. In all other respects D.R.'s conversations are appropriate and grammatical.

S.E. was a 67-year-old man who suffered from herpes simplex viral encephalitis at the age of 55 years [20,25,51]. Since then he has complained of severe problems with topographical orientation, mild deficits in face recognition, and a profound disruption of his previously happy interpersonal relationships. Obvious changes in S.E.'s behavior have been problems with turn-taking in conversations, and judging other people's emotional state.

A three-dimensional acquisition sequence MRI with coronal and horizontal reconstruction showed extensive destruction of the right temporal pole, uncus, amygdala (including all nuclei), hippocampus, parahippocampal gyrus, inferior and middle temporal gyri to the level of the insula, with compensatory dilation of the temporal horn of the right lateral ventricle. The left cerebral hemisphere was normal with the exception of a small region of high signal on the T2-weighted sequence in the region of the uncus and anteromedial amygdaloid area. See [51] for scan images.

Both D.R. and S.E., therefore, have bilateral damage to the amygdala acquired in adulthood; for D.R. this damage is more severe in the left amygdala, for S.E. in the right. In addition, S.E. has suffered extensive pathological changes affecting the right temporal lobe, and D.R. has some damage that extends beyond the amygdala.

2.1.2. Neuropsychological testing

Summaries of assessments of intelligence, perception, memory, language and executive functions are given in Table 1. D.R.'s latest assessment with the WAIS-R gave a full scale IQ of 87 (VIQ 82, PIQ 96). Her predicted premorbid IQ is 111 using the revised version of the National Adult Reading Test, but this figure is above both pre- and post-operative results with WAIS and WAIS-R. S.E.'s WAIS-R and NART both indicated average intelligence (WAIS-R full scale IQ 100, VIQ 99, PIQ 101; NART estimated premorbid IQ 100).

Table 1
Background neuropsychological information for D.R. and S.E.

Tests given	D.R.	S.E.
Intelligence		
WAIS-R		
Full scale IQ	87	100
Verbal IQ	82	99
Performance IQ	96	101
National Adult Reading Test		
Estimated premorbid IQ	111	100
Perception		
Visual fields		
Confrontation testing	Full	Full
Spatial contrast sensitivity function		
Vistech VCTS6000	Normal	Normal
VOSP Battery		
Fragmented letters	19/20	20/20
Cube analysis	10/10	10/10
Position discrimination	20/20	19/20
Memory		
Warrington Recognition Memory Test		
Words	47/50	38/50**
Faces	34/50+**	33/50+**
Language		
SCOLP Test (percentile)	25–50	25–50
Pyramids and Palm Trees Test	49/52	45/52+
Executive function		
Wisconsin Card Sorting (categories)	2+	6
FAS fluency	13**	41

Marked scores indicate some degree of impairment: (+) impaired on test's norms; (**) $z > 2.33$, $P < 0.01$, impaired in comparison to control participants reported by Young et al. [72].

There was no evidence of impairment of basic visual and spatial functions. Both individuals had full visual fields to confrontation testing and normal spatial contrast sensitivity function (Vistech VCTS6000) for both D.R. and S.E. Performance of tasks taken from Warrington and James' Visual Object and Space Perception (VOSP) Battery was entirely normal.

As documented in previous reports, both D.R. and S.E. showed problems in memory tests, including recognition memory for the faces part of the Warrington RMT.

For language, performance of Baddeley, Emslie and Nimmo-Smith's Speed and Capacity of Language Processing (SCOLP) Test was well within the normal range, but D.R. showed problems in FAS fluency, presumably due to her problems with word finding. On the Pyramids and Palm Trees Test of semantic comprehension, D.R. was within the normal control range (up to three errors) reported by Howard and Patterson, but S.E. scored less well.

Executive function refers to frontally based abilities such as planning, sequencing, working memory, and set-shifting. On executive function tests, D.R. showed problems with the WCST and FAS fluency, though, as noted above, the latter problem may be related to previous reports that she experiences word-finding difficulties, rather than to an executive function impairment per se. Similar 'frontal' effects are sometimes noted in other cases of temporal lobe epilepsy.

While it is, therefore, clear that D.R. and S.E. show some problems on background neuropsychological tests, their difficulties do not present a consistent pattern. The only task shown in Table 1 for which both D.R. and S.E. were impaired was recognition memory for faces.

The participants were tested on both tasks, "Reading the Mind in the Eyes" and "Recognition of Faux Pas", in a single session. D.R. was tested at her home and S.E. was tested at the Cognition and Brain Sciences Unit in Cambridge, UK.

2.1.3. Control participants

Ten British and 24 American control participants matched to D.R. and S.E. for age were tested on both the Faux Pas task and the Eyes task. This group included 18 females, 16 males, age range 52–67 years, mean age = 56.9 years, S.D. = 4.46 years. Control participants were screened to exclude individuals with any neurological or psychiatric disorders.

2.2. Tasks

2.2.1. Recognition of Faux Pas

This task has been described in detail in Stone et al. [66] and Gregory et al. [35]. There were 10 items on the Faux Pas task. Each item contained a story that told about a faux pas, such as someone insulting a wedding gift without remembering that they were speaking to the person who gave it (see example below). The experimenter read the story aloud to the participant while the participant read along on their own copy. The story remained in front of the participant while questions were asked, to reduce memory demands. After each story the participant was asked a faux pas detection question: "Did anyone say something they shouldn't have said? Did anyone say something awkward?" If the participant answered yes, they were then asked, "Who said something they should not have said?" If the participant identified the correct person, they were counted as having correctly identified the faux pas. Then two follow-up questions were asked: "Why shouldn't the individual in the story have said what they did?" (tests that the participant understood that the listener would be hurt or insulted, an inference about *affective* mental states), and "Why do you think they did say it?" (tests that the participant understood that the faux pas was unintentional, an inference about *epistemic* mental states and *intentionality*). Thus, there were four faux pas-related questions if the participant said that a faux pas had been committed. Finally, as a control for story comprehension, participants were asked a question about some important detail of the story, such as "What had Jeanette given Anne for her wedding?" or "What had Jill just bought?" Participants who answered "no" to the first question answered the control question immediately after question 1.

> Example: Jill had just moved into a new apartment. Jill went shopping and bought some new curtains for her bedroom. When she had just finished decorating the apartment, her best friend Lisa came over. "Oh, those curtains are horrible!" Lisa said, "I hope you're going to get some new ones!" Jill asked, "Do you like the rest of my bedroom?"

> Example: Jeanette bought her friend Anne a crystal bowl for a wedding gift. Anne had a big wedding and there were a lot of presents to keep track of. About a year later, Jeanette was over one night at Anne's for dinner. Jeanette dropped a wine bottle by accident on the crystal bowl, and the bowl shattered. "I'm really sorry, I've broken the bowl," Jeannette said. "Don't worry," said Anne, "I never liked it anyway. Someone gave it to me for my wedding."

Participants' answers were written down by the experimenter, and the session was tape-recorded as well. Shyu [64] has found evidence that the Faux Pas task is not affected by changes in working memory demands, and thus does not seem to place a strong load on working memory.

2.2.2. Reading the Mind in the Eyes

Baron-Cohen et al. [13] describe this task in detail. They validated the task on normal adults aged 18–48 years, high-functioning adults with autism or Asperger's syndrome, aged 18–49 years, and adults with Tourette's syndrome, aged 18–47 years. The task consists of 25 items, showing the eye region of black and white photographs of 25 different faces, both male and female. These photographs were taken from magazines, and each face was enlarged or reduced to a standard size (15 cm × 10 cm). The eye region selected for each face extended from just above the brows to halfway along the nose. Each picture has two mental state terms printed below it, such as "interested/disinterested" or "observing/daydreaming". These terms were always antonyms, and were different for each picture, except for two items that both had the terms "reflective/unreflective". Participants were shown each item and asked by the experimenter, "Which word best describes what this person is feeling or thinking?" "Correct" answers are those that a panel of eight judges all agreed on unanimously. Because judgment of the correct response on such items could be somewhat subjective, it was necessary to include only items in the test on which there was complete agreement between eight different judges, to minimize the subjectivity of the responses. The Reading the Mind in the Eyes task was designed to have no central coherence component[1] and no executive function demands, as false belief tasks do, because it does not have a "prepotent response", and does not require sequencing or set-shifting [13].

On this version of the Eyes task, items can be subdivided into two different types: those requiring inferences about *affective* mental states (17 items) and those requiring inferences about *epistemic* mental states (8 items). The epistemic mental state items primarily measured direction of attention, and included terms such as "ignoring you/noticing you" or "observing/daydreaming". These could be solved by judging gaze direction. The affective items included mental state terms such as "concerned/unconcerned" or "unsympathetic/sympathetic", and required subtle judgments of expression, brow position or tension around the eyes [13].

Although the Eyes task is a much less verbal task than the Faux Pas task, it is still possible for a participant to perform poorly on it because he or she does not understand the mental state terms used in the task. Accordingly, we assessed D.R. and S.E.'s comprehension of these words. S.E.'s vocabulary was tested in a separate later session. For each mental state term in the task, he was asked, "Can you give me a definition of this word, tell me what it means?" After he had answered, he was asked, "Can you use it in a sentence?" If he responded with a sentence that said only, for example, "He felt sympathetic," the experimenter said, "That doesn't really show me what it means. Can you use it

[1] Central coherence theory states that the normal brain has a strong drive for global meaning and "gist" rather than local detail and featural processing [33]. There is evidence from the Embedded Figures Test (in children and adults) that while the normal brain is relatively slow in identifying local features hidden in a global display, people with autism spectrum conditions are both faster and more accurate in such visual search [42,63]. People with autism also make less use of global context in deriving linguistic meaning [38,41].

in a sentence that shows what it means?" This procedure is lengthy. Because of time constraints, when D.R. was tested, a shorter procedure was used. She was asked if she understood the words on each item, and if she said no to any, the experimenter explained the meaning of the word to her. The following five word pairs (out of a total of 25 word pairs on the task) were explained to her: reflective/unreflective, happy reflection/sad reflection, dominant/submissive, flirtatious/uninterested, indecisive/decisive.

3. Results

3.1. *Recognition of Faux Pas*

On the Faux Pas task, there were 40 points possible for faux pas-related questions (1 point for each question), and 10 points possible for control questions measuring story comprehension. The control participants' average score for the faux pas-related questions was 35.5 (S.D. = 3.0), and for the control comprehension questions was 9.7 (S.D. = 0.45; see Table 2). Errors on the faux pas-related questions fell into three categories, answering a question with "I don't know", failing to indicate that someone would have hurt feelings, or misattributing the faux pas as an intentional insult. Two raters blind to the diagnostic category of the participants scored the task. The scoring of "Did anyone say something they should not have said, or say something awkward?" was straightforward, since the answer was yes or no, as was the scoring of "Who said something they should not have said?" as it was clear whether the participant indicated the correct character or not. The two questions, "Why should they not have said it?" and "Why do you think they did say it?", are more subjective. The raters were instructed to score these leniently, giving credit whenever the participants' answer could at all be interpreted as understanding that someone would be upset or understanding that the person committing the faux pas did not know or realize he or she should not say it. Thus, there was no requirement that a participant's answer contain explicit mental state terms to receive a full score. For example, in the story about the wedding gift, the answer "Because she gave her the bowl", was scored as a correct answer to "Why should they not have said it?" because it indicates an understanding of why someone would be upset. Only answers that clearly missed the point were scored as incorrect, such as attributing the faux pas to an intentional desire to do harm. An answer of, "She wanted to hurt her feelings" for "Why do you think they did say it?" would be scored as incorrect. Inter-rater reliability was 0.96.

Table 2
Performance of controls and participants with amygdala damage on faux pas-related and control questions on the Recognition of Faux Pas task

	Score on faux pas-related questions	Score on control questions
Control mean (S.D.)	35.5 (3.0)	9.7 (0.45)
D.R.	20	9
S.E.	30	9

The total number of faux pas-related questions for each story was four, so that the total score reflects a score out of 40. The total possible score on control questions was 10.

Relative to controls, D.R. was significantly impaired in recognizing faux pas. Her score on faux pas-related questions was 20 ($z = -5.17$, $P < 0.0001$), outside the range of scores for control participants. Her faux pas errors included four stories on which she did not recognize the faux pas, and four stories on which she recognized the faux pas, but gave explanations indicating she did not understand that someone's feelings would be hurt or that the insult was unintentional. In contrast to the faux pas-related questions, her score on the control comprehension questions was 9/10, not significantly different from controls. S.E. was also significantly impaired. His score on the faux pas-related questions was 30 ($z = -1.83$, $P < 0.05$). He recognized that a faux pas had occurred and who had made it on 9/10 stories, but like D.R., on 5 of the stories, gave explanations that indicated he did not understand that someone's feelings would be hurt or that the insult was unintended. S.E. also scored 9/10 on the control comprehension questions. See Table 2 for a summary of results on the Faux Pas task.

The faux pas-related questions can be further broken down into the two questions that determine whether or not the participant has correctly recognized the faux pas ("Did anyone say something awkward?" and "Who?"), and the follow-up questions that ascertain the participants' understanding of the faux pas ("Why should they not have said it?" "Why do you think they did say it?"). Thus, each participant can be given a "faux pas detection" score, and a "follow-up questions" score. For each of the 10 stories, we calculated the proportion of normal controls who got each type of question correct to get an objective measure of how difficult each item was. We then correlated these scores with whether S.E. and D.R. got those questions correct on that story. This analysis indicates that the items that control participants found most difficult were not those on which S.E. and D.R. made errors. For faux pas detection questions, this correlation between control participant scores and S.E.'s scores was −0.42; for D.R. the correlation was 0.17. S.E.'s one faux pas detection error, for example, was on the one story on which all control participants correctly detected a faux pas. For the follow-up questions, the correlation between controls' scores and S.E.'s scores was 0.07. The same correlation for D.R. was −0.73. The follow-up questions were more difficult both for the amygdala-damaged participants and for the control participants; however, the participants with amygdala damage were not more likely to make errors on the individual items that were most difficult for controls.

Between the two follow-up questions, there was no difference between control participants' number of errors. Thus, they were equally likely to fail to understand that someone would have hurt feelings (errors in answer to "Why should they not have said it?") as to misunderstand the intentionality of the faux pas (errors in answer to "Why do you think they did say it?"). S.E., however, made more errors in understanding that someone's feelings would be hurt (five errors) than he did in attributing intentionality (two errors). D.R.'s errors on the follow-up questions showed the reverse pattern. She made more errors in attributing intentionality (four errors) than in understanding that someone's feelings would be hurt (two errors).

3.2. Reading the Mind in the Eyes

The control participants' average score on the "Reading the Mind in the Eyes" task was 19.8 (S.D. $= 1.97$), or 82.3%. S.E. was significantly impaired on this task. He obtained 64% correct, or 16/25 ($z = -1.91$, $p < 0.05$). D.R.'s score of 68% correct, or 17/25 on this task, was also below normal, though not significantly so ($z = -1.40$, $P = 0.08$).

We also analyzed control participants' and S.E.'s and D.R.'s responses item by item on this task. We calculated how many control participants made errors on each item to get an objective measure of how difficult each item was. Then we correlated these scores with S.E.'s and D.R.'s scores. There was no relationship between the items that control participants found most difficult and those on which S.E. and D.R. made errors. For S.E., the correlation between control participant item scores and his score was 0.043; for D.R. the correlation was 0.012. Furthermore, there was also no consistency between S.E. and D.R. on which errors they made: the correlation between S.E.'s and D.R.'s scores was -0.16.

S.E.'s answers to the vocabulary questions showed full understanding of all of the mental state terms used in the task, except "reflective". If the two items including this word, one of which he got right and one of which he got wrong, are excluded from his data, the results do not change appreciably ($z = -1.73$, $P < 0.05$). D.R. had asked for explanations of five of the terms on the task and had them explained to her. She got four out of the six items involving these terms correct. See Table 3 for a summary of results.

3.2.1. Epistemic versus affective mental state items

As noted above, the Eyes task contains two types of items, those about epistemic mental states, which can primarily be answered using eye gaze direction (8 items), and those about affective mental states, which require more subtle assessment of facial expression (17 items). There is no clear difference in D.R.'s and S.E.'s performance on items involving epistemic versus affective mental state inferences (see Table 3). Though the *N*'s are too small to do a statistical analysis, it seems from these data that neither D.R.'s nor S.E.'s errors on the Eyes task can be accounted for solely by errors in one type of mental state judgment.

Table 3
Control participants' and D.R.'s and S.E.'s performance on the Reading the Mind in the Eyes task

	Overall	Items involving epistemic mental state inference	Items involving affective mental state inference
Control mean	19.8/25	6.5/8	13.4/17
D.R.	17/25	6/8	11/17
S.E.	16/25	5/8	11/17

Proportion correct on affective and epistemic mental state inference items for controls and participants with amygdala damage on the Eyes task.

4. Discussion

If the amygdala does play a role in theory of mind, there are three possibilities for what that role might be. First, the amygdala may be crucial for theory of mind abilities to develop properly. Second, the amygdala may play a critical "on-line" role during theory of mind processing in adults. Third, the amygdala may be crucial for both normal development of theory of mind and for "on-line" theory of mind processing. Previous research has found deficits on theory of mind tasks in an adult with amygdala damage acquired in childhood [32], but such findings do not allow one to decide between these three theories. We tested whether amygdala damage acquired later in life can also affect theory of mind functioning, and found evidence for theory of mind deficits in two individuals with amygdala damage acquired in adulthood. These results speak against the hypothesis that the amygdala's role in theory of mind is *only* in the development of theory of mind abilities.

Instead, these data provide evidence that the amygdala may play an "on-line" role in processing theory of mind inferences, whether or not it also plays a role in development. Both individuals with bilateral amygdala damage, D.R. and S.E., were significantly impaired relative to controls on the Recognition of Faux Pas task. Like individuals with orbitofrontal damage, their errors included not only difficulty recognizing that a faux pas had occurred, but also difficulty with epistemic mental state inferences and intentionality, i.e. inferring that the person committing the faux pas did not know or remember he or she should not say what he or she said, and difficulty with affective mental state inference, i.e. understanding that someone would be hurt or upset by the faux pas [35,65,66]. S.E. was significantly impaired on "Reading the Mind in the Eyes". D.R.'s score on the Eyes task was lower than normal, but the difference from controls was not statistically significant. Both individuals with amygdala damage made comparable numbers of errors on items on the Eyes task requiring judgments of affective and epistemic mental states.

An alternative explanation for these results is that D.R. and S.E. made errors on the tasks simply because cognitive limitations made it difficult for them to understand the tasks. This is particularly a concern in D.R.'s case, as her verbal IQ is quite low. We did not have IQ data on any but two of the control participants, who had IQ's of 115 and 116, so we do not know how the control participants' IQ's matched D.R.'s and S.E.'s. We note, however, that in a sample of frontotemporal dementia patients with ages and IQ's comparable to D.R.'s and S.E.'s, performance on the Faux Pas task was uncorrelated with IQ [35]. Baron-Cohen et al. [15] also found that IQ and Faux Pas task performance were uncorrelated in a younger sample. Errors on the Faux Pas task could reflect errors in verbal comprehension, but such comprehension problems are usually accompanied by a pattern of responses indicating confusion about who said what, or failure to remember who the story characters are, or incorrect answers on the control questions (cf. [35]). D.R. and S.E. did not show this pattern of errors.

S.E.'s impairment on the Eyes task does not seem to be accounted for by comprehension difficulties, as he correctly understood all the vocabulary terms except one. D.R.'s errors could possibly reflect difficulty understanding the mental state vocabulary words. Although she was prompted to ask the experimenter to explain words she did not know, she may not have done so, and may simply have answered some items without understanding the words. However, we note that D.R.'s performance on this task was slightly higher than S.E.'s, and did not reach statistical significance, so we cannot describe her as impaired on this task.

Furthermore, this alternative account of our results, explaining them in terms of general cognitive limitations, would predict that the items that control participants found most difficult would be those on which D.R. and S.E. would be most likely to make errors. Difficult items can be objectively defined operationally as those that elicit the most errors from control participants. However, on both the Faux Pas and the Eyes tasks, the individual items that were the most difficult for control participants were *not* most likely to be the items on which the amygdala-damaged participants made errors. Correlations between item scores for controls and for D.R. and S.E. were either close to zero or negative. For this reason, we believe it is unlikely that D.R.'s and S.E.'s errors on these tasks can be accounted for solely by general cognitive difficulties.

Several lines of evidence now converge on the possibility that the amygdala plays a crucial role in theory of mind: (1) Baron-Cohen et al. [14] found amygdala activation while participants performed the Eyes task; and Adolphs et al. [2] found that individuals with unilateral and bilateral amygdala damage were impaired on a similar task requiring judgments of social emotions from the eye region of the face; (2) Fine et al. [32] found deficits on theory of mind tasks in an individual with early left amygdala damage; and (3) we have found deficits on theory of mind tasks in two individuals with bilateral amygdala damage acquired in adulthood. The severity of D.R.'s and S.E.'s impairment on these tasks (z-scores in the range -1.4 to -5.1) was comparable to the severity of the theory of mind impairment in Fine et al.'s patient (z scores from -1.2 to -4.1) [32]; though the participants in each study were tested on different tasks. Thus, our results are consistent with theirs. Several studies have also found deficits in individuals with amygdala damage on tasks that arguably overlap with theory of mind tasks, such as the Heider and Simmel paradigm, or judgments of trustworthiness or cheating [4,39,67].

However, none of these studies is definitive by itself; in each study, alternative explanations are possible. The Baron-Cohen et al. imaging study [14] and the tasks used by Adolphs et al. [2] involved only judgments of affective mental states from pictures of the eyes. Given that some theorists argue that theory of mind should not include affective mental states [49], it is possible that the version of the Eyes task used may have tapped emotional processes more than theory of mind. The individual in Fine et al.'s study [32] was also diagnosed with schizophrenia and Asperger's syndrome, either of which could cause theory of mind deficits independent of amygdala damage. The two individuals we tested, D.R. and S.E., did not have complete bilateral damage to the amygdala, and also had damage that extended to some areas outside the amygdala. It is very possible that their deficits on these tasks could be attributed to damage outside the amygdala. It could be that temporal lobe areas around the amygdala are involved in theory of mind rather than the amygdala itself [24]. Future research with more individuals with amygdala damage acquired in adulthood would help clarify whether other individuals with damage restricted to the amygdala also have measurable theory of mind deficits. Imaging studies on a variety of types of theory of mind tasks can also shed light on whether the amygdala is active during certain tasks more than others. The evidence across studies so far is intriguing and suggests a role for the amygdala in theory of mind, but much research remains to be done to clarify these questions.

A "theory of mind inference" means an inference about another person's mental state. Mental states can include *epistemic mental states*, such as seeing, knowing, or attending to, *intentionality*, such as judging whether someone did something deliberately or accidentally, and *affective mental states*, such as feeling happy or wanting something. The Faux Pas task involves inferences about all these types of mental states, and D.R. and S.E. made errors on all three types of mental state inference. However, on the follow-up questions on the Faux Pas task, S.E. was more likely to make errors in affective mental state inferences—failing to understand that someone's feelings would be hurt—than in epistemic or intentional inferences, while the reverse was true for D.R. S.E. was also more impaired than D.R. on the Eyes task, the majority of which consisted of affective mental state term items. One possibility is that his greater right amygdala damage compromised the affective aspects of theory of mind more than did D.R.'s left amygdala damage. Fine et al.'s patient with left amygdala damage was tested on tasks involving epistemic mental state inferences [32], and thus his deficits may have reflected left amygdala involvement in epistemic mental state inferences as well. These are speculations on the relative role of the right and left amygdala, and one direction for future research would be to explore the roles of the right and left amygdala in different types of theory of mind tasks.

Our results indicate that the amygdala may be involved in all three types of mental state inference, but future research using a variety of theory of mind tasks, tapping intentionality judgments, epistemic mental state inferences, and affective mental state inferences, can help to clarify the amygdala's role in theory of mind. Neuroimaging of the amygdala while normal volunteers carry out these theory of mind tasks would also clarify whether the amygdala is more active during certain kinds of mental state inferences than others.

Mental state inferences can be made from perceptual information, as in the Eyes task, or from verbal information, as in the Faux Pas task. Many of the previous results on social inference deficits in individuals with amygdala damage have used perceptual input, i.e. the Heider and Simmel task, pictures of facial expressions, or of trustworthy or untrustworthy people. However, Fine et al. [32] found deficits with verbal material. D.R. and S.E. made errors on both of our tasks, indicating that the amygdala may be involved in processing verbal social information as well, a possibility that has been suggested by Brothers [21]. Neuroimaging studies of individuals doing both perceptual and verbal theory of mind tasks would illuminate this question further.

Our data contribute to evidence that the amygdala may specifically be involved in processing theory of mind inferences. These data are the first reported showing impaired performance on theory of mind tasks in individuals with amygdala lesions acquired in adulthood. Previous research indicating theory of mind impairments in patients with amygdala damage has used patients with amygdala damage acquired earlier in life or with other concurrent psychiatric diagnoses, and thus has left open the question of whether the amygdala is involved only in the development of theory of mind or whether it continues to be involved "on-line" in processing mental state inferences in adulthood. D.R. was 35 years old when her first surgery was done, and S.E. was 55 years old when he contracted encephalitis, thus their amygdala damage could not have affected the development of their theory of mind abilities. Rather, their theory of mind impairments provide evidence that the amygdala may play an "on-line" role in processing theory of mind inferences.

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