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Note

Impaired threat prioritisation after selective bilateral amygdala lesions

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ABSTRACT

The amygdala is proposed to process threat-related information in non-human animals. In humans, empirical evidence from lesion studies has provided the strongest evidence for a role in emotional face recognition and social judgement. Here we use a face-in-the-crowd (FITC) task which in healthy control individuals reveals prioritised threat processing, evident in faster serial search for angry compared to happy target faces. We investigate AM and BG, two individuals with bilateral amygdala lesions due to Urbach–Wiethe syndrome, and 16 control individuals. In lesion patients we show a reversal of a threat detection advantage indicating a profound impairment in prioritising threat information. This is the first direct demonstration that human amygdala lesions impair prioritisation of threatening faces, providing evidence that this structure has a causal role in responding to imminent danger.

1. Introduction

Extant theories implicate the amygdala in detection and prioritisation of threat-related information (LeDoux, 2000) and hence place it centre stage for disorders from the anxiety and fear spectrum. This view is based primarily on the non-human amygdala's role in learning to predict acute threat, exemplified by fear conditioning. Yet, although several human individuals with selective amygdala lesion (SM, AM, BG) are reported to be impaired in verbal recognition and intensity rating of fearful face expression when there are no time constraints (Adolphs, Tranel, Damasio, & Damasio, 1994; Becker et al., 2012), there is a spared ability in one of these individuals, SM, to detect fearful faces under time constraints, or when no explicit evaluation of the depicted emotion is required (Tsuchiya, Moradi, Felsen, Yamazaki, & Adolphs, 2009). These findings are interpreted as suggesting the human amygdala is not essential for early stages of fear

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processing but, instead, for modulation of recognition and social judgement (Tsuchiya et al., 2009).

These conflicting views can be reconciled if one assumes that fearful faces – used in previous human lesion studies – are reformulated as representing threat, but not necessarily a threat to the observer. Hence, they constitute an important cue for social communication but not an unambiguous threat signal. A non-human literature posits a role for the amygdala in detection of threat to oneself, rather than to others. In this framework, probing detection of fearful faces does not address the question of threat detection. Angry face expression on the other hand is a more unambiguous threat signal. Yet, the detection of angry facial expression after human amygdala lesion has only been probed in social judgement tasks requiring explicit intensity rating (Adolphs et al., 1994), free verbal response (Becker et al., 2012), or explicit comparison of threat potential (Tsuchiya et al., 2009). Hence, in the present study, we sought to address prioritised processing of angry faces in a task that does not require explicit evaluation.

In healthy humans, angry faces enjoy prioritised processing compared to other face expressions (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). Prioritised processing is evident as preferential spatial attention for angry face expression in a dot probe task (Macleod & Mathews, 1988; Macleod, Mathews, & Tata, 1986), as privileged access to memory when capacity is limited in the attentional blink task (de Jong & Martens, 2007), and as quicker response times (RTs) for angry than for happy faces in the face-in-the-crowd (FITC) task (Hampton, Purcell, Bersine, Hansen, & Hansen, 1989; Hansen & Hansen, 1988). Although these early FITC experiments were criticised for use of problematic stimuli (Purcell, Stewart, & Skov, 1996), several subsequent studies revealed similar effects both with photographic (Gilboa-Schechtman, Foa, & Amir, 1999; Horstmann & Bauland, 2006; Williams, Moss, Bradshaw, & Mattingley, 2005) and schematic stimuli (Esteves, 1999; Fox et al., 2000; Horstmann, 2007; Lundqvist & Ohmann, 2005; Ohman, Lundqvist, & Esteves, 2001; Schubo, Gendolla, Meinecke, & Abele, 2006; Tipples, Atkinson, & Young, 2002). Also, when RT is limited, search for angry faces is more precise than for happy faces (Schmidt-Daffy, 2011). In an FITC task, search speed depends linearly on the size of the crowd and is about half as fast when the target is absent than when present (Horstmann & Bauland, 2006). This indicates exhaustive serial search, i.e., each face in the crowd is searched one after the other until either the deviating face is found (which occurs, on average, after searching half of the crowd), or until the entire crowd has been searched and the target found to be absent. Crucially, search slopes are shallower for angry than for happy faces, indicating prioritised processing of threat information and causing more rapid detection of threat than of other stimuli.

Here we used the FITC task to probe prioritisation of angry faces in twin sisters AM and BG, two individuals with relatively selective bilateral amygdala lesions due to congenital Urbach–Wiethe disease (lipoid proteinosis). This disorder often leads to specific calcification of the amygdala that is thought to encroach on this structure gradually over the course of childhood and adolescence (Newton, Rosenberg, Lampert, & O'Brien, 1971). While BG suffered a single epileptic grand-mal seizure aged 12 leading to her diagnosis, AM never had epileptic seizures. Both twins attended regular neurological consultations after this diagnosis, and were recruited for neuropsychological experiments at the age of 21 (Strange, Hurlemann, & Dolan, 2003). Neuropsychological assessment one year before the present study, at the age of 34, (Talmi, Hurlemann, Patin, & Dolan, 2010) revealed impairments in phonemic fluency (Aschenbrenner, Tucha, & Lange, 2000) and short-term concentration (Brickenkamp, 1995). AM but not BG was impaired in figural learning and memory, as shown in the Complex Figure Test (Osterrieth, 1944) and the DCS (Weidlich & Lamberti, 2001). In behavioural experiments, BG was impaired in free verbal recognition of fearful faces, and in startle potentiation by threat-related scenes, and had a reduced social network compared to control participants, while all these functions were intact in AM (Becker et al., 2012). Further, both twins showed reduced anterograde and retrograde interference of emotional pictures on memory (Hurlemann et al., 2007).

On the other hand, the aforementioned neuropsychological assessment (Talmi et al., 2010) revealed average intelligence (L-P-S Leistungsprüfsystem) (Horn, 1983) and intact verbal learning and memory (Rey Auditory Verbal Learning test) (Helmstedter, Lendt, & Lux, 1981) as well as executive function measured with the Trail Making Test (Reitan, 1955), Wisconsin Card Sorting Test (Kongs, Thompson, Iversion, & Heaton, 2000), Stroop test (Bäumler, 1985), and semantic fluency (Aschenbrenner et al., 2000). The twins show neither depression nor anxiety (Hamilton, 1959; 1960). Further, both twins were unimpaired in rapid detection of negative-arousing words (Bach, Talmi, Hurlemann, Patin, & Dolan, 2011), forced-choice recognition of emotional expression in prosody (Bach, Hurlemann, & Dolan, 2013), and framing effects on economic gambles (Talmi et al., 2010).

Given the amygdala damage in AM and BG, and the posited function of the amygdala in prioritising threat information, we hypothesised a reduced angry face advantage in the FITC task in AM and BG, compared to healthy individuals.

2. Materials and methods

2.1. *Design*

The task followed a 3 (set size: 1/6/12 items) × 2 (target emotion: angry/happy) × 2 (target absent/present) factorial design with RT as dependent variable. Some previous studies have only analysed slopes of a serial search model. Here, because we did not know whether Urbach–Wiethe patients use a serial search strategy, we analyse both raw RTs and search slopes as dependent variables.

2.2. *Participants*

AM (previously also labelled patient 1) and BG (patient 2) (Becker et al., 2012), aged 35 years at the time of the present experiment, are monozygous twins with congenital Urbach–Wiethe syndrome due to a de novo mutation (Becker et al., 2012). The calcified volumes on high-resolution computer assisted tomography images included the whole