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Review

Translational Neuroscience of Basolateral Amygdala Lesions: Studies of Urbach-Wiethe Disease

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Urbach-Wiethe disease (UWD) is an extremely rare autosomal recessive disorder characterized by mutations in the extracellular matrix protein 1 gene on chromosome 1. Typical clinical manifestations include voice hoarseness in early infancy and neuropsychiatric, laryngeal, and dermatological pathologies later in life. Neuroimaging studies have revealed a pattern of brain calcification often but not exclusively leading to selective bilateral amygdala damage. A large body of work on amygdala lesions in rodents exists, generally employing a subregion model focused on the basolateral amygdala (BLA) and the central–medial amygdala. However, human work usually considers the amygdala as a unified structure, not only complicating the translation of animal findings to humans but also providing a unique opportunity for further research. To compare data from rodent models with human cases and to complement existing data from Europe and North America, a series of investigations was undertaken on UWD subjects with selective BLA damage in the Namaqualand region, South Africa. This review presents key findings from this work, including fear processing, social-economic behavior, and emotional conflict processing. Our findings are broadly consistent with and support rodent models of selective BLA lesions and show that the BLA is integral to processing sensory stimuli and exhibits inhibitory regulation of responses to unconditioned innate fear stimuli. Furthermore, our findings suggest that the human BLA mediates calculative–instrumental economic behaviors and may compromise working memory via competition for attentional resources between the BLA salience detection system and the dorsolateral prefrontal cortex working memory system.

SIGNIFICANCE:

Animal studies of selective bilateral amygdala damage have provided important information on the functional role of amygdala neurocircuitry. However, there are few data on humans with bilateral amygdala lesions. This review summarizes novel information obtained from patients with Urbach-Wiethe disease, a rare genetic disorder often characterized by bilateral BLA damage. Our work demonstrates that these patients have fear hypervigilance, generous economic investments, and paradoxically improved working memory. This work is consistent with laboratory findings on selective bilateral amygdala lesions and extends earlier human studies on North American and European populations with amygdala lesions.

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THE AMYGDALA: AN INTRODUCTION

In humans, the amygdala comprises a group of nuclei located medially within the temporal lobe. Although the amygdala has been treated as a single unit in the past, it is now widely accepted that it is not a homogenous structure. The amygdala's distinct nuclei may be categorized broadly as those whose internal structure is mainly striatal, involving the central–medial amygdala (CMA), and those that are cortical, including lateral, basolateral, and basomedial nuclei (BLA; Johnston, 1923; Krettek and Price, 1978; Swanson and Petrovich, 1998; Balleine and Killcross, 2006; Bos et al., 2015). The CMA projects to targets in the hypothalamus and the brainstem that mediate fear and underlie the execution of fear responses. By contrast, the BLA is the central structure for processing sensory information, including fear stimuli. It receives input from the thalamus and prefrontal cortex (PFC) and projects efferent fibers to the CMA and to the PFC, including its main sensory system, the orbitofrontal cortex (OFC) (Pitkänen et al., 1997; Davis and Whalen, 2001). This is the basis of the serial amygdala processing model, in which the BLA underlies fear conditioning and subsequent regulation of acute and innate fear responses at the level of the CMA, whereas the CMA facilitates fear execution at the level of the hypothalamus and the brainstem (Macedo et al., 2005; Tye et al., 2011; Terburg et al., 2012). Thus, the BLA may be viewed as the sensory amygdala, continuously involved in salience detection (Anderson and Phelps, 2001; Sander et al., 2003). An alternative model of amygdala function involves processing both of conditioned and of unconditioned stimuli via inputs to the CMA (see, e.g., Ciocchi et al., 2010; Haubensak et al., 2010). Thus, nociceptive and auditory sensory input received from the parabrachial nuclei and the thalamus, respectively, may in fact be processed directly in the CMA rather than via the BLA. Another theory of amygdala function posits that cortical sensory systems in mammals are organized hierarchically and include a connected frontolimbic complex (Scannell and Young, 1993; Young et al., 1994). Given that these frontal and limbic areas are associated with the least peripheral sensory processing areas, they are considered topographically central.

Although there is a compelling body of animal evidence on the effects of amygdala damage in rodents, these findings are not readily translatable to human cases. The vast majority of rodent models has employed a subregion approach to the amygdala, focusing on the BLA and the CMA, whereas human studies typically consider the amygdala as a unified structure. Thus, further research in humans with selective BLA and/or CMA damage is required to investigate whether animal findings apply. This review provides an overview of Urbach-Wiethe disease (UWD), a rare autosomal recessive disorder characterized by atypical calcification of the amygdala in humans. We discuss neuroimaging and neuropsychological and neurocognitive features of seminal clinical cases and provide novel data from a unique, understudied South African patient population with selective BLA damage. In so doing, we examine whether animal data may also be translated to human patients with UWD.

UWD: PHENOMENOLOGY

UWD, also known as *lipoid proteinosis* or *hyalinosis cutis et mucosae*, is an extremely rare autosomal recessive disorder (Rallis et al., 2006; van Honk et al., 2016), first documented in 1929 in Austria (Urbach and Wiethe, 1929). Clinical manifestations include neuropsychiatric, laryngeal, and dermatological signs and symptoms (de Rezende Pinto et al., 2014). Typically, patients present with hoarseness and a silent cry in early infancy. Dermatological manifestations may include yellowish infiltrative deposits on the skin and certain mucous membranes (including the tongue, pharynx, larynx, lips, and soft palate), waxy papulonodules, and acneiform or pox-like scars (Urbach and Wiethe, 1929; Hamada, 2002; Rallis et al., 2006). Reported extracutaneous features include neuropsychiatric abnormalities, epilepsy, and visceral pathologies (Caplan, 1967; Hamada, 2002; Thornton et al., 2008). This phenotype is caused by the widespread deposition of an amorphous hyaline-like material (Urbach and Wiethe, 1929; Hamada, 2002; Rallis et al., 2006). Neuroimaging of affected individuals generally reveals abnormal intracranial calcifications, with amygdala involvement occurring frequently but not exclusively; more extensive brain calcification may include the hippocampus, parahippocampal gyrus, and striatum (Gonçalves et al., 2010). Calcification of the amygdala tissue is most often slowly progressive and benign (not life threatening; Cordoro et al., 2013), and life span does not seem to be affected (van Honk et al., 2016). There are currently fewer than 100 known cases of UWD worldwide (van Honk et al., 2016), and evidence suggests that the prevalence of UWD is approximately equal in males and females (Hamada, 2002).

BLA VS. CMA: ANIMAL MODELS

There is a notable body of work documenting amygdala involvement in subjects with UWD. To date, diverse histological, neuroimaging, and pharmacological studies have investigated the role of the amygdala in socio-emotional functioning (van Honk et al., 2016). The vast majority of animal studies have focused on the BLA, with some studies also investigating the CMA. There is evidence that the BLA and the CMA may have separate, perhaps even antagonistic, effects on emotional behaviors. For example, in their study of natural amygdala volume variation in recombinant inbred mice strains, Yang and colleagues (2008) found that strains with relatively small BLA volumes exhibited stronger conditioned fear responses and significantly greater corticosterone responses to stress compared with those with a larger BLA. Similarly, Macedo and colleagues (2006) reported

that inactivation of the BLA of rats (using muscimol, a potent selective agonist for $GABA_A$ receptors) increased unconditioned fear. Thus, the BLA may exert inhibitory regulation of acute fear responses and responses to unconditioned innate fear stimuli (van Honk et al., 2016). There is also a strong body of evidence for the role of the BLA in modulating the consolidation of long-term memories (Cahill et al., 1995; McGaugh, 2004). Animal studies have shown that the BLA likely modulates memory consolidation via efferent pathways to other brain structures, including the cortex, caudate nucleus, and nucleus accumbens (McGaugh, 2004), a view in line with the hierarchical frontal-limbic connectivity hypothesis (see, e.g., Scannell and Young, 1993; Young et al., 1994; see above).

By contrast, there is some evidence to suggest that stimulation of the CMA elicits fear responses (Kapp et al., 1982) and that overall responsiveness of CMA nuclei to conditioned stimuli increases in high fear states (Duvarci et al., 2011). It seems that the BLA and CMA may have antagonistic effects on social and emotional functions.

UWD: EVIDENCE FROM EUROPE AND NORTH AMERICA

UWD case SM046 is an adult U.S. female first described in 1990 (Tranel and Hyman, 1990; see also Adolphs et al., 1994), with complete focal and bilateral amygdala damage. Through extensive neuropsychological and psychophysiological assessment, SM046 was found to have significant defects in nonverbal visual memory, social behavior, and executive control functions, whereas general intellect, language, and skin conductance responses were normal (Tranel and Hyman, 1990). More recent investigation has revealed that SM046 exhibited no fear response when exposed to live snakes and spiders, a "haunted house," or emotionally evocative films (Feinstein et al., 2011) but did respond with fear and panic attacks triggered by inhalation of 35% CO_2 (Feinstein et al., 2013). Furthermore, she exhibited impaired emotion recognition in simulated scenes containing facial expressions (Adolphs and Tranel, 2003), inaccurate attribution of approachability and trustworthiness to unfamiliar individuals on the basis of facial appearance (Adolphs et al., 1998), and a lack of any sense of personal space (Kennedy et al., 2009). More recently, it has been found that SM046's impaired ability to recognize fear from facial expressions may result from her lack of automatic fixing on the eyes while viewing these faces (Adolphs et al., 2005). Because information from the eye region of faces is the most important feature for identifying fear, this would account for SM046's diminished fear recognition.

Although not warranting a psychiatric diagnosis, SM046 has also been found to be notably dispassionate when relating to highly emotional and traumatic life experiences (Tranel et al., 2006) and has shown impairments in long-term declarative memory (i.e., memory for facts that can be assessed verbally) for emotionally arousing occurrences (Adolphs et al., 1997). This series of studies has provided vast insight into fear response and social judgment and has contributed notably to social and affective neuroscience research.

Several other affected individuals have also provided noteworthy data on the behavioral manifestations of UWD and on the role of the amygdala in emotional memory. For example, in their case study of two German patients (brother and sister) with circumscribed bilaterally symmetrical amygdala damage, Markowitsch and colleagues (1994) reported that both showed memory impairments, with these impairments more pronounced and accompanied by marked affective–emotional fluctuations in one patient. Similarly, Cahill and colleagues (1995) reported impaired emotional memory in these patients.

In addition, two German patients, female monozygotic twins each with congenital UWD and focal amygdala damage, were recently investigated. Hurlemann and colleagues (2007) found that these patients exhibited an absence both of valence-dependent retrograde modulation and of arousal-dependent anterograde regulation of episodic memory, as well as impairments in oxytocin-sensitive aspects on learning and emotional empathy tasks; but performed normally in assessments of cognitive empathy (Hurlemann et al., 2010). These patients were also found to respond in the same way to CO_2 inhalation as did SM046 (Feinstein et al., 2013); i.e., all three individuals exhibited fear and panic responses. One explanation is that the modulating role of the amygdala may differ for externally and internally triggered fear (van Honk et al., 2016). Another potential explanation is that the amygdala may not be necessary for the production of such responses. In keeping with this explanation, an investigation by Anderson and Phelps (2002) of 10 left and 10 right amygdala-damaged patients, one patient with bilateral amygdala damage, and 20 controls, showed no differences in positive or negative affect between patients with amygdala damage and the unaffected controls.

In a more recent series of behavioral, psychophysiological, and functional magnetic resonance imaging (MRI) experiments, Becker and colleagues (2012) reported an intriguing discrepancy between the German twins (patient 1 and patient 2). These authors found that only patient 1 (and not patient 2) showed preserved recognition of fearful faces, acoustic startle responses, and socialization. Neuroimaging data revealed that patient 1 also showed potentiated fear responses in the left premotor cortex face area and in the inferior parietal lobule bilaterally, both key regions of the cortical mirror neuron system (MNS). The MNS comprises a group of specialized neurons "mirroring" the behavior and actions of others (Rajmohan and Mohandas, 2007) and is thought to play a role in neurocognition and neuropsychiatric disorders. The MNS mediates learning of observed actions, thus promoting imitation and empathy (Becket et al., 2012). Overall, these findings suggest that neuroplasticity in the MNS may compensate for amygdala pathology, thus preserving fear processing in patient 1.

This body of work provides compelling evidence for the role of the amygdala in social and affective

functioning. However, because single or dual case reports remain inherently limited, we recently undertook research among the South African UWD population, seeking to provide new data that would complement data obtained from prior studies.

UWD: THE SOUTH AFRICAN PERSPECTIVE

Genetic Predisposition

The genetic basis of UWD was first characterized by investigators at the University of Witwatersrand, Johannesburg, South Africa (see Hamada et al., 2002). Using DNA from three affected siblings in a consanguineous Saudi Arabian family and from 28 affected individuals from five other unrelated consanguineous families from different regions, these authors were able to identify six different homozygous loss-of-function mutations in the extracellular matrix protein 1 gene (ECM1) located on chromosome 1. ECM1 is a glycoprotein that has been shown to play a key role in many important biological processes, including skin homeostasis (Chan et al., 2007). The ECM1 mutation in UWD has been shown to affect males and females equally but is infrequent, variable, and recessive in nature. It is likely that specific variants determine the distribution of brain calcification. This may account for the diverse brain damage seen in UWD patients; i.e., not all exhibit focal bilateral amygdala damage (see Gonçalves et al., 2010). In the South African population, the Q276X mutation in exon 7 of the ECM1 gene has been identified as causal (Van Hougenhouck-Tulleken et al., 2004). It is noteworthy that this mutation has not been described for any other UWD-affected population.

Geographic Distribution

Since the 1970s, it has been recognized that South Africa has one of the largest UWD populations worldwide (Heyl, 1970; Hofer, 1973; Van Hougenhouck-Tulleken et al., 2004), with an estimated 50% of identified cases occurring in this country (van Honk et al., 2016). This remarkably high prevalence suggests a founder effect (Van Hougenhouck-Tulleken et al., 2004), which may be traced to the arrival of European settlers in South Africa in 1652. During this time, two German siblings, Jacob and Else Cloete, who are now widely believed to be the progenitors of UWD in the South African patient population, joined a colony of Dutch settlers (Stine and Smith, 1990; Van Hougenhouck-Tulleken et al., 2004). Subsequently (in 1790), it is believed that the ECM1 gene was spread into the mixed-race population of Namaqualand (an arid region of Namibia and the Northern Cape of South Africa) by a descendent of the Cloetes (Van Hougenhouck-Tulleken et al., 2004). As of 2014, approximately 30 adults with UWD, more than 25% of the currently known population worldwide, live in Namaqualand (Thornton et al., 2008; Morgan et al., 2012; Terburg et al., 2012; van Honk et al., 2013; Klumpers et al., 2015). This genetic mutation was also carried by a small group of white South Africans who migrated from Namaqualand to the city of Johannesburg in the Gauteng province. The current prevalence of UWD in Johannesburg, an urbanized environment, is approximately 12 affected individuals, which may decrease further in coming generations.

UWD in Namaqualand

The largest neuropsychiatric and neuropsychological study of UWD patients in South Africa to date was undertaken by Thornton and colleagues (2008). These authors investigated 34 affected adults, including a homogenous group of 27 living in the Namaqualand region (Northern Cape) matched with 47 controls. They reported that patients with UWD from Namaqualand had a higher incidence of neuropsychiatric disorders (including anxiety) and performed more poorly on facial emotion recognition than did control subjects. Affected individuals also exhibited impairments on a number of measures of IQ, particularly memory and executive function. Thus, it seems that these findings differ from those described with respect to SM046, who, although found to have impaired executive control functions and visual memory, exhibited normal intellect and hypovigilance (see above). However, because neuroimaging was not performed on the Namaqualand study population, differences in brain calcifications could not be delineated.

More recently, a series of follow-up studies (e.g., see Morgan et al., 2012; Terburg et al., 2012; van Honk et al., 2013, 2016; Klumpers et al., 2015) has focused on otherwise healthy female UWD patients from Namaqualand (i.e., those with secondary brain pathology were excluded). Only females were recruited because comorbid psychopathology appears to be less prevalent among female UWD patients compared with males, and female data may be more easily compared with the findings from SM046 and European subjects, all of whom are also female. Furthermore, there is evidence that sex hormones may affect brain neuroplasticity (van Honk, 2009). To expand the initial findings from Thornton and colleagues (2008), these follow-up studies examined five otherwise healthy UWD subjects and a group of 12 healthy female controls from the same mountain–desert villages in Namaqualand of the same age and with similar IQs. Although all UWD subjects were found to be homozygous for the ECM1 mutation, no significant differences were noted between subjects and controls on full-scale IQ, performance IQ, or verbal IQ tests. Explanations for the discrepancy between these findings and the IQ findings reported previously by Thornton and colleagues (2008) may be due to the exclusion of individuals with secondary brain pathology in the follow-up group or to the use of assessment tools in the Thornton and colleagues group, such as the Wechsler Adult Intelligence Scale (Wechsler, 1997), which was initially designed for use in Western, educated, industrialized, rich, and democratic populations, which are culturally discordant from those in South Africa (Morgan et al., 2012).

Neuroimaging. Structural and functional MRI investigations, including an "emotion-matching task," were undertaken in these five UWD subjects. The emotion-matching task is a validated measure of amygdala activation during the comparison of multiple facial expressions (Hariri et al., 2002) and was performed during the functional MRI scanning. The combined structural–functional MRI analyses confirmed bilateral damage in all five subjects that was confined to the BLA, with sparing of the other areas of the amygdala. These findings were further supported by significant activation of the central–medial and superficial amygdala during the emotion-matching task, indicating that these regions were intact and functional (Terburg et al., 2012).

Therefore, it is clear that these UWD subjects exhibited notably less extensive amygdala damage than did SM046 and the German UWD twins, with no damage to the CMA in the Namaqualand cases. These differences may be accounted for by the different ECM1 mutation and/or by different gene–environment interactions resulting in more gradual calcification beginning in the cortical-type neuronal tissue of the BLA, without progressing to the striatal-type CMA in the Namaqualand subjects.

Such selective BLA damage is likely to result in behavioral effects that are distinct from those caused by lesions encompassing both the BLA and the CMA. In the case of SM046, who exhibited complete, bilateral amygdala damage (i.e., including the BLA and the CMA), fear hypovigilance was demonstrated (Feinstein et al., 2011; see above). This may be attributable to the disruption of efferent signals to the hypothalamus and brainstem, resulting in diminished fear execution behaviors. In contrast, from animal findings in rodent subjects with selective BLA damage (see above), it can be hypothesized that human UWD patients with this neuropathological pattern may display fear hypervigilance, i.e., increased fear responses to innate danger cues (van Honk et al., 2016), because the normal fear processing function of the BLA is impaired. However, before this hypothesis can be investigated further, a discussion of the sensory role of the BLA as it relates to working memory performance is warranted.

Working memory. Recent neuroimaging evidence suggests that the sensory activity of the BLA (see above) may be at the expense of working memory performance (see, e.g., Anticevic et al., 2010). This association may be underpinned by the BLA's consumption of resources required by the dorsolateral PFC (DLPFC) via its connections to the OFC, which may in turn lead to impaired working memory. These ideas are consistent with current neuroevolutionary perspectives of amygdala function in network rather than modular terms (Bos et al., 2015).

In their investigation of working memory performance in three adult female patients from the Namaqualand UWD population with bilateral BLA calcification, Morgan and colleagues (2012) reported significantly enhanced working memory in BLA-damaged subjects relative to 10 matched controls. This phenomenon may be termed *paradoxical functional facilitation* (PFF) (Kapur, 1996; van Honk et al., 2016). PFF occurs in situations in which an individual with neurological pathology performs better than control subjects on a specific task. In this case, normal competition for processing resources between the BLA salience detection system and working memory systems within the DLPFC may be absent or diminished because of BLA damage in UWD subjects. An unconstrained DLPFC in these individuals would perform better on working memory tasks. However, further research in this field, including neuroimaging studies with validated working memory tasks (see, e.g., Yun et al., 2010) and investigations under high-load and variable-threat stimuli, are required to understand further these preliminary findings in the Namaqualand cohort.

Threat detection. In their functional MRI study of volunteer subjects pursued through a maze by a virtual predator, Mobbs and colleagues (2007) found that, as the predator (threat) grew closer to the subjects, the subjects' brain activity shifted from the BLA and the OFC to the CMA and brainstem periaqueductal gray matter (PAG). These findings suggest that mild, distant threat cues may recruit the BLA and the OFC to enhance fear evaluation and processing and to exert inhibitory regulation as long as fear execution behavior is not yet necessary. Activation of the CMA and the PAG then occurs when the threat is imminent and unavoidable, and the BLA and the OFC are deactivated, as also evidenced in rodent studies (Martinez et al., 2007; Graeff and Del-Ben, 2008; see above). Thus, the BLA may be viewed as the "switchboard" (van Honk et al., 2016), regulating the inhibition or the activation of the fear response/execution via the OFC at the level of the CMA.

Although SM046 demonstrated lack of fear responses when confronted with threatening stimuli (Feinstein et al., 2011), the Namaqualand UWD population seemed predisposed to fear, given their high prevalence of anxiety disorders (Thornton et al., 2008). To investigate this apparent discrepancy, van Honk and colleagues (2016; see also Terburg et al., 2012) assessed emotion recognition and processing of innate fear stimuli by the five Namaqualand UWD patients and the 12 healthy matched controls. Each woman watched short video clips of facial expressions transitioning from neutral to emotional, angry, fearful, happy, sad, surprised, and disgusted in varying levels of intensity. The UWD patients were found to perform better in the recognition of full-blown facial fear compared with the controls, a finding opposite to the response of SM046 (see above).

This discordance may be explained by the differing visual attention to the eyes in these two study groups. Although SM046 did not fix spontaneously on the eyes of fearful faces (Adolphs et al., 2005), the five Namaqualand UWD subjects looked longer than control subjects did at fearful eyes (Terburg et al., 2012), strengthening the case for the association between hyperattention to the eyes and normal fear recognition. The hyperattention to eyes exhibited by these five subjects may be attributable to

fear hypervigilance. To test this hypothesis, Terburg and colleagues (2012) examined unconscious emotional responses with a modified emotional Stroop task. These authors found that all five UWD subjects demonstrated hypervigilant responses to unconsciously presented fearful faces and recognized facial fear significantly better than did the matched controls. It may be that, without proper regulation by the damaged BLA, the CMA in these subjects acts reflexively on fear stimuli and threat, thus executing inappropriate fear responses (Macedo et al., 2005; Tye et al., 2011). This dysregulation of fear responses seems to work both ways, as confirmed by one recent study (Klumpers et al., 2015). Using a classical delay fear conditioning experiment, Klumpers et al. found that, in line with the serial amygdala model, impairment of implicit (physiological) fear conditioning was evident in the UWD subjects ($n = 4$). This suggests that the BLA is integral to facilitating fast conditioned defensive reflexes (Klumpers et al., 2015). Furthermore, the UWD subjects showed normal declarative memory of the conditioned association after the experiment. Thus, although the human BLA does not appear to be essential for the acquisition of declarative knowledge of contingent threats, it does seem to be key for coupling fear memories to fast classically conditioned defense reflexes (Klumpers et al., 2015). To the best of our knowledge, this is the first study to demonstrate the role of the human BLA in memory consolidation and forms a novel complement to work by McGaugh (2004) in animal models (see above). Thus, both the downregulation of innate fear and the acquisition of conditioned fear responses seem to be affected in UWD subjects, which is in keeping with rodent evidence that discrete modulatory mechanisms in the BLA are recruited during conditioned and unconditioned fear, respectively (Macedo et al., 2006).

However, the question remains of how, then, does sensory input in these BLA-damaged subjects reach the CMA to produce fear hypervigilance? Potential explanations include sparing of certain regions of the BLA in the Namaqualand UWD cohort (because the lesions in these cases were focal and bilateral and did not cover the complete BLA) or that sensory processing shifted to the OFC as a compensatory mechanism (neuroplasticity). Although further research in both human and animal subjects is required to test these hypotheses, the serial amygdala processing model (see above) appears to be consistent across rodent and human cases of BLA damage.

Interpreting conflicting sensory input. To investigate further whether unconscious fear hypervigilance in the Namaqualand UWD subjects (Terburg et al., 2012) may lead to behavioral impairment in the context of mild threat cues, de Gelder and colleagues (2014) employed the "face–body compound task." This task is based on the fact that a facial expression that is incongruous with body language may result in emotionally conflicting information (Meeren et al., 2005). From their study of the three youngest Namaqualand UWD patients, de Gelder and colleagues (2014) reported that these subjects had great difficulty ignoring task-irrelevant bodily threat signals; i.e., their processing of emotionally conflicting facial and bodily information was profoundly impaired. This gives further credence to the hypothesis that lack of inhibitory regulation of the CMA by the dysfunctional BLA results in inappropriate fear activation to mild threats.

Economic behaviors. The different, perhaps even opposing, effects of the BLA and the CMA on socioemotional functioning have been further demonstrated in economic behavioral studies of rodents. There is evidence to suggest that the BLA promotes calculative–instrumental economic behaviors, whereas the CMA stimulates impulsive–affective behaviors (Phillips et al., 2003; Balleine and Killcross, 2006; Bos et al., 2015; van Honk et al., 2016). These differential roles may be affected by the modulation of basal and evoked efflux of dopamine in the forebrain, particularly the nucleus accumbens (NAc).

In keeping with these animal findings, economic decisions in humans are also likely to occur at the level of the NAc and the amygdala (Haruno et al., 2014). To investigate whether the parallel amygdala model of economic behavior in rodents (i.e., that the BLA promotes "selfish" behaviors, whereas the CMA is "prosocial") may be translated to human subjects, van Honk and colleagues (2013) studied the behavior of three young adult Namaqualand UWD patients in a trust game. These authors found that the affected patients invested nearly 100% more money in unfamiliar others in a study test game (see also Kosfeld et al., 2005) than did 12 matched healthy controls. Underlying this study was the dual-process model of economics that humans are correspondingly instrumental (promoted by the BLA) or impulsive (promoted by the CMA; Camerer et al., 2005; Fehr and Camerer, 2007). Furthermore, the UWD subjects did not expect higher returns or perceive people as more trustworthy, suggesting that their generous economic investments were not calculative–instrumental in nature (i.e., were not subserved by the BLA) but were rather impulsive–affective (i.e., subserved by the CMA; see also Phillips et al., 2003; Balleine and Kilcross, 2006; Tye et al., 2011; Terburg et al., 2012; Bos et al., 2015). Further research, including neuroimaging investigations, would be useful to elucidate these findings.

UWD in Gauteng

Concurrently with the seminal research conducted in Namaqualand, Siebert and colleagues (2003) undertook an investigation of the smaller UWD population in Johannesburg, Gauteng, South Africa. Using computed tomography and single-photon emission computerized tomography techniques, these authors demonstrated temporal lobe perfusion abnormalities in all UWD patients. Furthermore, although complete bilateral amygdala damage was apparent in more than half of the affected cases, many subjects exhibited lesions beyond the amygdala, suggesting more extensive damage than was present in the Namaqualand UWD group. More recently, van Honk,

Adolphs, and colleagues (unpublished) have collected MRI data on four subjects from Gauteng, two children and two adults. These researchers found greater damage than was evident in the Namaqualand group but that was selective to the BLA in all cases.

After neuropsychological assessments, Siebert and colleagues (2003) also found that their UWD patients had difficulty judging the intensity of all emotions in facial expressions and showed subtle impairments in emotional memory (both of positive and negative matters). However, these patients showed no overt secondary pathology and little (if any) cognitive deviation from control subjects. This is in contrast to the findings reported by Thornton and colleagues (2008), which detailed the IQ deficits exhibited by the Namaqualand UWD patients. This inconsistency may be due to a number of factors. First, the educational level of the Gauteng UWD subjects was notably higher than that of their Namaqualand counterparts. The Gauteng UWD group comprised white South Africans with, on average, a higher socioeconomic status and who were living in an urban environment. Second, secondary pathology within the initial Namaqualand UWD group might have contributed to IQ deficits (compared with control subjects in that study). This premise is further supported by the fact that the IQ differences were no longer present when comparing the Gauteng UWD subjects with the Namaqualand UWD population in the follow-up series (see, e.g., Morgan et al., 2012; Terburg et al., 2012; van Honk et al., 2013; Klumpers et al., 2015). Because these investigators excluded subjects with secondary pathology, it is not unreasonable to assume that this variable contributed to impaired IQ in the earlier Namaqualand UWD group investigated by Thornton and colleagues (2008).

CONCLUSIONS

Research undertaken in the Namaqualand UWD population (and the smaller Gauteng UWD cohort) of South Africa has provided novel insight into the effect of selective bilateral BLA damage in humans. Not only are these findings in line with prior rodent models, but they also afford an opportunity to engage with earlier studies documenting those UWD subjects with complete (or near-complete) amygdala damage in humans (see Adolphs et al., 1994, 1997, 1998, 2005; Adolphs and Tranel, 2003; Siebert et al., 2003; Hurlemann et al., 2007, 2010; Feinstein et al., 2011, 2013; Becker et al., 2012). In summary, selective BLA damage may be seen to decouple subcortical threat and reward mechanisms from instrumental control by the BLA (and the OFC) and to decouple other cortical executive functions (via the DLPFC). Subsequent phenotypic manifestations include fear hypervigilance, generous economic investments (impulsive–affective), and paradoxically improved working memory. Although important steps have already been taken in elucidating the pathophysiology and clinical manifestations of UWD in the South African population, much is still unknown. A unique opportunity now exists for further research in this relatively large, and largely unexplored, patient population.

CONFLICT OF INTEREST STATEMENT

During the past 3 years, D. Stein has received research grants and/or consultancy honoraria from AMBRF, Biocodex, Cipla, Lundbeck, National Responsible Gambling Foundation, Novartis, Servier, and Sun. No authors have any other conflicts of interest to report.

ROLE OF AUTHORS

NK consulted with all authors and completed a first draft of the manuscript. All co-authors provided input for the final article.

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