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Commentary

The dynamic consequences of amygdala damage on threat processing in Urbach–Wiethe Disease. A commentary on Pishnamazi et al. (2016)

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The amygdala, a small region in the subcortical part of the brain, has captured the attention of physiologists, psychologists and neuroscientists for more than 50 years. Early work by Klüver and Bucy (1939), Weiskrantz (1956) and Downer (1961) showed the importance of this region in social-emotional behavior. For instance, bilateral amygdalectomy in rhesus monkeys resulted in impaired acquisition of avoidance behavior, a reduction in fear responses and overall tameness (Weiskrantz, 1956). While in contemporary social and affective neuroscience the amygdala is almost synonymous with the emotion of fear, human evidence is largely based on correlational studies and its role and associated mechanisms still remain poorly understood. Besides animal studies, exciting and important findings come from human lesion studies. Urbach–Wiethe Disease (UWD) provides the neuroscience community with a unique possibility to study the functions of the amygdala in a causal way. UWD or lipoid proteinosis is an extremely rare autosomal recessive genetic disease that leads to thickening of the skin, beaded eyelid papules, other dermatological symptoms and calcification of brain tissue (Quirici & da Rocha, 2013). So far, 250 to 300 cases have been described in the literature, with current estimations of less than 100 individuals alive (van Honk, Terburg, Thornton, Stein, & Morgan, 2016). Selective calcification of amygdalar tissue has been reported in a subset of the UWD cases and the study of these rare cases has already provided valuable new insights into the role of the amygdala (for recent reviews see Adolphs, 2016; Koen et al., 2016; Patin & Hurlemann, 2016; van Honk et al., 2016). UWD-based amygdala damage is progressive (Siebert, Markowitsch, & Bartel, 2003) and therefore a developmental perspective is crucial for a better understanding of the amygdala.

A recent study by Pishnamazi et al. (2016) addresses this gap and reports on fear processing in a 14-year old girl (S.F.)

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with UWD and bilateral amygdala damage. First, compared to control participants fewer situations and objects elicit a fearful response in S.F. Second, while her recognition accuracy for facial expressions of anger, disgust, happiness, sadness and surprise did not differ from controls, S.F. did not recognize fearful facial expressions. Instead, she labeled these expressions as surprised. Third, the authors assessed spatial attention to fear by measuring reaction times in an emotional dot-probe task. In order to investigate automatic versus strategic stages of an attentional bias, the authors manipulated the exposure time of the fearful cue. S.F. showed opposite attentional bias scores compared to controls. While she showed an attentional bias towards fear with short exposure and no bias with medium exposure, she showed a weak bias away from fear with long exposure. Here, we place this timely study in the context of outstanding issues in the literature on amygdala damage in UWD. While the study by Pishnamazi et al. provides new evidence it also may add to the existing confusion in the literature. We discuss how damage to the amygdala due to UWD has heterogeneous consequences for threat processing and we offer several considerations for future research. We conclude that further progress in understanding the role of the amygdala requires us to move beyond attributing a single role to the amygdala, to focus on its subnuclei and study the dynamic interaction between subnuclei damage and associated neural network.

1. Fear recognition and fear detection

The reduced fear sensitivity and impaired recognition of fearful facial expressions in S.F. is in line with several early reports on bilateral amygdala calcification in UWD (Adolphs, Tranel, Damasio, & Damasio, 1994; Feinstein, Adolphs, Damasio, & Tranel, 2011; Tranel, Gullickson, Koch, & Adolphs, 2006), although focused instruction can improve anomalous recognition of fearful faces (Adolphs et al., 2005). More recently Becker et al. (2012) reported that while one female UWD case showed impaired recognition of fearful faces, the accuracy scores of her monozygotic twin sister did not differ from control participants. A careful investigation of facial expression recognition in a large cohort of UWD further nuanced this picture (Siebert et al., 2003). The authors concluded that "amygdaloid lesions do not necessarily produce impairments in the recognition of basic emotions such as fear and anger" (p. 2635, Siebert et al., 2003). Indeed, superior recognition of fearful facial expressions has been reported (Terburg et al., 2012). Recognition of bodily signals (Atkinson, Heberlein, & Adolphs, 2007; de Gelder et al., 2014), and auditory signals of fear (Adolphs & Tranel, 1999; Bach, Hurlemann, & Dolan, 2013) and of scenes containing threatening information (Adolphs & Tranel, 2003) are not necessarily impaired after amygdala damage. Similarly, unimpaired automatic attentional bias to fear is consistent with most (Bach, Talmi, Hurlemann, Patin, & Dolan, 2011; Terburg et al., 2012; Tsuchiya, Moradi, Felsen, Yamazaki, & Adolphs, 2009; de Gelder et al., 2014), but not all (Bach, Hurlemann, & Dolan, 2015), reports on UWD-related amygdala damage. Even more so, in a recent study we showed that five individuals with UWD responded with hypervigilance to non-consciously processed threat signals (Terburg et al., 2012). In another study we showed that this hypervigilance results in stronger interference from task-irrelevant bodily postures of threat on facial emotion recognition (de Gelder et al., 2014). A different finding that adds to the complexity is the high prevalence of anxiety and mood disorders in UWD (Thornton et al., 2008). In sum, the literature reports variable consequences on the processing and perception of fearful signals after UWD-driven amygdala damage. This underscores the need of more detailed analyses of UWD physiology and behavior.

2. Beyond the amygdala as a single structure

The amygdala is the summary term for a set of different subnuclei and can be divided in at least three subnuclei with each having different afferent and efferent connectivity and functional profiles (Bzdok, Laird, Zilles, Fox, & Eickhoff, 2013; McDonald, 1998; Swanson & Petrovich, 1998). Next to the superficial amygdala (SFA), the basolateral (BLA), and centralmedial amygdala (CMA) constitute the amygdala. The latter two are of importance for social emotion behavior (Benarroch, 2015; Fox, Oler, Tromp, Fudge, & Kalin, 2015; Likhtik & Paz, 2015; Mosher, Zimmerman, & Gothard, 2010). Emerging evidence indicates that the size and location of the lesion is crucial for the behavioral consequences. S.F. showed complete bilateral amygdala damage (Omrani et al., 2012), similar to the majority of UWD cases reported in the literature (Adolphs, 2016; Siebert et al., 2003). Unfortunately, in some UWD case studies the exact size and location is often not reported. Such reports may however reveal important new information. Becker et al. (2012) showed that the calcification in the monozygotic twins, of whom one showed intact fear recognition, was predominantly visible in the BLA, with possible intact tissue present in regions corresponding to the SFA and CMA. Detailed functional and structural assessment of the calcification in individuals with UWD from the Northern Cape province in South Africa revealed that while the BLA was damaged, the CMA was still functional (Klumpers, Morgan, Terburg, Stein, & van Honk, 2015; Morgan, Terburg, Thornton, Stein, & van Honk, 2012; Terburg et al., 2012); crucially, these individuals show hypersensitivity for fear and other threat signals rather than hyposensitivity.

Because six different homozygous mutations in the extracellular matrix protein 1 gene (ECM1) on chromosome 1 (1q21) exist in UWD (Hamada et al., 2002), the differences in calcification might be related to the exact mutation. Both the Northern Cape individuals and monozygotic twins have a mutation on exon 7, respectively a Q276X and p.W237R mutation. S.M., the most studied individual with UWD, has a 507deIT/507deIT mutation on exon 6 leading to a more severe form of UWD (Feinstein, Adolphs, & Tranel, 2016). Sequencing of ECM1 together with detailed structural and functional assessment using high-field MRI should allow to further map the calcification of the amygdala subnuclei as well as the developmental trajectory in S.F. and other UWD cases. Future studies will provide important new insights on this matter. However, it might well be that heterogeneity in calcification and behavioral profile can be observed early on in UWD; while the entire amygdala was damaged in S.F., a recent report

described an 8-year old UWD boy with starting calcification restricted to the BLA (van Honk et al., 2016).

3. Beyond a single role for the amygdala

For decades the amygdala has been the core of a neural network model important for social emotional behavior (LeDoux, 2000). Whether it was fear, valence, or relevance detection (Pessoa, 2010; Sander, Grafman, & Zalla, 2003), the tendency was to attribute a single function to the amygdala. But more powerful imaging methods have become available allowing a more detailed view of the amygdala. In view of conflicting findings in the literature, we should and can now go beyond the single role perspective of the amygdala and emphasize its multiple roles in the light of multiple processing routes in which it is involved. In a recent review we have highlighted this perspective (de Gelder, Hortensius, & Tamietto, 2012), in line with several other dual route perspectives on visual processing of affective signals (Dalgleish, 2004; Garrido, Barnes, Sahani, & Dolan, 2012; Rudrauf et al., 2008; Tamietto & de Gelder, 2010; Vuilleumier, 2005; de Gelder, 2006) and with the structural complexity of the amygdala nuclei. In this perspective, the amygdala plays a role in early as well as in late emotion processing and these roles are not identical. A superior colliculus – pulvinar – amygdala route supports an early detection of the emotional signal, while a network consisting of the amygdala and cortical areas (e.g., orbitofrontal cortex, posterior cingulate), is related to later emotion and cognitive processes (de Gelder et al., 2012). Detection of a threatening signal is not necessarily accompanied by conscious recognition of the signal (Hortensius, van Honk, de Gelder, & Terburg, 2014). While this dissociation is indeed manifest in the results of S.F., Pishnamazi and colleagues suggest that early detection, or attentional bias, can be independent of the amygdala. But this conclusion requires further scrutiny. The dual route perspective together with an amygdala subnuclei focus provides a different view on this matter.

First, the basolateral nucleus of the amygdala is a sensory hub with afferent and efferent connections throughout the cortex (Ghashghaei & Barbas, 2002; Heimer, Harlan, Alheid, Garcia, & de Olmos, 1997), coding the affective label and value, and regulation of the emotional signal (Benarroch, 2015; Likhtik & Paz, 2015), suggesting the involvement in late emotion processing (de Gelder et al., 2012). In a recent study in healthy individuals, BLA activity was a marker of congruence between two simultaneous presented bodily expressions (de Borst & de Gelder, 2016). Importantly, BLA damage results in increased interference of task-irrelevant threat signals, but not necessarily in impaired recognition (Terburg et al., 2012; de Gelder et al., 2014). It might well be that in the case of S.F., non-selective damage early in life, results in impaired recognition of fear. Second, the CMA might be implicated in the early, automatic, emotion processing leading to reflexive reactions to threat sustained by connections with the hypothalamus and the periaqueductal grey (Fox et al., 2015; Mosher et al., 2010). Particularly when a threat is distal or irrelevant to the task at hand this role of the CMA can normally be regulated by the BLA. Damage to the latter can therefore result in enhanced, or hypervigilant, reactions to threat (Terburg et al., 2012). In the case of S.F. it might be possible that early CMA-mediated emotion processing is intact. To substantiate this claim more information is warranted on the size and location of the lesion. It might even be possible that a third, amygdala-independent route, underlies reflexive reactions to threat as suggested by Pishnamazi and colleagues. For example, panic anxiety can be experimentally induced in a UWD case with complete amygdala damage and impaired fear responses (Feinstein et al., 2013). In this model the role of the amygdala might particularly focus on switching between fear responses depending on contextual factors like relevance, distance and whether there is an escape possible (Gozzi et al., 2010; Mobbs et al., 2007; Pellman & Kim, 2016). Future research must therefore incorporate multiple measures of early and late emotion processing, focus on distal and proximate threat signals, and innate versus acquired fear, to further delineate the role of amygdala subnuclei in emotion processing.

4. Changes in neural networks

A few studies have used magnetic resonance imaging to map the functional and structural consequences of amygdala damage on other brain regions (Becker et al., 2012; Boes et al., 2012; Hampton, Adolphs, Tyszka, & O'Doherty, 2007; Hortensius et al., 2016; Mihov et al., 2013). Boes et al. (2012) tested two UWD cases with bilateral amygdala damage and showed increased cortical thickness in the prefrontal midline. Cortical thickness was altered for regions in the ventral stream, but not in a consistent manner. Importantly, the older UWD case with complete bilateral amygdala damage showed more robust morphometric changes compared with the younger UWD case with calcification of about 50% of the amygdala. For the latter case, unfortunately no detail on amygdala subnuclei calcification is available. Besides behavioral differences, subtle differences have been observed in brain activation in response to facial signals of fear between the monozygotic twins (Becker et al., 2012), and the authors suggest that possible compensatory changes underlie these differences. Indeed, complex dynamics between lesion size and location, developmental influences, and plasticity might be at play. Recently, we showed a reorganization of activity in the ventral and dorsal stream underlying perception of faces in natural contexts (Hortensius et al., 2016). While in neurotypical subjects ventral stream activity dominates (Van den Stock, Vandenbulcke, Sinke, Goebel, & de Gelder, 2014), BLA damage results in a ventral-to-dorsal processing shift during perception of threat signals in a naturalistic context. Again, future research should stress the role and connectivity of the subnuclei and use functional activation and structural and functional connectivity analyses to further investigate the impact of damage to parts of the amygdala and the variety in consequences on threat processing. This is especially important given that UWD is a developmental disorder with first manifestations of the symptoms during childhood. Considering the ongoing brain development in that period, the possibility of neural recalibration and plasticity as a function of endogenous and exogenous influences (Callaghan & Tottenham, 2016; Cramer

et al., 2011; Fareri & Tottenham, 2016), should be investigated using longitudinal studies.

5. Conclusion

Amygdala damage in UWD has heterogeneous consequences on threat processing. In order to move forward, we have to deal with the structural and functional complexity of the amygdala. First, future studies should provide a careful examination of the calcification in each of the subnuclei in order to go beyond the traditional notion of a single functional role of the amygdala in threat, valence or relevance processing. New ways of amygdala subnuclei segmentation might provide the necessary means (Balderston, Schultz, Hopkins, & Helmstetter, 2015; Entis, Doerga, Barrett, & Dickerson, 2012). Second, the interactions between lesion size and location, developmental and environmental factors, and neural networks have to be carefully mapped using neuroimaging and behavioral tools. Clearly, the study of developmental UWD cases opens new and exciting doors for advancing our understanding of the complexities of human threat processing.

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