Behavioral/Cognitive

A Protective Mechanism against Illusory Perceptions Is Amygdala-Dependent

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Most people have a clear sense of body ownership, preserving them from physical harm. However, perceptual body illusions - famously the rubber hand illusion (RHI) - can be elicited experimentally in healthy individuals. We hypothesize that the amygdala, a core component of neural circuits of threat processing, is involved in protective mechanisms against disturbed body perceptions. To test this hypothesis, we started by investigating two monozygotic human twin sisters with focal bilateral amygdala damage due to Urbach–Wiethe disease. Relative to 20 healthy women, the twins exhibited, on two occasions 1 year apart, augmented RHI responses in form of faster illusion onset and increased vividness ratings. Following up on these findings, we conducted a volumetric brain morphometry study involving an independent, gender-mixed sample of 57 healthy human volunteers (36 female, 21 male). Our results revealed a positive correlation between amygdala volume and RHI onset, i.e., the smaller the amygdala, the less time it took the RHI to emerge. This raised the question of whether a similar phenotype would result from experimental amygdala inhibition. To dampen amygdala reactivity, we intranasally administered the peptide hormone oxytocin to the same 57 individuals in a randomized trial before conducting the RHI. Compared with placebo, oxytocin treatment yielded enhanced RHI responses, again evident in accelerated illusion onset and increased vividness ratings. Together, the present series of experiments provides converging evidence for the amygdala's unprecedented role in reducing susceptibility to the RHI, thus protecting the organism from the potentially fatal threats of a distorted bodily self.

Key words: **amygdala; body ownership; oxytocin; rubber hand illusion**

Significance Statement

Compelling evidence indicates that the amygdala is of vital importance for danger detection and fear processing. However, lethal threats can arise not only from menacing external stimuli but also from distortions in bodily self-perception. Intriguingly, the amygdala's modulatory role in such illusory body perceptions is still elusive. To probe the amygdala's involvement in illusory body experiences, we conducted a multi-methodological series of experiments in a rare human amygdala lesion model, complemented by a morphological and pharmaco-modulatory experiment in healthy volunteers. Our findings convergently suggest that the amygdala's integrity is indispensable for maintaining an unbiased, precise perception of our bodily self. Hence, the amygdala might shield us against distortions in self-perception and the resultant loss of behavioral control of our organism.

Introduction

The amygdala is of vital importance for threat processing and danger detection (LeDoux, 2007) and both its structure and function are highly conserved across species (Janak and Tye, 2015). Case studies of rare patients with focal bilateral amygdala lesions show that these patients have impairments in their ability to recognize fearful faces (Adolphs et al., 1994) and misjudge social threat signals (Adolphs et al., 1998). In line with this notion, accumulating evidence from clinical neuroimaging studies suggests amygdala dysfunction as a shared neural feature of mental disorders associated with altered emotional processing, such as autism, social anxiety, or post-traumatic stress disorder (Baron-Cohen et al., 2000; Etkin and Wager, 2007; Stark et al., 2015). Intriguingly, little is known about human amygdala functions beyond emotional processing. For example, electrical stimulation of the amygdala in patients with temporal lobe epilepsy not only elicits sensations of fear but also produces hallucinations,

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illusions, and memory flashbacks (Gloor et al., 1982; Vignal et al., 2007), suggesting that abnormal amygdala functionality comes along with biased body and self-perception.

The rubber hand illusion (RHI; Botvinick and Cohen, 1998) constitutes an established experimental paradigm to measure perceptual body illusions. Specifically, the RHI manifests in the sense of ownership for an alien limb, which typically arises following several minutes of synchronous stroking of both the participant's real hand, which is hidden from view, and an artificial rubber hand in a body-congruent position. Imaging studies of the RHI emphasize the role of the premotor area in multisensory integration and ownership feelings (Botvinick, 2004; Ehrsson et al., 2004; Ehrsson, 2012). Notably, body-incongruent positions of the rubber hand decrease illusory experiences and elicit bilateral amygdala activation (Tsakiris et al., 2007). Although both bottom-up (i.e., the integration of temporally congruent visual, tactile, and proprioceptive input) and top-down processes (i.e., the incorporation of the rubber hand's visual appearance into one's pre-existing body representation) have been implicated as neural substrates, the exact mechanism underlying illusory body ownership feeling during the RHI is still under debate (Yeh et al., 2017).

Interestingly, the occurrence and intensity of the RHI seem to be linked to individual social proficiency. For example, higher levels of emotional intelligence are associated with higher illusion vividness (Perepelkina et al., 2017), whereas alexithymia and autistic-like traits show negative correlations with the perception of body ownership during the RHI (Grynberg and Pollatos, 2015; Ide and Wada, 2017). In line with these observations is the finding that individuals on the autistic spectrum are less prone to the RHI (Cascio et al., 2012; Palmer et al., 2015). Moreover, previous studies found enlarged amygdala volumes (Gibbard et al., 2018) and increased amygdala response to social stimuli in this group of patients (Kleinhans et al., 2009). Last, higher levels of the hypothalamic peptide hormone oxytocin (OXT) are associated with stronger illusory body ownership (Ide and Wada, 2017), and we have previously shown that intranasal administration of OXT dose-dependently inhibits amygdala reactivity (Spengler et al., 2017) and modulates cross-modal sensory integration (Maier et al., 2019).

Given this empirical background, we hypothesize that illusion susceptibility is, at least in part, determined by amygdala engagement. This hypothesis is based on three lines of evidence: first, preliminary findings from intracranial stimulation studies suggest that functional manipulation of the amygdala is associated with the emergence of illusions and hallucinations (Gloor et al., 1982; Vignal et al., 2007). Second, the amygdala has been found to respond differentially to variations of the RHI, which suppress the emergence of an illusion (Tsakiris et al., 2007), and third, illusion experience in the RHI is altered in groups of patients characterized by alterations in amygdala structure and function (Cascio et al., 2012; Palmer et al., 2015).

Materials and Methods

To probe the amygdala's involvement in illusory perceptions, we conducted a series of experiments comprising a human amygdala lesion model, volumetric analysis, and OXT-induced modulation of amygdala reactivity: first, we tested unique twin women with bilateral amygdala lesions due to Urbach–Wiethe disease and compared their illusory perceptions during the RHI to an age- and education-matched control sample of 20 healthy women (Experiment 1). In a second step, we assessed volumetric amygdala data in an independent sample of 57 healthy participants to investigate correlations with RHI susceptibility (Experiment 2A). Last, we conducted a randomized, placebo (PLC)-controlled, double-blind study in which we administered intranasal OXT to the same 57 participants to reduce amygdala responses during the RHI experiment (Experiment 2B).

Ethics and enrollment

The present study was approved by the local ethics committee of the Medical Faculty of the University of Bonn, Germany. All participants gave their written informed consent in accordance with the latest revision of the Helsinki Declaration. Participants with past or current physical or psychiatric illnesses were excluded as assessed by medical history and a clinical interview (Mini-International Neuropsychiatric Interview; Sheehan et al., 1998). Moreover, participants were naive to prescription-strength psychoactive medication and had not taken any over-the-counter psychoactive medication in the preceding 4 weeks. Female participants receiving OXT completed a pregnancy test to confirm that they were not pregnant.

Experimental design and statistical analysis

Experimental setup and procedure. All participants were tested individually in a quiet room with standardized temperature and air conditions. Participants were seated at a table opposite to the experimenter. They placed both arms on the table in front of them, with palms facing downwards. A point on the table indicated the left index finger's target position. Next, the participants' left hand was concealed from his or her view by placing a wooden box over it. At each end of the box was an opening, including a small opening with a black curtain facing toward the participant and a large opening facing toward the experimenter. At the right side of the box, a 0.5×0.5 m large, horizontally installed screen concealed participants' view of the opening facing the experimenter. An artificial rubber hand was located 10 cm right of the screen (i.e., the actual and the rubber index finger were positioned 20 cm apart), in a position compatible with participant's own posture and in the participant's field-of-view. To further increase visual resemblance with the participants' own limb, participants were asked to wear a black sweatshirt with an artificial second sleeve on the left side leading to the rubber hand.

Participants were asked to fixate their gaze on the rubber hand's index finger over the whole course of the experimental procedure. Furthermore, they were instructed not to move their hidden hand or fingers. The experimenter then simultaneously stroked both the participants' actual hand and the rubber hand for 5 min with two paintbrushes, according to a standardized stroking protocol. A soundless digital clock allowed the experimenter to optimize the speed of stroking and to track the time elapsed before participants reported experiencing the illusion. The experimenter memorized this time point of illusion onset and recorded it immediately after finishing the experiment.

Outcome measures. We quantified participants' RHI experience via two main outcome parameters: the illusion onset and illusion vividness ratings. Recent evidence suggests that the RHI onset time provides a sensitive measure for illusion susceptibility with incremental validity beyond that acquired via self-report questionnaires (Kalckert and Ehrsson, 2017). Participants were thus asked to inform the experimenter once the illusionary experience appeared ("illusion onset", recorded in seconds from the start of the stroking). To assess the illusion vividness, we additionally used a German translation of the well established 9-item self-report questionnaire originally published by Botvinick and Cohen (1998). Participants were asked to indicate their agreement with each statement on a 7-point Likert scale, ranging from 1 ("I do not agree at all") to 7 ("I totally agree"). The RHI questionnaire (RHIQ) comprises three core questions (Items 1–3), regarding the localization of the felt touch (Item 1: "It seemed as if I were feeling the touch of the paintbrush in the location where I saw the rubber hand touched."), the origin of the felt touch (Item 2: "It seemed as though the touch I felt was caused by the paintbrush touching the rubber hand."), and ownership feelings toward the rubber hand (Item 3: "I felt as if the rubber hand were my hand."). Item 3 has been found to be particularly informative to quantify susceptibility for body ownership illusions, whereas Items 1 and 2 are instead closely related to touch localization (Marotta et al., 2016). We thus operationalized "illusion vividness" as the mean response to RHIQ items 1–3 (for a similar approach, see Morgan et al., 2011), whereas the single response to Item 3 was defined as "body ownership experience".

Another six control items (Items 4–9) capture illusory perceptions that are not directly related to the expected RHI experience [e.g., "It felt as if my (real) hand were turning rubbery." or "The rubber hand began to resemble my own (real) hand, in terms of shape, skin tone, freckles or some other visual feature."]. In case of a successful illusion induction, participants are expected to report high agreement with the target items, Items 1–3, while scoring much lower on the control items, Items 4–9 (Marotta et al., 2016). Because it is still elusive how subjects without illusory experience in the RHI differ from subjects with illusion experience, data from subjects reporting no illusion experience in either run of the experiment ($N = 5$ in Experiment 1, $N = 5$ in Experiment 2) were discarded from the final dataset. However, the main results remained significant even when we incorporated these data into our analyses.

Experiment 1: participants and protocol

Two 41-year-old monozygotic female twins (Patient 1 and Patient 2), diagnosed with the rare congenital, autosomal recessive genetic disorder Urbach–Wiethe disease (UWD; also known as "lipoid proteinosis") participated in our study. Among other clinical signs, UWD causes a bilateral calcification of the amygdala, which gradually evolves over the course of childhood and adolescence. In both patients, amygdala regions affected by the calcification include the basolateral amygdala and most other amygdala nuclei, except for anterior and ventral cortical amygdaloid parts at an anterior level, lateral and medial parts of the central amygdaloid nucleus, and the amygdala-hippocampal transition area at posterior levels (Bach et al., 2013). We acquired high-resolution anatomical images to confirm these previously described lesion patterns (Fig. 1*A*). Anatomical images from both twins were acquired on a 3.0-tesla Siemens TRIO MRI system, using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1660 ms, TE = 2.54 ms, matrix size: 320 × 320, voxel size: 0.8 × 0.8 × 0.8 mm, flip angle 9°, 208 sagittal slices). Comprehensive information on demographical and neuropsychological characteristics as well as molecular-genetic findings are summarized in previous papers (Hurlemann et al., 2007; Becker et al., 2012). Importantly, both patients display an average IQ and only mildly impaired performance in standard neuropsychological test batteries (Hurlemann et al., 2007; Talmi et al., 2010; Becker et al., 2012).

We additionally recruited 20 age- and education-matched healthy women as control participants. These control participants did not differ from the UWD twins in terms of cognitive functioning, or clinical traits as assessed via tests for visual attention and task-switching (Trail-making test A and B; Raitan, 1958), tests for verbal and nonverbal reasoning (Mehrfach–Wortschatz–Intelligenztest part B: Lehrl et al., 1995; Leistungsprüfsystem subtest 4: Horn, 1983), and psychometric measures of trait anxiety [State Trait Anxiety Inventory (STAI); Spielberger et al., 1970], depression (Beck Depression Inventory, Version II; Beck et al., 1996), and social anxiety (Social Interaction Anxiety Scale and Social Phobia Scale; Stangier et al., 1999). Of 20 control participants, 5 did not report any illusory experience during the RHI task. Further two participants were not able to participate because of pregnancy or were not able to complete the trial because of personal reasons. Thus, the final sample included in the analyses comprised the 2 patients and 13 matched controls. After giving written informed consent, patients and controls participated in the RHI task and were then asked to fill out the RHI questionnaire. Patients were tested consecutively in randomized order (Patient 1 first, Patient 2 second) under standardized conditions. They were neither able to see each other nor to communicate between the two testing sessions.

Experiment 1: statistical analyses. We analyzed data using standard procedures in IBM SPSS Statistics 24. We first compared behavioral data from the UWD patients with the 99% confidence interval of the healthy controls. Next, to confirm our results while avoiding inflated type I errors, we conducted the more conservative Crawford and Howell's *t* test (Crawford and Howell, 1998; Crawford and Garthwaite, 2012), which tests whether an individual's score is significantly different from a control or normative sample. Crawford and Howell's *t* tests were also used to compare demographical data between patients and controls. Effect sizes are given as measures of Cohen's *d*.

Before the analyses, Kolmogorov–Smirnov tests were used to assess normal distribution for all variables of interest. Neither the illusion onset, nor the sum of the target outcome items (RHIQ Items 1–3) or the control items (RHIQ Items 4–9) showed significant deviations from normal distribution. As expected, some of the demographical variables such as "years of education" did not fulfil the requirement of normal distribution. We nonetheless used Crawford and Howell's *t* tests for comparisons of demographical data, as this method is known to be rather insensitive to moderate violations of the normality assumption (Crawford and Garthwaite, 2012).

Experiments 2A and 2B: participants and protocol

In a second step, we conducted a randomized, PLC-controlled, double-blind study to experimentally probe amygdala's crucial role in the illusion experience. Specifically, we conducted a voxel-based morphometry analysis in a gender-mixed sample of 57 healthy volunteers to extract amygdala gray matter volumes and correlated the individual amygdala volume with RHI outcome measures after PLC treatment (Experiment 2A). Furthermore, the same participants received intranasal OXT (in a randomized within-subject design) to pharmacologically reduce amygdala function before conducting the RHI experiment (Experiment 2B). All volunteers participated in Experiments 1 and 2 after giving their written, informed consent (males = 21, females using hormonal contraception = 17, females not using hormonal contraception = 19; mean age = 24.14 years ± 3.52). Anatomical images from male participants were acquired on a 1.5-tesla Siemens Avanto MRI system, using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1660 ms, TE = 3.09 ms, matrix size: 256 × 256, pixel size: 1 × 1 × 1 mm, flip angle = 15°, 160 sagittal slices). The anatomical images of the female participants were acquired on a 3.0-tesla Siemens Trio MRI system using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1660 ms, TE = 2.54 ms, matrix size: 256 × 256, pixel size: 0.8 × 0.8 × 0.8 mm, slice thickness = 0.8 mm, FoV = 256 mm, flip angle = 9°, 208 sagittal slices). After completion of the experiment, male and female participants took part in two different studies, requiring the completion of unrelated tasks in the 1.5-tesla or 3.0-tesla scanner, respectively.

Following a PLC-controlled, double-blind, within-subject design, participants performed the rubber hand illusion (RHI) task twice (once after intranasal OXT and once after intranasal PLC administration) on 2 different days. Study appointments were scheduled at least 24 h apart. After completion of the RHI, participants filled out the RHI questionnaire. Five (3 female, 2 male) of 57 participants did not report any illusory experiences, neither under PLC nor under OXT, and were excluded from further analyses. Moreover, 15 participants experienced the illusion but did not report the time point of illusion onset in one of the testing sessions, resulting in 37 valid cases for repeated measures analyses of illusion onset.

Intranasal administration of oxytocin. Participants self-administered nasal sprays containing synthetic OXT or PLC at the beginning of the testing session. The administration instructions were in accordance with the latest standardization guidelines (Guastella et al., 2013) and administration was supervised by a trained research assistant. Participants received an OXT dose of 24 IU (3 puffs per nostril, each with 4 IU OXT). The synthetic OXT and the PLC solution were provided by Sigma-Tau Pharmaceuticals. The PLC solution contained the identical ingredients except for the peptide itself. The order of substance administration was randomized across testing days and the mean latency between application of treatment and task onset was 83.21 (±10.43) minutes. The strongest effects of intranasal OXT on amygdala activation have been observed 45 min after nasal spray administration, but amygdala inhibition has been evident up to a latency of 95 min (Spengler et al., 2017). In fact, a previous study even detected effects of intranasal OXT on emotion intensity ratings after 120 min (Cardoso et al., 2014).

Experiments 2A and 2B: statistical analyses. In Experiment 2A, imaging data were preprocessed and analyzed using standard procedures in statistical parametric mapping software (SPM 8, Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2017b, v7.10.0 (MathWorks). More specifically, structural MRI images were visually inspected for motion artifacts and

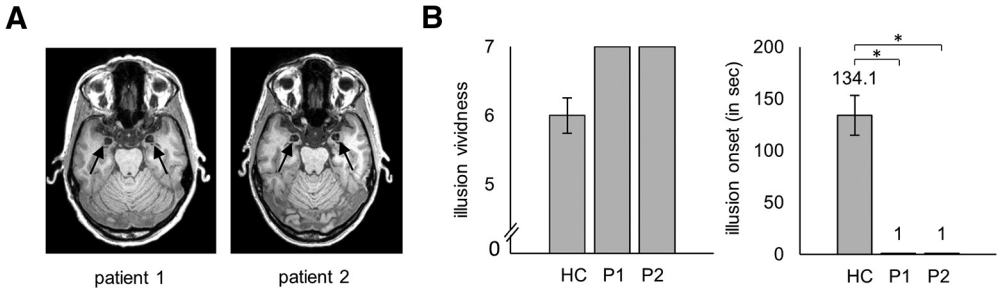

Figure 1. The RHI in patients with amygdala lesions. We applied the RHI task in a rare human amygdala lesion model, testing two homozygotic twin sisters suffering from bilateral amygdala lesions due to UWD. Displayed are high-resolution axial (horizontal) T1-weighted MRI sections of the anterior medial temporal lobes with arrows indexing the focal bilateral amygdala calcification damage (***A***). In both patients, the subjective illusion vividness was enhanced (***B***, left) and the illusion onset was substantially accelerated (***B***, right) compared with a matched control group ($N = 13$). Error bars indicate SEM. HC, Healthy controls; P1, Patient 1; P2, Patient 2. *$p < 0.05$.

subsequently preprocessed using the voxel-based morphometry toolbox VBM8 (http://dbm.neuro.uni-jena.de/vbm) and recommended default parameters. Diffeomorphic anatomic registration through an exponentiated lie algebra algorithm (DARTEL; Ashburner and Friston, 2005; Ashburner, 2007) was used to improve the registration of the MRI images. Images were normalized to International Consortium for Brain Mapping (MNI) space using high-dimensional DARTEL normalization and segmented into gray matter (GM), white matter (WM), and CSF using the tissue probability map provided in SPM12. Normalized segmented GM images were modulated by applying a nonlinear deformation, which allows comparing relative differences in regional GM volume corrected for individual brain size. Finally, the intensity-modulated gray matter segments were spatially smoothed with a 3-dimensional isotropic Gaussian kernel of 8 mm full-width at half-maximum.

Regional GM volumes were extracted for each participant using anatomically defined masks of the right and left amygdala as regions-of-interest, provided by the WFU Pickatlas toolbox for SPM (http://fmri.wfubmc.edu/software/pickatlas; Maldjian et al., 2003). Anatomical masks of the centromedial, laterobasal, and superficial nuclei of the amygdala were created using the SPM Anatomy toolbox v1.8 (Eickhoff et al., 2005). The extracted values (in milliliters) were further processed and analyzed using SPSS 24. Here, we performed correlation analyses via Pearson's product-moment correlation for normally distributed data.

For Experiment 2B, we ran mixed ANOVAs to identify main effects and interactions of the within-subject factor "treatment" (OXT, PLC) and the between-subject factor "gender" (female, male) on the dependent variable "illusion onset" and "illusion vividness rating". Including the covariate "hormonal contraception" (yes, no) did not yield any change in outcome. Hence, contraception was not considered relevant in further analyses.

All reported p values are two-tailed if not stated otherwise. Effect sizes are given as measures of Eta-squared and Cohen's d. Kolmogorov–Smirnov tests were used to assess normal distribution for all variables of interest. Healthy participants' amygdala gray matter volume (GMV) and illusion onset values did not show significant deviation from the normal distribution. The questionnaire data did not fulfill the requirement of normal distribution across all items assessed. We thus compared ratings of illusion vividness between the OXT and PLC session by applying the nonparametric Wilcoxon signed rank test and calculated spearman's rank correlation coefficient (Spearman's rho, r_s) as nonparametric correlation for analyses including the questionnaire data. ANOVA is known to be rather insensitive to moderate violations of the normality assumption (Glass et al., 1972; Harwell et al., 1992; Lix et al., 1996).

Results

Experiment 1: the RHI in patients with amygdala lesions

Both patients showed a significantly enhanced RHI: after the start of the stroking, both patients immediately reported experiencing the illusion (onset ~1 s). In addition, they chose the highest scores when rating the illusion vividness (target items of the RHIQ: Item 1 = 7, Item 2 = 7, Item 3 = 7 for both patients), but not for the control items (mean answer Items 4–9 = 1 for Patient 1, and 2.5 for Patient 2; Table 1). This exact pattern of results was replicated 1 year later in a follow-up assessment of the RHI in the same two patients.

Patients and controls were matched for age and education level and did not differ in any other demographical or clinical data. Both patients' illusion scores lay outside the 99% confidence interval for the healthy control sample mean (Table 1; Fig. 1*B*). Applying Crawford and Howell's method (Crawford and Howell, 1998; Crawford and Garthwaite, 2012), we confirmed the statistical significance of the case-control difference for the illusion onset while avoiding inflated type I errors [$t_{(12)} = -1.85$, $p_{\text{one-tailed}} = 0.04$, $d = -1.90$ with a 95% confidence interval of (-2.68 to -0.96)]. The difference in self-reported illusion vividness did not reach significance [$t_{(12)} = 1.08$, $p_{\text{one-tailed}} = 0.15$, $d = 1.11$ with a 95% confidence interval of (0.51–1.69)].

Experiment 2A: correlation between illusion experience and amygdala volume

In line with our findings from Experiment 1, data from volumetric brain morphometry analysis in the sample of healthy participants revealed a positive correlation between GMV in the bilateral amygdala and the individual illusion onset under PLC ($r_{(40)} = 0.34$, $p = 0.029$; Fig. 2). The larger the amygdala, the longer it took for the illusion to emerge.

To control for confounding effects of laterality, gender, or scanner type, we repeated the correlation analysis for split samples: The correlation remained significant when left and right amygdala volumes were analyzed separately (left: $r_{(40)} = 0.32$, $p = 0.038$; right: $r_{(40)} = 0.32$, $p = 0.040$), thus excluding an effect of laterality. Likewise, comparable correlations between illusion onset and bilateral amygdala volume were evident in male and female participants at significant and trend-significant level, respectively (males: $r_{(17)} = 0.44$, $p = 0.060$; females: $r_{(21)} = 0.49$, $p = 0.018$; correlation coefficients did not differ significantly between the male and female subsample, as analyzed via Meng's test, Meng et al., 1992; $Z = 0.19$, $p = 0.43$). Importantly, illusion onset did not correlate with total GMV ($r_{(40)} = -0.05$, $p = 0.748$), which underlines the specificity of the observed correlation with amygdala GMV. Controlling for total GMV in a partial correlation analysis even increased the amygdala GMV correlation (bilateral amygdala GMV: $r_{p(39)} = 0.43$, $p = 0.005$; left amygdala GMV: $r_{p(39)} = 0.42$, $p = 0.006$; right amygdala GMV: $r_{p(39)} = 0.37$, $p = 0.016$). The amygdala GMV of five subjects who failed to experience the illusion was not significantly different from other participants who reported the illusion (all p values >

Table 1. Illusion experience in two amygdala lesion patients and 13 matched controls

	Healthy controls				
	N	Mean	99% CI	Patient 1	Patient 2
Illusion onset (in sec)	13	134.08 (69.97)	[74.80, 193.36]	1	1
Illusion vividness index[a]	13	5.97 (0.93)	[5.18, 6.77]	7	7
Body ownership rating[b]	13	6.00 (0.91)	[5.22, 6.77]	7	7

Values are given as mean ± SD (in parentheses). CI, Confidence interval; *N*, number of subjects.

[a]Mean Response to RHIQ Items 1–3 (main items).

[b]RHIQ, Item 3: "I felt as if the rubber hand were my hand."

Table 2. Illusion experience in subjects from Experiment 2B

	N	OXT	PLC
Illusion onset (in sec)	37	87.08 (54.09)	109.98 (65.56)
Illusion vividness index[a]	51	5.93 (1.14)	5.55 (1.48)
Body ownership rating[b]	51	5.61 (1.42)	5.08 (1.83)

Values are given as mean ± SD (in parentheses). *N*, number of subjects.

[a]Mean Response to RHIQ Items 1–3 (main items).

[b]RHIQ, Item 3: "I felt as if the rubber hand were my hand."

0.5) indicating that an intact amygdala is not sufficient for the illusion experience.

In addition, to explore possible differential effects of amygdala subregions, we conducted a correlation analysis for the centromedial, laterobasal, and superficial nuclei of the amygdala. Intriguingly, both the laterobasal ($r_{(40)} = 0.32$, $p = 0.041$) and the superficial ($r_{(39)} = 0.37$, $p = 0.019$) subregion volume of the amygdala positively correlated with illusion onset, whereas the volume of the centromedial part of the amygdala did not significantly correlate with illusion onset ($r_{(40)} = 0.19$, $p = 0.23$). However, inferences about localization to specific nuclei should be considered preliminary and necessitate replication at a higher magnetic field strength and higher spatial resolution.

Experiment 2B: illusion experience following intranasal oxytocin administration

Repeated-measures ANOVAs revealed main treatment effects on the illusion vividness (RHIQ Items 1–3; $F_{(1,50)} = 5.27$, $p = 0.026$, $\eta^2 = 0.10$) and onset ($F_{(1,36)} = 6.40$, $p = 0.016$, $\eta^2 = 0.15$; Fig. 3). The treatment effect remained significant after including gender as a between-group factor into the analysis (illusion onset: $F_{(1,35)} = 6.26$, $p = 0.017$, $\eta^2 = 0.15$; illusion vividness: $F_{(1,49)} = 4.11$, $p = 0.048$, $\eta^2 = 0.08$), but there was no main or interaction effect of gender on the illusion experience ($p > 0.05$). *Post hoc* comparisons revealed an accelerated illusion onset ($t_{(36)} = -2.53$, $p = 0.016$) and increased illusion vividness (nonparametric Wilcoxon signed rank test, $Z = -2.56$, $p = 0.01$) after OXT compared with PLC treatment. The latter effect was driven by increased vividness ratings on the second ($Z = -2.89$, $p < 0.01$) and third ($Z = -2.06$, $p = 0.04$) RHIQ item, whereas ratings on the first item did not differ between PLC and OXT sessions ($Z = -0.25$, $p = 0.80$). Ratings on the control items of the RHIQ did not show significant differences between the OXT and PLC sessions (mean rating OXT: 2.45 ± 1.08, mean rating PLC: 2.34 ± 1.12; $Z = -0.21$, $p = 0.83$). Furthermore, measures of mood (Positive and Negative Affect Schedule; Watson et al., 1988) and anxiety (STAI; Spielberger et al., 1970) were assessed before and after the RHI procedure and did not show significant differences between the OXT and the PLC sessions, thus rendering modulatory effects of current mood rather unlikely.

Discussion

The role of the amygdala in fear perception and danger detection has been examined extensively across species (Janak and Tye, 2015), but surprisingly little is known about human amygdala functions beyond emotional processing. We observed remarkably increased illusion vividness and accelerated illusion onset in two patients with bilateral amygdala damage, compared with a matched control sample. Volumetric brain morphometry analysis confirmed a correlation between amygdala volume and latency until illusion onset in healthy participants. Moreover, pharmacological dampening of amygdala activation via intranasally administered OXT resulted in increased illusory body experiences (both vividness and speed) compared with PLC treatment. Thus, our conclusions from the amygdala lesion model and the healthy control samples converged by suggesting that susceptibility to the RHI varies as a function of amygdala structural integrity and activation. This notion is in line with previous findings of hallucinations, illusions, and memory flashbacks (Gloor et al., 1982; Vignal et al., 2007) after amygdala stimulation in epilepsy patients. In light of previous findings linking undistorted self-perception not only with the defense against bodily harm but also with measures of social proficiency (Cascio et al., 2012; Grynberg and Pollatos, 2015; Perepelkina et al., 2017), our results also allude to an important role of the amygdala in mediating both feelings of disturbed body ownership and interpersonal deficits in patients with psychiatric disorders.

The observed relationship between amygdala integrity and illusion experience accords well with clinical studies assessing body ownership in patients with autism spectrum disorder (ASD). In ASD patients, it has been found that amygdala volumes are enlarged (Rausch et al., 2018; Gibbard et al., 2018) and functional amygdala responses to social stimuli are increased (Kleinhans et al., 2009) compared with healthy controls. Intriguingly, these patients show reduced susceptibility to the RHI (Cascio et al., 2012; Palmer et al., 2015). Furthermore, post-traumatic stress disorder (PTSD) is associated with smaller amygdala volumes (Karl et al., 2006; Bruno et al., 2017), and increased vulnerability to manipulation of embodiment was evident in PTSD patients of the dissociative subtype (Rabellino et al., 2016, 2018), which is characterized by hyper-inhibition of the amygdala (Lanius et al., 2010). The increased illusion experience after OXT treatment is also in line with previous findings on correlations between peripheral OXT concentrations and body ownership feelings in the RHI (Ide and Wada, 2017).

As such, it can be speculated that different intertwined mechanisms modulate our perception of reality: in a given context of close proximity and social touch, the release of OXT may decrease self-centeredness (Zhao et al., 2016) and foster feelings of closeness, eventually facilitating trust (Kosfeld et al., 2005) and bonding (Scheele et al., 2013; Kreuder et al., 2017, 2019), thereby promoting a socially biased perception. If a context is ambiguous or even dangerous, an intact amygdala seems to counteract these processes by sustaining a clear self-perception and protecting us against maladaptive loss of reality. Building on this hypothesis, one would assume that an imbalance between these two processes either due to artificially increased central OXT levels or due to dysfunctional amygdala functioning in lesion patients could thus contribute to disturbed danger detection and interpersonal trust. Along these lines, both healthy subjects treated with OXT and UWD patients with amygdala lesions have been reported to exhibit significantly increased interpersonal trust (Adolphs et al., 1998; Kosfeld et al., 2005).

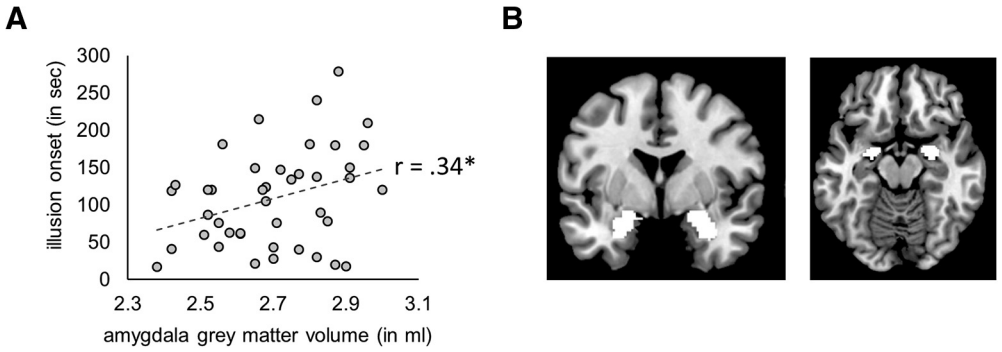

Figure 2. Correlation between illusion experience and amygdala volume. In line with the results from the lesion model, volumetric brain morphometry in a gender-mixed healthy sample ($N = 42$) revealed a positive correlation between bilateral amygdala GMV and illusion onset speed (***A***). We used an anatomically defined bilateral amygdala mask provided by the WFU Pickatlas toolbox for SPM (for visualization overlaid over a standard brain at MNI coordinates −23, 0, −14) to extract individual amygdala GMVs (***B***). $*p < 0.05$.

Mechanistically, the observed illusion susceptibility could be related to interoceptive processing or sensory integration. Damage to the amygdala can diminish cardiorespiratory interoception (Khalsa et al., 2016) and OXT may encode the precision of interoceptive signals (Quattrocki and Friston, 2014). However, a recent study did not detect a link between interoceptive sensitivity and the subjective experience of body ownership (Crucianelli et al., 2018). Furthermore, we have previously shown that intranasal OXT modulates the processing of affective touch in a context-dependent manner rather than altering touch perception per se (Scheele et al., 2014; Kreuder et al., 2017). Thus, our data suggest that the amygdala may play an important role in multisensory integration of temporally congruent tactile, visual, and proprioceptive information (i.e., bottom-up processes in the RHI) or may be involved in the integration of external stimuli into one's own body representation (i.e., top-down processes in the RHI; Marotta et al., 2016). Importantly, the observation that a complete absence of the RHI in a subsample of five participants was not associated with significantly larger amygdala volumes underscores the importance of multisensory integration in other brain areas like the premotor cortex (Ehrsson et al., 2004) or the temporoparietal junction (Olivé et al., 2015). Further studies are needed to gain mechanistic insights into the amygdala's function in illusory experiences and to elucidate neural networks involved in not only the emergence but also the prevention of body illusions.

Previous neuroimaging studies did not report on the amygdala as a core region involved in the RHI (Ehrsson et al., 2004). One reason for the paucity of previous results might lie in the amygdala's small size and its vulnerability to susceptibility artifacts in functional MRI measures (e.g., signal dropout and image distortions) caused by local magnetic field inhomogeneities (Merboldt et al., 2001). Because of this methodological challenge, whole-brain analyses of functional MRI data frequently fail to detect differences in amygdala activation at a significant magnitude, whereas studies with an a priori focus on the amygdala often rely on region-of-interest approaches. Furthermore, previous studies have preferentially examined regions showing increased activation during the illusion experience. Our hypothesis of a dampening effect of the amygdala on the illusion suggests activation patterns in the contrary direction, which might have been neglected in classical study designs focusing on regions activated during illusion experience. Also, we focus on illusion onset times, whereas previous studies on neural underpinnings of the RHI have compared synchronous to asynchronous conditions or focused on subjective questionnaire data and proprioceptive drift as outcome measures.

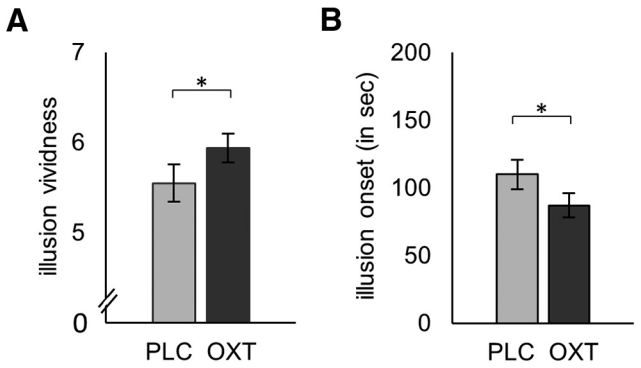

Figure 3. Illusion experience following intranasal oxytocin administration. Intranasal administration of OXT, known to dampen amygdala functioning, resulted in enhanced illusion vividness ratings (***A***) and accelerated illusion onset (***B***) in a healthy gender-mixed sample ($N = 52$). Error bars indicate SEM. $*p < 0.05$.

The present study has some limitations. First, we did not examine the RHI in a lesion control group and it is conceivable that extra-amygdalar lesions would also alter illusory perceptions. It is also noteworthy that the patients' lesions extend into the hippocampal area (Bach et al., 2013). As the hippocampus has been implicated in bodily illusions (Guterstam et al., 2015) and has been shown to be modulated by OXT (Tirko et al., 2018), it is possible that regions other than the amygdala or that the connectivity between the amygdala and these regions are also involved in the modulation of the illusion. Second, we administered 24 IU of OXT to the participants in Experiment 2B. Although this dose seems to be the most efficient in terms of amygdala-dampening effects in men (Spengler et al., 2017), it is still not clear whether female participants differ in their response to OXT. Depending on the chosen task and administration protocol, previous studies have even reported diminished or contrary effects in women compared with men (Domes et al., 2010). Hence, we cannot rule out that female subjects would have exhibited a stronger effect at a different dose. In addition, meta-analytic evidence indicates that OXT modulates task-related responses in the insula across several studies (Wigton et al., 2015; but see Grace et al., 2018), which could provide an alternative neural mechanism via which OXT influences susceptibility to the RHI. However, in light of the highly congruent results from three experiments, the most parsi-

monious explanation is that intensity of illusion experience is indeed linked to amygdala functioning.

Together, our results suggest a so far undescribed protective role of the amygdala, shielding us from delusions and potentially harmful illusory perceptions. The refined integration of interoceptive and exteroceptive information into a genuine reflection of environmental conditions may depict an additional mechanism by which the amygdala gains its evolutionary significance. Eventually, these novel insights may contribute to our understanding of the complex interplay of amygdala functions in fostering self-awareness and reality perception and may stimulate further research to broaden our understanding of amygdala function over and above fear processing.

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