Fear Processing and Social Networking in the Absence of a Functional Amygdala

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Background: The human amygdala plays a crucial role in processing social signals, such as face expressions, particularly fearful ones, and facilitates responses to them in face-sensitive cortical regions. This contributes to social competence and individual amygdala size correlates with that of social networks. While rare patients with focal bilateral amygdala lesion typically show impaired recognition of fearful faces, this deficit is variable, and an intriguing possibility is that other brain regions can compensate to support fear and social signal processing.

Methods: To investigate the brain's functional compensation of selective bilateral amygdala damage, we performed a series of behavioral, psychophysiological, and functional magnetic resonance imaging experiments in two adult female monozygotic twins (patient 1 and patient 2) with equivalent, extensive bilateral amygdala pathology as a sequela of lipoid proteinosis due to Urbach-Wiethe disease.

Results: Patient 1, but not patient 2, showed preserved recognition of fearful faces, intact modulation of acoustic startle responses by fear-eliciting scenes, and a normal-sized social network. Functional magnetic resonance imaging revealed that patient 1 showed potentiated responses to fearful faces in her left premotor cortex face area and bilaterally in the inferior parietal lobule.

Conclusions: The premotor cortex face area and inferior parietal lobule are both implicated in the cortical mirror-neuron system, which mediates learning of observed actions and may thereby promote both imitation and empathy. Taken together, our findings suggest that despite the pre-eminent role of the amygdala in processing social information, the cortical mirror-neuron system may sometimes adaptively compensate for its pathology.

Key Words: Acoustic startle reflex, amygdala lesion, compensation, emotion, face, fear, fMRI, mirror-neuron system, social network

Perceiving and responding appropriately to facial expressions of emotion are critical for social cohesion, survival, and reproductive success (1) and engage a widely distributed neural network centered around the amygdala (2). The amygdala modulates cortical responses to facial expressions (3) and its size is positively correlated with that of social networks (4). A crucial question, however, is whether the social brain is dependent upon an intact amygdala. Case studies of rare patients with focal bilateral amygdala lesion show that despite their preserved ability to generate facial expressions of emotion (5), they lack any subjective experience of fear, even in the face of potent fear elicitors ([6], but see [7]) and tend to misinterpret emotional facial expressions in others, particularly fearful ones (8,9). However, there is substantial interindividual variability in this deficit (10), perhaps reflecting adaptive compensation to pathology in at least some amygdala-damaged patients. Other variables could also account for such differences between patients, including the anatomical extent of amygdala damage and genetic and environmental influences.

To investigate the brain's functional compensation for amygdala lesion, while controlling for these other variables, we performed a series of behavioral, psychophysiological, and functional magnetic resonance imaging (fMRI) experiments in two 36-year-old female monozygotic twins (patient 1 and patient 2) with selective bilateral amygdala pathology as a sequela of lipoid proteinosis due to Urbach-Wiethe disease (LP) (11–13). This rare autosomal-recessive genodermatosis is caused by mutations in the extracellular matrix protein 1 gene (*ECM1*) located on chromosome 1q21 (14,15). Interestingly, in a previous study, patient 1 displayed preserved fear recognition abilities, as opposed to patient 2, who was severely impaired (11). After genetic characterization, we first tested the twins and 15 age- and education-matched female control subjects on a behavioral facial emotion recognition task. Replicating our previous findings (11), we observed intact fear recognition in patient 1 but not in patient 2. This result may be due to her having greater sparing of amygdala tissue compared with her sister (hypothesis 1) or to functional compensation based on adaptive reorganization (hypothesis 2). The concept of lesion-induced adaptive plasticity describes the mechanisms that, following brain injury, lead to a rearrangement of cerebral organization promoting functional recovery (16). Functional recovery based on plasticity has been described for acute brain lesions such as stroke and trauma (17), as well as for slow-progressing brain lesions such as low-grade gliomas (18).

To test hypothesis 1, both twins underwent x-ray computed tomography (CT) and high-resolution T1-weighted structural magnetic resonance imaging (MRI), enabling us to determine the anatomical extent of their amygdala damage by co-registering the two imaging modalities. Hypothesis 2 was addressed using fMRI. Specifically, we predicted that preserved fear recognition in patient 1 would be accompanied by exaggerated activity in brain regions mediating adaptive compensation.

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A related question is whether the functional compensation of patient 1 allowing accurate recognition of fearful faces extends to other amygdala-dependent domains. These include top-down interactions with brainstem structures to modulate basic reflexive (acoustic startle response [ASR]) and autonomic (skin-conductance response [SCR]) responses, as well as bottom-up interactions with cortical structures mediating mentalizing and social competence functions that can support extensive social networks (4). In two further experiments, we have tested these exciting possibilities.

Methods and Materials

Background information on Urbach-Wiethe disease and a detailed synopsis of all experimental procedures are provided in Supplement 1.

Volunteers

Two female monozygotic twins suffering from lipoid proteinosis of Urbach-Wiethe (synonyms Urbach-Wiethe disease or hyalinosis cutis et mucosae; Online Mendelian Inheritance in Man 247100) ([11–13]; see also [19–21]) and 15 age- and education-matched healthy female control subjects (Table S1 in Supplement 1) volunteered in a series of behavioral, psychophysiological, and functional MRI experiments after providing written informed consent. The study was approved by the Institutional Review Board of the Medical Faculty of the University of Bonn.

Molecular Genetics

Lipoid proteinosis of Urbach-Wiethe disease is caused by mutations in the extracellular matrix protein 1 gene (*ECM1*) located on chromosome 1q21 (Table S2 in Supplement 1) (14,15). To specify the mutation causing Urbach-Wiethe disease, *ECM1* was sequenced in both twins.

Structural Imaging

High-resolution T1-weighted structural MRI scans of both twins were acquired on a 1.5 Tesla Siemens Sonata system (Siemens, Erlangen, Germany), and magnitude images (Figures 1A[i] and 1B[i]), as well as phase images (Figures 1A[ii] and 1B[ii]) were generated (22,23). Additionally, the twins were scanned on a 16-row multidetector x-ray CT device (Brilliance 16, Philips, Best, The Netherlands), thus enabling accurate CT–MRI co-registration (PMOD 3.1, PMOD Inc., Zurich, Switzerland). To assess the lesion extent, volumes of interest were manually defined and measured in the axial, coronal, and sagittal planes. For visualization purposes, these CT-derived lesion contours were superimposed onto the MRI scans (Figures 1A[iii] and 1B[iii]).

Experiment 1

The twins and 15 matched control subjects were tested on a behavioral facial emotion recognition task. Specifically, subjects were exposed, in a computer-based paradigm, to photographs depicting angry, disgusted, fearful, happy, neutral, and sad facial expressions of 12 different individuals selected from the validated

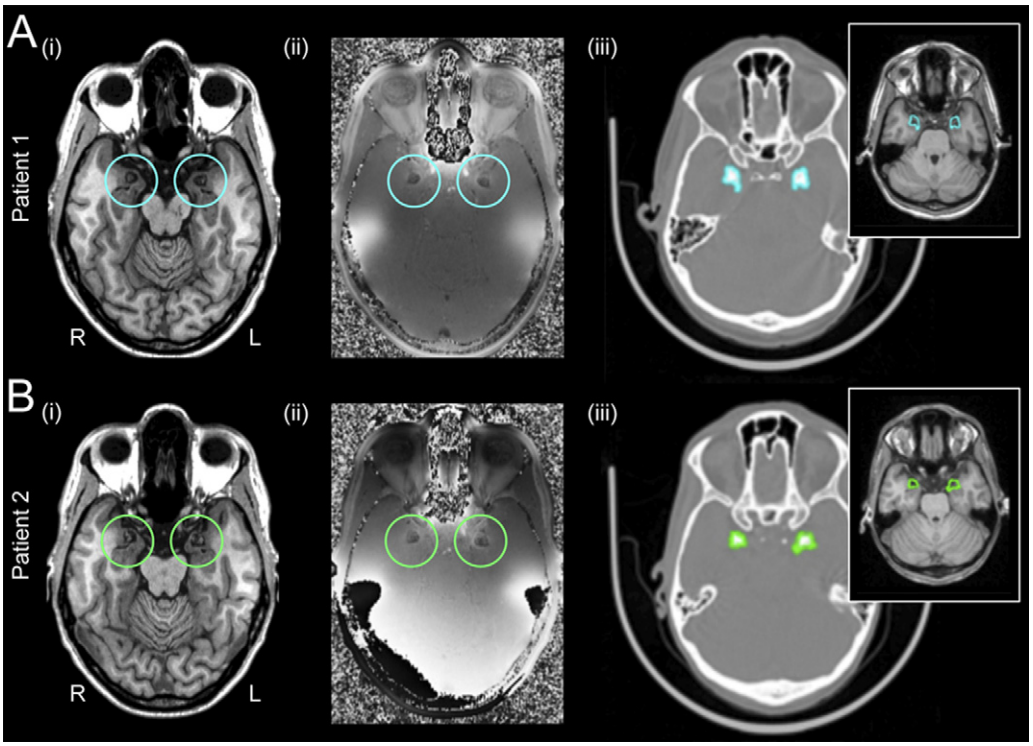

Figure 1. Lesion imaging. Lipoid proteinosis of Urbach-Wiethe led to selective bilateral calcification lesions of the amygdala in patient 1 **(A)** and patient 2 **(B)**, however, without significant volumetric differences between them. (i) Displayed are high-resolution axial (horizontal) T1-weighted magnetic resonance imaging sections of the anterior medial temporal lobes with circles indexing the focal bilateral amygdala calcification damage. Magnetic resonance images are derived from reconstructed five-average data sets acquired with .8 mm isotropic resolution. In the conventional magnitude images, the lesion signal is reduced compared with intact tissue due to the combined effect of enhanced intravoxel dephasing (susceptibility inhomogeneities) and calcification (reduced water content). (ii) Due to differential susceptibility between calcified regions and intact tissue, the amygdala lesions can be delineated more accurately in the phase images. (iii) Projection of the individual calcifications as measured by x-ray computed tomography onto high-resolution magnetic resonance imaging, documenting equivalent, extensive amygdala damage in both twins. L, left; R, right.

Karolinska Directed Emotional Faces database (24,25). To measure peripheral physiological reactions to the presented stimuli, electrodermal activity (EDA) was recorded by two EDA electrodes attached to the thenar and hypothenar of the nondominant hand throughout the experiment. A commercial system (Contact Precision Instruments, Cambridge, Massachusetts) was used for stimulus delivery and EDA recording.

Experiment 2

fMRI Paradigm. To specifically test our prediction that preserved fear recognition in patient 1 (experiment 1) would be accompanied by exaggerated activity in brain regions mediating adaptive compensation, we adopted a modified version of an established fMRI face perception task (26) to specifically stimulate fear responses in control subjects and to evoke compensatory neural responses in the LP patients. Stimulus material comprised photographs depicting 40 individuals showing fearful facial expressions. Specificity of effects was controlled for by also measuring responses to happy and neutral facial expressions of the same individuals. The photographs were, again, selected from the validated Karolinska Directed Emotional Faces database (24,25) and presented blockwise by means of liquid crystal display video goggles (Nordic NeuroLab, Bergen, Norway) connected to a stimulus-delivery computer running Presentation 14 (Neurobehavioral Systems Inc., Albany, California).

fMRI Data Acquisition. Functional MRI employing blood oxygenation level-dependent contrast was carried out on a 1.5 Tesla Siemens Avanto MRI system (Siemens) using a T2*-weighted echo planar imaging sequence. Functional MRI data were preprocessed and analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) implemented in Matlab 7 (The MathWorks Inc., Natick, Massachusetts).

fMRI Data Analysis. To test whether the face-perception task evoked amygdalar activity in control subjects and thus had the capability of evoking compensatory responses in the patients, separate one-sample *t* tests for the conditions fearful faces and happy faces were computed. Because of the small size of the control sample and our a priori anatomical hypothesis, analyses were restricted to the bilateral amygdala, and regions of interest (ROIs) were anatomically defined using the WFU PickAtlas (version 3.0; ANSIR Laboratory, WFU School of Medicine, Winston-Salem, North Carolina), which provides a method for generating ROI masks based on the Talairach Daemon database (for a detailed description of the WFU PickAtlas and the anatomical masks employed, see [27–29]). Region of interest based one-sample *t* tests were computed with a threshold of $p < .05$ and familywise error (FWE)-corrected for multiple comparisons, implemented in a small volume correction based on the size of the amygdala ROI.

To address the question whether the adaptive compensation to amygdala pathology is accompanied by supranormal activity in other brain regions, separate two-sample *t* tests (patient 1 vs. control subjects, patient 2 vs. control subjects) with pooled estimates of the error variance (30) for the conditions fearful faces, neutral faces, and happy faces were computed. Because of no a priori hypotheses on the brain regions that might be involved in a potential compensatory process, whole-brain analyses were performed ($p < .05$, FWE-corrected for multiple comparisons).

To detect altered activity patterns of the twins within the fearful face-processing network defined by a recent meta-analysis (31), individual parameter estimates for the following regions were extracted for the conditions neutral faces and fearful faces: bilateral inferior frontal gyrus, bilateral fusiform gyrus, bilateral inferior parietal gyrus, bilateral medial frontal gyrus, and bilateral insula. Differences between patients and control subjects were analyzed using *Z* tests.

Experiment 3

To test for an emotional modulation of the ASR, the paradigm contained 20 neutral and 20 negative (mostly fear-eliciting) stimuli with social content selected from the International Affective Picture System (32). Facial electromyographic activity was recorded throughout this experiment by means of a commercial system (Contact Precision Instruments, Cambridge, Massachusetts). After the psychophysiological recording, all subjects were administered the Self-Assessment Manikin (32) to obtain behavioral pleasure and arousal ratings for each stimulus on a scale ranging from 1 (minimum) to 9 (maximum).

Experiment 4

To examine the social networks of the control subjects and the twins, we administrated the Social Network Index questionnaire (SNI) (33). The SNI comprises two subscales, number of people in social network (reflecting social network size) and number of embedded networks (reflecting social network complexity). To integrate network size and network complexity, composite scores were calculated.

Results

Molecular Genetics

The twins showed the same genotype in all sequenced regions. We found a novel homozygous missense mutation in exon 7 of *ECM1*, resulting in an exchange of tryptophan to arginine: c.709T>C; p.W237R (Figure S1 in Supplement 1). The alignment of proteins belonging to the *ECM1* family confirmed that tryptophan 237 is highly conserved, thus underlining the potential pathogenic relevance of the p.W237R mutation (Figure S2 in Supplement 1).

Structural Imaging

The extracted volumes of interest did not significantly differ between patients (patient 1, mean = 1.12 ccm; patient 2, mean = 1.15 ccm). Consistent with previous probabilistic analyses (11), inspection of all scans by a neuroanatomist (K.Z.) revealed complete destruction of the basolateral amygdala and minor sparing of anterior amygdaloid and ventral cortical amygdaloid parts at a rostral level, as well as lateral and medial parts of the central amygdaloid nucleus and the amygdalohippocampal area at more caudal levels in both twins (Figure S3 in Supplement 1).

Experiment 1

Results from the facial emotion recognition task revealed dissociable fear recognition deficits in the Urbach-Wiethe disease twins compared with 15 control subjects: whereas patient 1 demonstrated preserved emotion recognition abilities (her error rate ranged from 0% to 33% across all emotional categories compared with 0% to 16% for the control subjects; all *p* values > .05, two-tailed *Z* tests), patient 2 was severely compromised in recognizing fearful faces (error rate: control group = 16.1%, SEM = 4.1; patient 2 = 91.7%, $Z = -4.6$, $p < .001$) and to a much lesser extent, angry ones (error rate: control group = 6.7%, SEM = 1.8; patient 2 = 25.0%; $Z = -2.6$, $p = .009$; Figure 2A). The patterns of autonomic responses to emotional faces for patient 1 and control subjects were comparable. Notably, patient 1, as well as control subjects, generated the strongest skin conductance response to fearful faces (patient 1, .06 μS; control subjects, .05 ± .02 μS; Figure S4 in Supplement 1). These

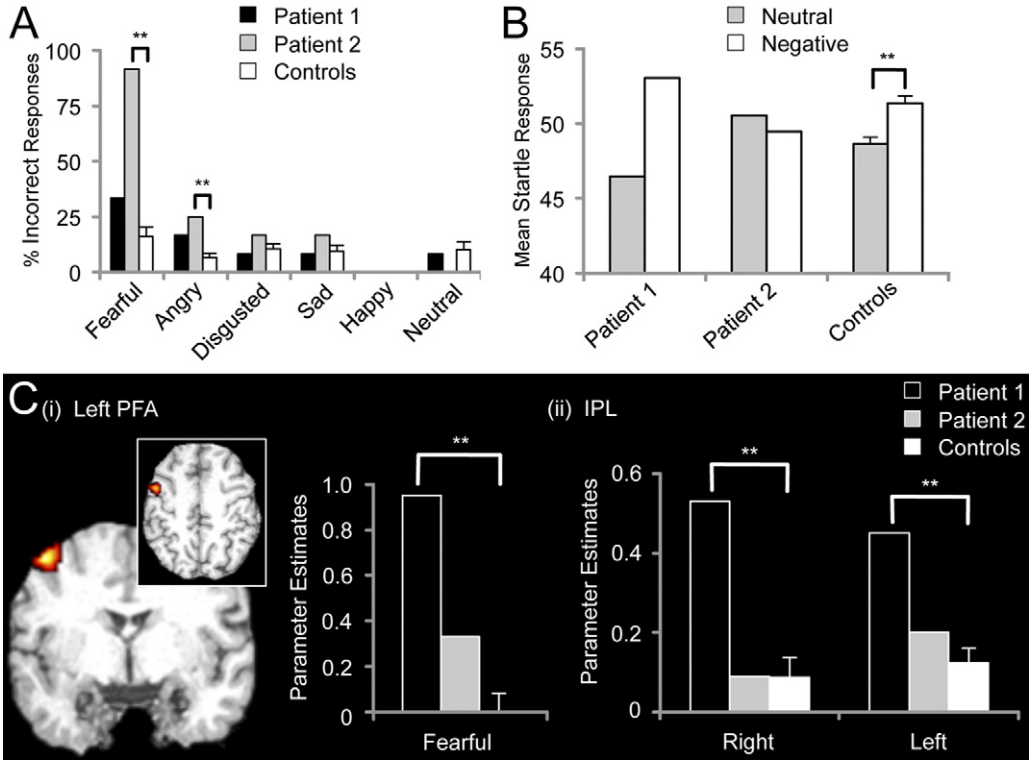

Figure 2. Results of experiments 1 through 3. **(A)** Facial emotion recognition task (experiment 1). Bars indicate percent incorrect responses (for the control sample, mean error rates ± SEM are shown, $^{**}p < .01$). The behavioral data show that patient 1, but not patient 2, has preserved recognition of fearful faces. **(B)** Emotional startle response-modulation task (experiment 2). Bars indicate startle responses (in *T* scores) during exposure to neutral and negative pictures (for the control sample, mean error rates ± SEM are shown, $^{**}p < .01$). The psychophysiological data show that that patient 1, but not patient 2, has an intact modulation of acoustic startle responses by fear-eliciting scenes. **(C)** Functional magnetic resonance imaging face perception task (experiment 3). The functional magnetic resonance imaging data show that patient 1 has increased activation of the left premotor cortex face area (PFA) and bilateral inferior parietal lobule (IPL) in response to fearful faces. (i) Results from a two-sample *t* test (with pooled error variance) for the condition fearful faces, determining the brain regions where patient 1 displayed significantly ($p < .05$, familywise error-corrected) larger fear responses than control subjects. For illustration purposes only, results are displayed at an uncorrected threshold ($p < .001$) in coronal and axial (horizontal) view (left panel). The maximum *t* value ($t = 11.12$) was located in the left PFA (Talairach space at $x = -32$, $y = 9$, $z = 58$). Parameter estimates were extracted from a spherical region of interest centered at the coordinates of the maximum *t* value. For the control sample, mean ± SEM responses are shown (right panel). $^{**}p < .01$. (ii) Parameter estimates extracted from the condition fearful faces in the left and right IPL. For the control sample, mean ± SEM responses are shown. $^{**}p < .01$.

results further support the hypothesis that patient 1 can at least partially compensate for her amygdala damage.

Experiment 2

Consistent with a recent meta-analysis on the neural substrates of emotional face perception (31), control subjects displayed enhanced bilateral amygdalar activity in response to fearful and happy versus neutral faces ($p < .05$, FWE-corrected for the size of the amygdala ROI). In support of the hypothesis that in patient 1 supranormal responses to fearful faces should occur in brain regions implicated in compensation, the direct comparison of patient 1 with the control subjects revealed significantly greater activation in her left premotor cortex face area (PFA; whole-brain analysis, FWE-corrected for multiple comparisons; $t = 11.12$, $p < .05$; cluster size = 4 voxels; maximum *t* value at $x = -32$, $y = 9$, $z = 58$; Figure 2C[i]), an effect specifically restricted to the condition fearful faces. Comparisons of responses from patient 2 yielded no significant differences from control subjects in any emotion category. None of the patients showed decreased activity in comparison with the control subjects. For further analysis, individual parameter estimates for the condition fearful faces were extracted from a spherical ROI (radius = 10 mm) centered at the maximum *t* value of the left PFA cluster. Relative to control subjects, patient 1 displayed increased activity ($Z = 5.24$, $p < .001$), whereas patient 2 ($Z = 1.82$, $p = .068$) did not differ significantly (Figure 2C[i]). Extraction of parameter estimates from anatomically defined regions that form the fearful face-processing network revealed that the twins did not differ from control subjects for the neutral condition (*p* values > .05, two-tailed *Z* tests). In response to fearful faces, patient 1 displayed increased activity in the left and right inferior parietal lobule (IPL; right: $Z = 2.95$, $p = .009$; left: $Z = 2.52$, $p = .011$), whereas patient 2 did not differ significantly from control subjects ($Z = .017$, $p = .992$ and $Z = .589$, $p = .560$; Figure 2C[ii]).

Experiment 3

The twins and 12 control subjects were tested for an emotional modulation of the acoustic startle response. As expected, the ASR magnitude in control subjects was significantly potentiated by aversive scenes (*T* score = 51.36) compared with neutral pictures (*T* score = 48.64, $t = 3.94$, $p = .002$, paired *t* test). Whereas patient 1 showed an intact ASR potentiation ($Z = 1.12$), her sister did not (her startle magnitude difference between valence categories was 1.5 standard deviations below that of control subjects, $Z = -1.50$; Figure 2B). Thus, functional compensation of patient 1 includes top-down modulatory influences on reflexive brainstem-mediated responses to fear-related stimuli. Patient 1 also had similar SCRs to control subjects in response to a range of emotional face categories (experiment 1), confirming that compensation also affects auto-

nomic physiological responses (Figure S4 in Supplement 1). In line with previous studies of amygdala-damaged patients (8,9), patient 2 scored low on arousal ratings, even for highly aversive stimuli. In patient 2, this aberrance extended to valence ratings, such that aversive stimuli were rated as less unpleasant (Table S3 in Supplement 1).

Experiment 4

In control subjects, social network size and social network complexity measures were positively correlated (Spearman's $\rho = .68$; $p = .01$ two-tailed; Pearson's $r = .62$, $p = .01$ two-tailed; Figure S5 in Supplement 1), corroborating the plausibility of the compound measure. Control subjects had two to six embedded networks and a total network size comprising 9 to 37 people. Strikingly, the SNI scores of patient 1 for both social network size and complexity were about double those of patient 2 (17 vs. 9 for size and 4 vs. 2 for complexity, respectively) and in the middle of the range for control subjects (empirical distribution function score, $F_{ecdf} = .47$ and $F_{ecdf} = .86$, respectively; Figures 3A and 3B). However, her sister scored at the lower end of the empirical distribution in both subscales ($F_{ecdf} = .07$ and $F_{ecdf} = .07$, respectively; Figures 3A and 3B). When a composite SNI score, integrating social network size and complexity, was computed, patient 1, again, was average ($F_{ecdf} = .6$), whereas patient 2 had the lowest score in the entire sample ($F_{ecdf} = 0$; Figure 3C). Notably, in control subjects, a higher social network complexity correlated positively with overall facial emotion recognition performance in experiment 1 (Spearman's $\rho = .63$, $p = .02$).

Discussion

There is extensive evidence that patients with focal bilateral amygdala lesions are impaired in recognizing fear from faces (8,9) and lack any subjective experience of fear ([6], but see [7]). However, substantial interindividual variability in the extent of these impairments (10) suggests the emergence of functional compensation to pathology in at least some amygdala-damaged patients. Here, we demonstrate a potential compensatory mechanism in one of monozygotic adult female twins with LP and equivalent, extensive bilateral amygdala lesions through a series of behavioral, psychophysiological, and fMRI experiments.

Our results show that the twins share the same genotype in all sequenced regions. Specifically, a novel homozygous missense mutation in exon 7 of *ECM1* (c.709T>C; p.Trp237Arg) was found. This is in line with evidence that exons 6 and 7 are the most common sites for *ECM1* mutations in LP (Table S2 in Supplement 1).

Despite their shared genetic profile and common environment as both children and adults, the twins exhibited markedly different abilities in recognizing fearful faces. In line with previous reports on LP patients with complete bilateral amygdala damage (10), patient 2 was severely impaired. Patient 1, however, showed preserved recognition of fearful faces (experiment 1; see also [11]). Lesion mapping by means of CT–MRI co-registration revealed an equivalent lesion anatomy between the twins, suggesting that a greater sparing of amygdala tissue in patient 1 might not account for her preserved fear-recognition abilities.

Using fMRI, we found that patient 1, but not patient 2, showed a specific enhancement of neural activity in the right PFA and bilateral IPL in response to fearful faces (experiment 2), possibly reflecting the neural substrate of a functional compensation. In a subsequent psychophysiological examination, patient 1, but not patient 2, demonstrated an intact modulation of the emotional ASR (experiment 3). Finally, social network size and complexity were unaffected in patient 1 but severely decreased in patient 2 (experiment 4).

Our findings suggest that the preserved fear-recognition abilities of patient 1, as opposed to patient 2, are not based on a greater sparing of amygdala tissue compared with her sister (hypothesis 1) but on compensatory mechanisms enabling patient 1 to recognize fearful faces (hypothesis 2). Specifically, our findings implicate the PFA and IPL in this functional compensation. Notably, both the PFA and IPL respond to emotional faces (31,34) and form an integral part of the cortical mirror-neuron system that mediates imitation of observed actions and may thus contribute to empathic responses (35–37). We note that the IPL has been shown to specifically respond to fearful faces (38) and other negatively valenced stimuli in healthy subjects (39). Furthermore, there is substantial evidence that lesions of the IPL specifically impair recognition of fear and sadness in faces (40). Selectively increased activity in the bilateral IPL of patient 1 might therefore represent a compensatory recruitment of other interconnected brain regions within the fear-processing network. Similar adaptive mechanisms have been postulated to occur in subjective memory impairment (41) and Alzheimer's disease (42), as well as during spatial orientation in congenital blindness (43).

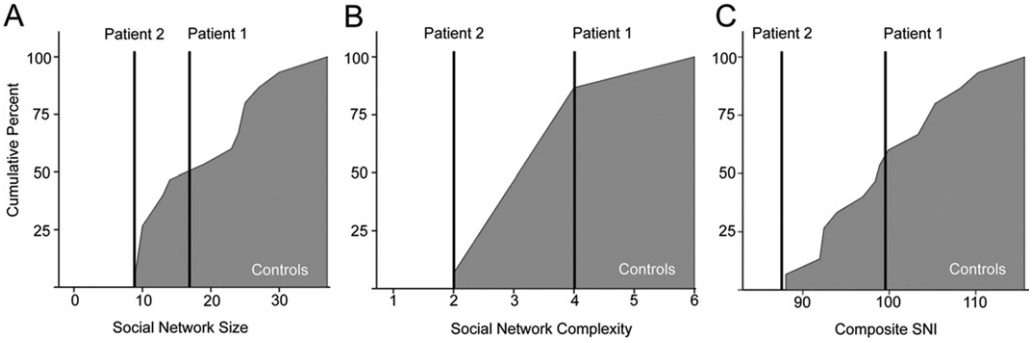

Figure 3. Results of experiment 4. As opposed to patient 2, patient 1 showed an average social network. The gray area represents the cumulative count of the control subjects, and the black bars indicate the scores of both patients. **(A)** Cumulative count function of the Social Network Index (SNI) subscale number of people in social network, representing social network size. Whereas patient 1 reported average social network size and complexity ($F_{ecdf} = .47$), patient 2 scored at the lower end of the empirical distribution ($F_{ecdf} = .07$). **(B)** Cumulative count function of the SNI subscale number of embedded networks, reflecting social network complexity. Patient 1 reported average social network size and complexity ($F_{ecdf} = .86$); patient 2 scored at the lower end of the empirical distribution ($F_{ecdf} = .07$). **(C)** Cumulative count function of the composite SNI score, integrating social network size and complexity. Patient 1 scored on the average ($F_{ecdf} = .6$); patient 2 reported the lowest score in the entire sample ($F_{ecdf} = 0$).

Furthermore, patient 1 displayed a fear-selective increase in PFA activity. In monkeys, the premotor cortex (area F5) is activated during performance of hand and mouth actions or during observation of actions made by others (44). Mirror neurons also seem to exist in the human brain in a neural circuitry that comprises the PFA, along with regions such as Broca's area and the primary motor cortex (45). The human mirror-neuron system is involved in the development of social-emotional interactions, including face processing and empathy (46), and may provide internal representations of other people's facial expressions, thus facilitating emotion recognition (47). In line with these findings, a recent transcranial magnetic stimulation study has identified a direct relationship between PFA activity and facial emotion recognition abilities (48). Interestingly, a previous study on the LP twins investigated here showed that patient 1 had preserved emotional empathy responses to negatively, but not to positively, valenced pictures of humans exhibiting strong emotions, whereas patient 2 was severely impaired on both (13). Our findings that patient 1 uniquely demonstrated fear-selective potentiated PFA and IPL activity suggest that the slowly developing amygdala lesion as a result of LP has enabled her to develop a functional reorganization of her cortical fear-processing network. Additionally, her cortical mirror-neuron system appears to support her fear recognition abilities in the absence of a functional amygdala.

To explore whether functional compensation of patient 1 extends to other functional domains that receive modulatory input from the amygdala, we assessed peripheral physiological activity through ASR and SCR recordings. While the ASR per se is independent of the amygdala (49), its modulation by emotional stimuli is not and critically requires amygdala integrity (50). Normally, negatively valenced stimuli increase the ASR magnitude (51,52). The observation that patient 1 showed intact modulation of the ASR (experiment 3) suggests that her functional compensation extends to top-down modulatory influences of the amygdala on reflexive brainstem-mediated responses to fear-related stimuli. In line with this finding, she showed normal SCRs in response to a range of facial expression categories (experiment 1), confirming that compensation also affects autonomic physiological responses.

Assessment of the SNI (33) revealed an impoverished real-life social network in patient 2, whereas patient 1 reported a social network of normal size and complexity (experiment 4). Due to its correlational nature, this finding can be interpreted in two directions. On the one hand, decreased social network scores may result from amygdala damage. In line with this, amygdalectomized monkeys have been shown to become social outcasts (53–55). Recent studies in healthy individuals have extended these observations by demonstrating a positive correlation between amygdala volume and SNI scores (4). Thus, our findings of discrepant SNI scores would support the conclusion that extra-amygdalar compensation in patient 1 has led to more appropriate responses to social signals (including fear) and the establishment of an extensive social network. On the other hand, recognition of facial emotions is an essential component of everyday social interactions and may vary as a function of social network size and complexity. Investigations of neural plasticity after brain injury suggest that compensation is promoted by frequent practice of functions associated with the affected brain region (56). Indeed, improvements in emotion processing deficits after training have been shown (57,58). In line with this, mirror-neuron system activity is modulated by experience (59). Thus, the adaptive compensatory changes in patient 1 might have been contributed to by more frequent social interactions during the early stages of the disease.

Our investigation has several limitations. First, given the lesion emphasis on the basolateral amygdala as documented by the present analysis and previous probabilistic lesion mapping (11), we cannot rule out that there is intact residual tissue in the remaining amygdala subregions, which are characterized by distinct connectivity and neuroreceptor profiles (60,61). However, even the functional integrity of spared amygdalar tissue in these subregions is unlikely to account for our observation of differential behavioral, psychophysiological, and neural fear responses between the twins. Although their amygdala lesions largely overlap, patient 1, but not patient 2, might have developed an intra-amygdalar functional adaptation to pathology in addition to an extra-amygdalar compensation, thus enabling a different connection strength with extra-amygdalar areas involved in functional compensation.

Second, we cannot exclude that different lesion onsets might have contributed to the development of adaptive compensatory changes in only one of the twins. Lipoid proteinosis due to Urbach-Wiethe disease is thought to start early during childhood, initiating a slowly progressing amygdala degeneration over time (62). Brain lesions during childhood superimpose injury on developing neural circuitries, and the onset of the injury, particularly with respect to age and developmentally critical periods, can have substantial impact on plasticity and functional architecture (17).

Third, we cannot rule out the possibility that compensation in patient 1 is related to a cognitive strategy. One such strategy is reflected in findings that deficient fear recognition as a result of amygdala degeneration in LP normalizes if the patient is instructed to fixate the eyes in faces (2,63). It is unlikely, though, that differential fear recognition abilities between the twins are solely rooted in a discrepant attentional gaze to the eyes, as such eye contact-dependent cognitive compensation cannot account for a preserved top-down modulation of brainstem-mediated reflexive responses to nonface stimuli (experiment 3).

Taken together, our findings provide converging evidence for adaptive compensation of focal bilateral amygdala damage, resulting in intact fear recognition, preserved social-emotional modulation of the startle reflex, and a normal-sized social network in patient 1. The observation that key aspects of this functional reorganization appear to involve the cortical mirror-neuron system (see also [64]) suggests that imitation of face expression and empathic responses made by others may have considerably contributed. It remains a challenge for future studies to further characterize the compensatory mechanism(s) and underlying neurocircuitry enabling functional adaptation to amygdala pathology in patient 1.

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Supplementary material cited in this article is available online.

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