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Supplemental Information

The Human Amygdala and the Induction and Experience of Fear

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Supplemental Data

Knowing No Fear

SM's apparent lack of fear, even during fear-provoking situations, raises the question of whether she understands the concept of fear, and whether she knows the meaning of the word "fear." Elsewhere [1,2], we have argued that she does. For example, SM is able to use words such as *fear*, *terror*, *panic*, *afraid*, *scared*, and *frightened* appropriately in conversation. Likewise, when read sentences depicting emotional situations, she is able to tell with 100% accuracy which situations are supposed to evoke fear [3]. She can also recognize fear from body cues [4] and from the prosody of someone's voice [5]. Indeed, her fear recognition deficit seems to be mostly restricted to static images of facial expressions [6] since her recognition abilities appear to be largely normal in response to multi-modal, dynamic stimuli such as film clips. Finally, SM remembers several instances during childhood where she was able to feel fear (see section titled, "Fear in SM's childhood"), suggesting that she understands, at an experiential level, what fear is supposed to feel like.

Given that SM has appropriate knowledge with regard to fear, one might expect her to be acutely aware of her fear-related deficits. In turn, this raises the issue of demand characteristics, and specifically, the extent to which SM's behavior might be due to her desire to conform to our expectations. For multiple reasons, we find it highly unlikely that demand characteristics would explain our findings. Firstly, our specific fear-related hypotheses are never explicitly mentioned to SM. Most of our experiments do not focus exclusively on fear, but rather, have fear items mixed in amongst stimuli related to a variety of other emotions. Likewise, our informed consents mention the overarching goals of advancing our knowledge with regard to general concepts such as *emotion*, *memory*, and *social behavior*, but never specifically state our interest in probing fear. Such a set-up reduces the likelihood that SM is able to predict our hypotheses and alter her behavior accordingly. Secondly, and perhaps most importantly, after over two decades of extensive testing with SM, we have been repeatedly impressed by her lack of insight into her specific fear impairments. For example, she claims to have "no idea" why so many of our experiments involve pictures of faces. In everyday life, she continually finds herself in precarious situations, yet is completely unaware that her lack of fear is often the very reason why she is in these situations. When explicitly asked why we study her, she mentioned her rare condition ("lipoid proteinosis") and that we are interested in understanding how her brain

damage has affected her behavior. When encouraged to elaborate, SM appeared puzzled and was unable to provide an explanation. Thus, SM's profound lack of insight into her own condition mitigates the possibility that our findings are attributable to demand characteristics.

Interview with SM's Son

SM has three children. Her eldest child is in his early twenties. We recently had a chance to interview him about his experiences growing up with SM. With regard to emotions, he commented that SM doesn't seem to have any problems experiencing most emotions, and on occasion "her emotions sometimes get the better of her," especially with regard to emotions like sadness or loneliness. However, with regard to fear, he commented that he could not recall a single instance where he remembers his mom feeling fear or looking like she was scared. He did, however, remember a very vivid instance when he was a child and his mom fearlessly handled a rather large snake. In his own words, "Me and my brothers were playing in the yard and mom was outside sitting on the porch. All of a sudden we see this snake on the road. It was a one lane road, and seriously, it touched from one end of the yard all the way to the other side of the road. I was like, 'Holy cow, that's a big snake!' Well mom just ran over there and picked it up and brought it out of the street, put it in the grass and let it go on its way... She would always tell me how she was scared of snakes and stuff like that, but then all of a sudden she's fearless of them. I thought that was kind of weird."

The Knife Incident

The knife incident occurred when SM was 30 years old and her recollection of the event has remained consistent over the years. We had SM take us to the same location where this knife incident occurred and had her recount the event, step by step. It was approximately ten o'clock at night and completely dark outside as SM was walking home by herself. To her left was a church where she could hear the local choir finishing up their nightly practice, and to her right was a small park where a man was sitting on a bench. There were no other people in the area except for the man, whom SM described as looking "drugged-out." As she walked past the park, the man called out and motioned for her to come over. SM made her way to the park bench. As she got within arm's reach of the man, he suddenly stood up, pulled her down to the bench by her shirt, stuck a knife to her throat, and exclaimed, "I'm going to cut you, bitch!" SM claims that she remained calm, did not panic, and did not feel afraid. In the distance she could hear the church choir singing. She looked at the man and confidently replied, "If you're going to kill me, you're gonna have to go through my God's angels first." The man suddenly let her go. Instead of running away, SM reports "walking" back to her home. On the following day, she walked past the same park again. There were no signs of avoidance behavior and no feelings of fear.

Fear in SM's Childhood

Has SM ever experienced an episode of fear at any point during her adult life? The answer is probably "no." We have had numerous conversations with SM about her past, we have scoured through her personal diary entries, and we have spoken with close family members. In all cases, we were unable to find a single episode in which SM unequivocally experienced fear as an adult. However, as we probed further back in time, remote autobiographical recollections (all occurring

before the age of 10) suggest that SM may have experienced fear as a young child. For example, she recalls being afraid of the dark and seeking shelter in her older sister's bed. She also remembers an incident when she was walking through a cemetery at night and her older brother jumped out from behind a tree and scared her, causing her to run away screaming and crying. Another telling event occurred at the home of her mother's friend, Miss W. While her mother was socializing in another room, SM attempted to pet Miss W's dog, a large Doberman Pinscher. In SM's own words, "All of a sudden it got me in a corner and it started growling at me and it wouldn't let me go. I hollered for my mom. I said, 'Mama! Mama! Mama! Help me Ma!' And every time I tried to holler, the dog would get closer and snarl at me. And Miss W. came into the room and said, 'Don't you move. Don't you move.' And she grabbed ahold of his chain and she said, 'Now slow. Head towards the door. Don't go fast because he'll jump ya. Go slow.' I can remember my gut tightening up. I was afraid to move. I was crying, 'I want to go home!' That's the only time I really felt scared. Like gut-wrenching scared." These examples underscore that SM understands, at an experiential level, what it means to feel fear. Moreover, in this latter example, SM's vivid description suggests that she legitimately experienced a full-blown episode of fear, replete with freezing behavior, a strong urge to withdraw, bodily arousal, visceral responses, emotion-congruent thoughts, and an intense feeling of dread.

The disparity between SM's fear during childhood and her apparent lack of fear during adulthood may be explained by the time course of her amygdala pathology. SM's first brain scan, taken during her early twenties, revealed clear signs of bilateral amygdala calcifications [7]. There is evidence, however, that the calcifications caused by Urbach-Wiethe disease are not entirely congenital, but develop progressively over the course of life, usually beginning in childhood and adolescence [8,9]. In fact, there is a growing consensus that in most patients the intracranial calcifications begin to emerge sometime around 10 years of age [8,10-12]. The last time that SM remembers feeling fear occurred around age 10. This brings forth the possibility that SM's loss of fear happened in tandem with the progressive bilateral degeneration of her amygdala during adolescence.

A Mechanism for SM's Fear Impairment

Once fear is induced, the execution of a fear response is known to depend on hypothalamic nuclei and on nuclei of the brainstem's periaqueductal gray, both of which receive downward projections from amygdala nuclei [13,14]. In the absence of damage to those key regions in SM, her lack of fear indicates that fear-inducing signals which normally activate the amygdala, and which originate in varied sensory and association cortices, have no effective alternative route to reach the hypothalamus and brainstem. Whether such signals result from actual perception of an object or situation, or from recall of memories, the amygdala appears to be a necessary broker in the process. Moreover, in the absence of any induced fear responses, the brain would not receive any signals depicting emotional changes and thus could not generate an experience of fear.

We have suggested that emotions and feelings can be simulated at the cortical level by using an "as-if-body-loop" that bypasses the body, making it unnecessary to generate an actual emotional response [15]. The as-if-body-loop uses memory of the past execution of emotional responses (which can be activated from regions such as the prefrontal cortices) to lead structures such as the insular cortex to adopt a pattern of activity comparable to what would have resulted from

signals hailing from the body via the brainstem and diencephalon. Given that SM has intact cerebral cortices, namely intact prefrontal and insular cortices, why should she not have simulated fear states? The possible answer is that the circuitry required to build up and activate the as-if-body-loop for fear includes the amygdala. In SM, this circuitry would have been damaged since fairly early in life resulting in an especially pervasive defect; the circuitry was not sufficiently exercised and would not have learned how to evoke simulated states of fear. Patients with less extensive amygdala damage [e.g., 16] or with damage acquired during adulthood [e.g., 17] are likely to have experienced many instances of fear and have learned, both cognitively and behaviorally, a comprehensive set of fear manifestations. In these cases, it would be more likely for patients to make use of an as-if-body-loop mechanism for feeling fear, even in the absence of overt fear manifestations.

Finally, SM is able to exhibit and experience other emotions. How are these emotions being induced and subsequently experienced? It is likely that non-fear-related emotions in SM are triggered by brain sites whose projections to the hypothalamus and brainstem remain intact. This is indeed the case for a variety of structures in the prefrontal and anterior cingulate cortices which can project to the hypothalamus and brainstem without an intermediate link in the amygdala [18]. This anatomical arrangement would allow for the induction and execution of non-fear-related emotions in SM and, in a subsequent step, the respective signals of body change would be conveyed to brainstem, diencephalon, insular cortex, and beyond, ultimately leading to a feeling of emotion.

Limitations

The evidence regarding SM's fear impairment is compelling, but our study has several limitations. Firstly, SM's lesion is not entirely selective to the amygdala (see Figure S1), and the findings should thus be qualified to acknowledge that her lack of fear may arise from a combination of extensive damage to the amygdala plus partial damage to surrounding territories including the entorhinal cortex and adjacent white matter. Secondly, the primary focus of our study was on fear, and thus, we can not comment on whether SM's experience of non-fear-related emotions is entirely "normal"; the preliminary findings reported in this study do suggest that SM is capable of triggering and feeling emotions other than fear. Thirdly, SM is a single case, and it will be important to study other comparable cases in order to solidify our findings. There have been a few other accounts, primarily anecdotal, of altered experience of fear following amygdala damage in human subjects [17,19,20]. Although none of these studies probed fear experience in a systematic and comprehensive way, the reports generally paint a picture consistent with ours: damage to the human amygdala diminishes fear. One human lesion study suggested that the amygdala is not essential for the experience of fear [16], but as noted earlier, variables such as the age of lesion onset, etiology, and extent of amygdala damage may account for the differences between findings. Here we provided a set of results that, for two reasons, is more decisive: (1) we tested a patient whose bilateral amygdala lesions are focal and virtually complete, and (2) we utilized a broad battery of tasks extending from the experience sampling method to real-life challenges with fear-inducing stimuli. To our knowledge, no other human lesion study has characterized a patient's fear experience using such a wide range of tasks.

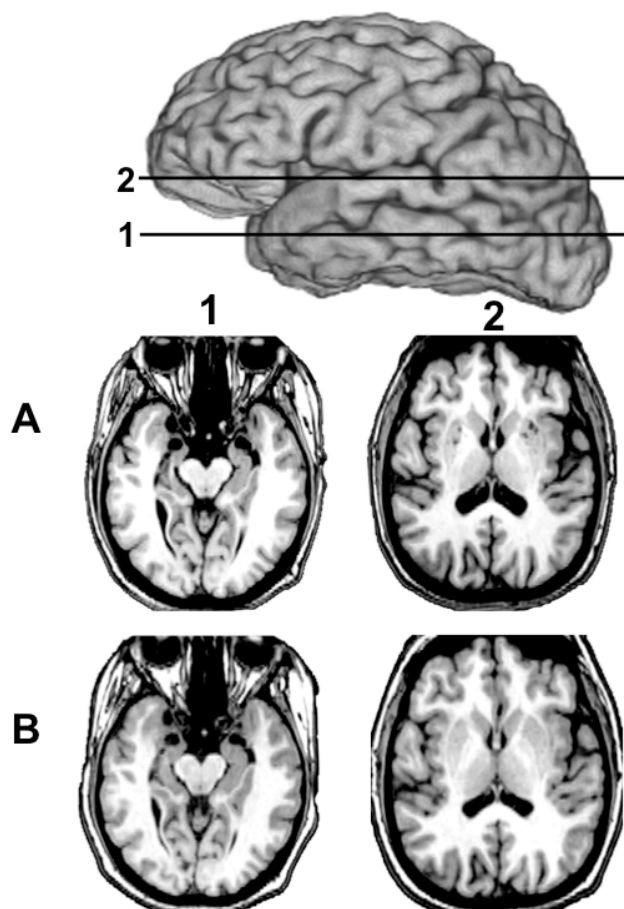


Figure S1. Structural MRI of SM's Brain

Images were acquired at (A) the onset of this study and (B) 10 years earlier. Axial slices (1A and 1B) reveal focal bilateral amygdala lesions caused by calcium deposits due to lipoid proteinosis (also known as Urbach-Wiethe disease), a rare congenital genetic disorder [21-23]. We have previously described SM's brain damage and pointed out that she also has a circumscribed area of damage to white matter in the vicinity of the amygdala and to the anterior entorhinal cortex [1,6]. The hippocampus proper as well as temporal neocortex appear entirely intact, as do other key neural structures related to emotion, namely, both insular cortices, both ventromedial prefrontal cortices, and the hypothalamus and brainstem, notably the periaqueductal gray. Although it is not possible to date the onset of SM's lesions with precision, it is likely that they began in late childhood. We have been studying SM for over two decades and both her lesions and her behavior have been remarkably stable throughout this period. While her behavior is unchanged and while her extensive lesions in the amygdala and the small lesions of the entorhinal cortex remain unchanged as well, an MR scan obtained at the time we conducted the studies reported here revealed additional lesions located in the putamen (slice 2A). These new lesions cannot reasonably account for the fear-processing defects that have been present in SM for the past two decades—the lesions appeared only recently (while SM's fear processing deficits have been extant for decades), and the lesions are not in structures that have ever been associated prominently with fear processing.

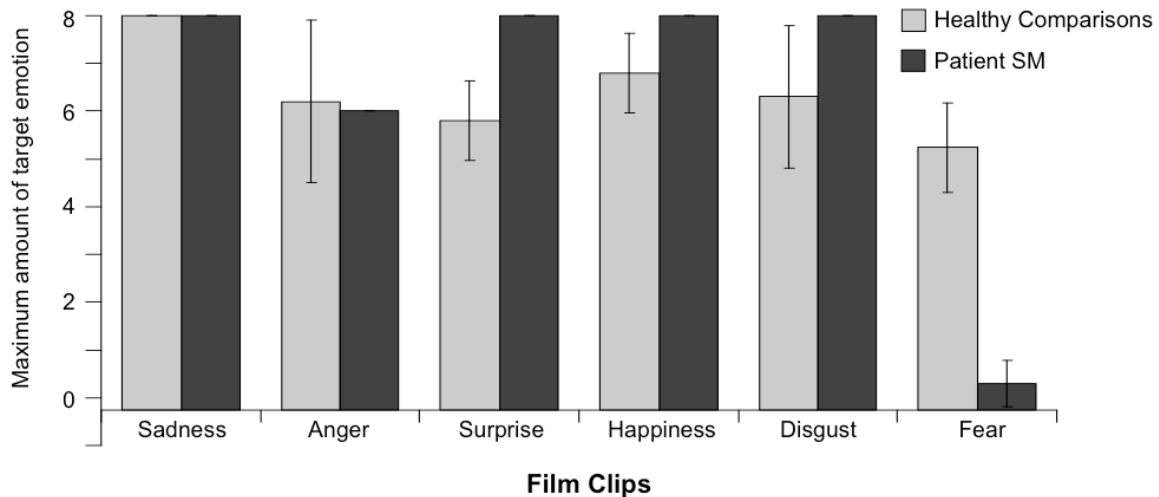


Figure S2. Emotion Induced by Films

Subjective ratings for the maximum amount of emotion induced while watching a series of different emotional film clips. Ratings were provided immediately after viewing each individual film clip using a modified visual analogue scale (VAS) ranging from 0 (no emotion) to 8 (extreme emotion). Comparison data for the sadness, surprise, and happiness films were obtained from five females with no history of neurological or psychiatric illness. Comparison data for the anger and disgust films were derived from a previous study that tested a large sample of healthy participants [24]. The fear scores are an average composite of all the fear films shown in Figure 2. For all of the film clips, many healthy subjects reported experiencing the maximum amount of the target emotion. Due to this ceiling effect, we can not comment on whether SM experiences abnormally high levels of non-fear-related emotions. She does, however, experience abnormally low levels of fear. Descriptions of all film clips can be found in Table S2. Error bars represent the standard deviation.

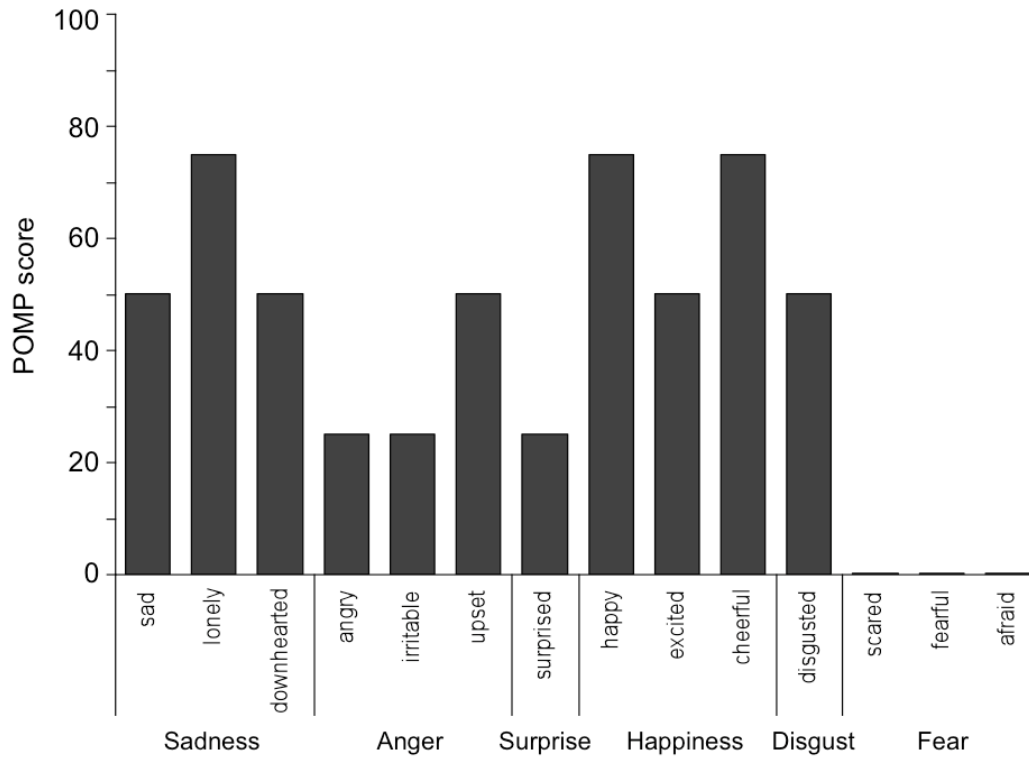


Figure S3. SM’s Experience-Sampling Results

The highest level of each basic emotion reported by SM across 156 trials collected over a 3-month period during the experience sampling study. The x-axis lists the specific emotion terms that were probed. SM never reported experiencing any fear. For all basic emotions other than fear, SM reported numerous instances of experiencing the emotion, with intensity levels varying from “a little” to “quite a bit.” All scores have been converted to POMP units [25] representing the “percent of maximum possible.”

Table S1. Self-Report Questionnaires Probing SM's Experience of Fear

Most of the questionnaires were administered multiple times over a 3-year period. The normative datasets are based on large samples of healthy individuals. All scores are rounded to the nearest tenth. Mean scores are displayed in Figure 3.

Questionnaire	Type of Fear Questions	# Times Completed by SM	Range of Possible Scores	Range of SM's Scores	SM's Average Score	z-Score	Normative Mean (SD)
Fear Survey Schedule II [26]	Probes an individual's level of fear across a range of different objects and situations that commonly evoke fear	2	51 – 357	65 – 69	67.0	-1.1	108.5 (36.8) n=868 [27]
Fear of Negative Evaluation Scale [28]	Measures fear of being evaluated negatively by others	2	0 – 30	4 – 5	4.5	-1.3	15.5 (8.6) n=205 [28]
Social Avoidance and Distress Scale [28]	Measures fear of social situations	1	0 – 28	NA	1.0	-1.0	9.1 (8.0) n=205 [28]
Anxiety Sensitivity Index [29]	Measures fear of experiencing different bodily sensations and feelings	5	0 – 64	4 – 8	6.0	-1.4	19.0 (9.1) n=4,517 [29]
Beck Anxiety Inventory [30]	Measures fear and panic-related symptoms experienced over the prior week	4	0 – 63	2 – 6	4.5	-0.7	12.7 (11.2) n=159 [31]
Albany Panic and Phobia Questionnaire [32]	Has the subject estimate the amount of fear they would experience in different situations	3	0 – 216	5 – 21	13.3	-1.0	48.5 (36.7) n=39 [33]
Fear Questionnaire [34]	Measures the degree of avoidance due to fear	4	0 – 120	2 – 8	4.8	-2.6	46.1 (16.2) n=63 [35]
PANAS-X Fear (general) [36]	Measures how much, in general, a person feels fear-related affective states	2	6 – 30	NA	7.0	-1.1	11.3 (3.8) n=1,657 [36]
PANAS-X Fear (moment) [36] [experience sampling using a computerized emotion diary over a 3-month period]	Measures how much, during the present moment, a person feels fear-related affective states	156	6 – 30	6 – 8	6.1 (SD = 0.3)	-0.8	9.9 (4.5) n=1,027 [36]

Table S2. Description of the Film Clips Shown in Figure 2 (Fear Films A-J) and Figure S2

<u>Title</u>	<u>Length</u>	<u>Brief Description</u>
A – <i>The Ring</i>	6:29	The ghost of a murdered child infiltrates the lives of her soon-to-be victims
B – <i>Blair Witch Project</i>	2:44	Campers are attacked by an unknown apparition during the middle of the night
C – <i>CSI</i>	3:14	A man struggles to survive after being buried alive
D – <i>The English Patient</i>	1:16	A man is tortured by the Germans during World War 2
E – <i>Seven</i>	1:21	A mutilated man awakes from the dead
F – <i>Cry Freedom</i>	1:08	Armed trespassers attack a woman who is home alone during the night
G – <i>Arachnophobia</i>	0:46	A large poisonous spider attacks a girl in the shower
H – <i>Halloween</i>	1:44	A woman is being chased by a murderer
I – <i>The Shining</i>	1:22	A young boy hears voices in the hallway of a haunted hotel
J – <i>Silence of the Lambs</i>	3:29	A female FBI agent tries to capture a twisted serial killer who is hiding in a dark basement
<hr/>		
Sadness – <i>Faces of Death</i>	1:32	Real footage of starving adults and children in third-world countries
Anger – <i>Cry Freedom</i>	2:36	A large group of innocent children and teenagers are shot and killed by an army of soldiers
Surprise – <i>internet video</i>	0:18	A pizza delivery man walking across the street is suddenly hit by a car
Happiness – <i>America's Funniest Home Videos</i>	2:46	A collage of funny scenes involving babies and small children laughing
Disgust – <i>Pink Flamingos</i>	0:30	A large transvestite eats dog feces

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