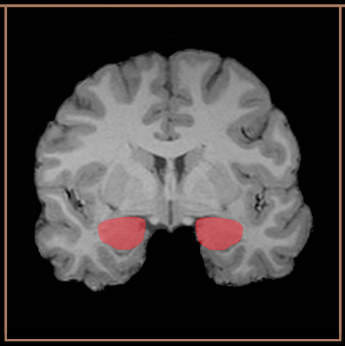
LIVING WITHOUT AN AMYGDALA



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THE GUILFORD PRESS
New York London

A Division of Guilford Publications, Inc.
370 Seventh Avenue, Suite 1200, New York, NY 10001
www.guilford.com

Printed in the United States of America

This book is printed on acid-free paper.

Last digit is print number: 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data
is available from the publisher.

ISBN 978-1-4625-2594-2 (hardcover)

CHAPTER 1

A Tale of Survival from the World of Patient S. M.

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Patient S. M. is one of the most renowned lesion cases in the history of neuropsychology. Her focal bilateral amygdala damage has led to a host of behavioral impairments that have been well-documented across dozens of research publications. This chapter provides an overview of S. M.'s seminal contributions to the study of brain–behavior relationships, with an emphasis on the role of the human amygdala in the emotion of fear. For the first time, we also provide a detailed exploration of the real-world ramifications of living life without an amygdala. For S. M., the consequences have been severe. Her behavioral deficits and impoverished experience of fear repeatedly lead her back to the very situations she should be avoiding, highlighting the amygdala's indispensable role in promoting survival by compelling the organism away from danger in the external world. In stark contrast, threats arising from the internal world of S. M.'s body are capable of inducing a primal state of fear and panic, even in the absence of a functioning amygdala. The unique case of S. M. reveals that the brain contains specialized circuits for fear and multiple fear pathways, notably, an interoceptive pathway that bypasses the amygdala and an exteroceptive pathway that requires the amygdala. So much of the extant neuroscience research investigating fear has focused almost exclusively on the exteroceptive pathway. If there is one final lesson that S. M. can teach the world, it is that we need to refocus our efforts toward exploring the relatively uncharted terrain of interoceptive fear.

The year was 1968 and the world was in a state of pandemonium. Amid the chaos of wars, protests, and assassinations, a young psychiatrist by the name of Arthur Kling began a series of experiments that had never

been tried before, and to this day have never been tried again. The aim was simple: Capture a group of wild monkeys, surgically remove their amygdalae, release them back into the wild, and see if they could survive. In the first experiment (Dicks, Myers, & Kling, 1969), the investigators studied a group of rhesus monkeys on Cayo Santiago, a small island just off the coast of Puerto Rico. Upon their return to the wild, the amygdalectomized monkeys were quickly alienated from their social group, often times attacked and chased into the ocean by the other monkeys. Within 2 weeks, all of the older amygdalectomized monkeys were found dead, either from starvation, attack wounds, or having drowned in the ocean. It was concluded that the amygdalectomized monkeys "appear retarded in their ability to foresee and avoid dangerous confrontations. . . . they are vulnerable to attack and unable to compete for food" (p. 71). Meanwhile, on the other side of the world, Kling carried out another experiment (Kling, Lancaster, & Benitone, 1970), this time in wild vervet monkeys living along the Zambezi River in Africa, only a few miles upstream from the great Victoria Falls. Once released, the amygdalectomized monkeys immediately isolated themselves from the other monkeys by hiding in the low brush or climbing to the high branches of a nearby tree. Despite an abundance of natural food and water nearby, the monkeys were never observed eating or drinking. Within 7 hours, all of the amygdalectomized monkeys were literally lost in the wild, never to be seen again. Years later, Dr. Kling speculated that the amygdalectomized monkeys "had been taken by predators" (Kling, 1986). Both field experiments were over almost as soon as they began. The answer was clear: Living without an amygdala does not bode well for survival.

Around the same time that Dr. Kling's team of observers had given up hope of ever finding the missing amygdalectomized monkeys, an experiment of nature was already under way in America. No monkeys would be required this time, however, since this new experiment was being carried out in a living human being. There would also be no need for any invasive brain surgeries. Instead, the amygdala was naturally and selectively damaged by an extremely rare genetic mutation. The damage would take many years and even decades to unfold. In the winter of 1968, as Dr. Kling was scouring through the forests of Zambia for signs of survival, a young girl who would become known to the world as "Patient S. M." was celebrating her third birthday. Little did S. M. know at the time, but her life would soon be catapulted into a trajectory akin to that of Dr. Kling's amygdalectomized monkeys. A key difference is that somehow, someway, S. M. has managed to stay alive, and in 2015 she celebrated her 50th birthday. This chapter provides a rare glimpse into the life of S. M. and her half-century struggle for survival.

The Case of Patient S. M.

Shortly after birth, the doctors could tell something was amiss. Whereas most babies have no trouble screaming and crying, S. M. could barely emit a muffled whimper. Doctors soon discovered abnormal thickening of the tissue around her vocal cords, as well as characteristic lesions on her skin, leading them to an eventual diagnosis of a rare autosomal recessive genetic condition known as Urbach–Wiethe disease (UWD) or lipoid proteinosis (Hofer, 1973). The rarity of this genetic condition cannot be overstated, as there have only been several hundred reported cases, worldwide, over the past century. S. M.'s genetic diagnosis was officially confirmed by Dr. Wolfram Kunz at the University of Bonn, who sequenced S. M.'s DNA and found a single nucleotide deletion in exon 6 of the gene encoding her extracellular matrix protein 1 (*ECM1*). Her particular genetic mutation (a homozygous 507delT/507delT) predicts a more severe clinical phenotype (Hamada et al., 2003) and, indeed, S. M.'s condition is more severe than most other patients with UWD (see van Honk, Terburg, Thornton, Stein, & Morgan, Chapter 12, and Patin & Hurlemann, Chapter 11, this volume). Hoarseness of voice is one of the disease's cardinal symptoms, and S. M. has spent the bulk of her life being alienated and belittled by her peers for sounding so different. She also has to undergo laser surgery several times a year to ensure that the buildup of hyaline deposits around her vocal cords and throat does not obstruct her airway. The condition has also affected her skin, causing excessive scarring and a waxy appearance that makes her look much older than her actual age. S. M. finds this aspect of her condition to be particularly upsetting and openly admits that her rapidly aging skin has taken a toll on her self-esteem and makes her feel unattractive. In recent years, her overall state of health has been deteriorating, and it appears that her disease is progressing more rapidly as she ages, infiltrating her tongue, gums, teeth, lips, eyelids, tear ducts, and uterus, and causing a host of complications, some of which we discuss later on.

Beyond these widespread systemic effects on S. M.'s body, the disease has also spread into her brain. In one of the most perplexing medical mysteries of our time, mutations in the *ECM1* gene can lead to calcifications that infiltrate the brain and selectively destroy the amygdala, bilaterally, while leaving the rest of the brain largely unaffected. And while there have been some isolated case reports of patients with damage to other brain regions, the disease's predilection for calcifying the amygdala is striking. This is precisely what happened to S. M., who has one of the most complete amygdala lesions ever reported with UWD (Figure 1.1; see Adolphs, Chapter 10, this volume).

On November 7, 1986, Dr. Daniel Tranel met S. M. for the very first time when a neurologist referred her to the Benton Neuropsychology

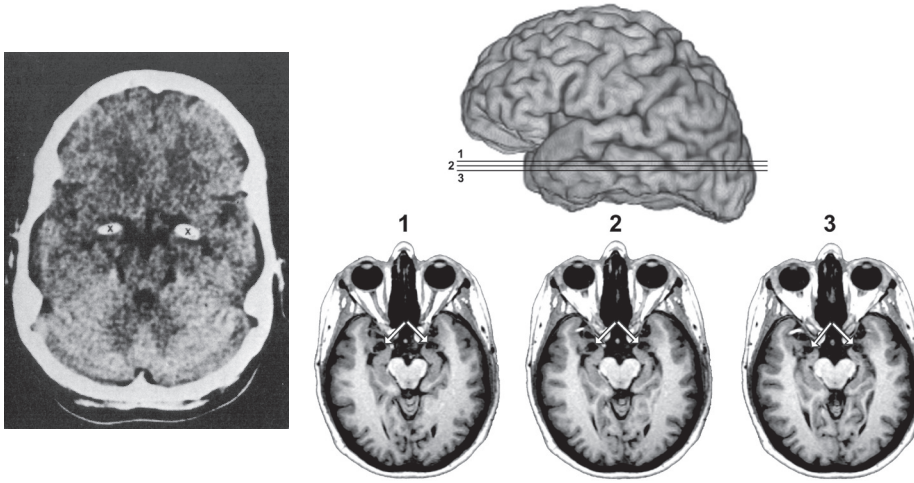

FIGURE 1.1. S. M.'s brain. On the left is the original computed tomography (CT) scan of S. M.'s brain, taken in 1986, when she was 20 years old. By this point in life, her amygdala lesions were clearly present, as evidenced by the bilateral bean-shaped hyperdense signals (X marks the spots). Over 20 years later, much more detailed magnetic resonance imaging (MRI) scans of S. M.'s brain reveal circumscribed bilateral amygdala lesions appearing as vacant black holes underneath the white arrows. The lesions affect not only gray matter in the local vicinity but also fibers of passage and tissue immediately adjacent to the amygdala, including the anterior entorhinal cortex. Both the hippocampus and parts of the extended amygdala (e.g., bed nucleus of the stria terminalis) appear to be intact. Other key neural structures related to emotion also appear to be intact, including the insular cortices, the ventromedial prefrontal cortices, and the hypothalamus and brainstem (including the periaqueductal gray).

Clinic at the University of Iowa. She was 20 years old, and what started as a simple neuropsychological evaluation quickly turned into a lifelong project. S. M. was subsequently inducted into the Iowa Neurological Patient Registry established at the University of Iowa by Drs. Antonio and Hanna Damasio. The registry has now accrued over 3,000 lesion patients, but at the time of her induction, S. M. was patient number 46.

After viewing S. M.'s first brain scan (Figure 1.1), it was evident that her focal and symmetrical amygdala lesions were unlike anything that had been seen before. It was not uncommon to test patients with unilateral amygdala lesions stemming from stroke or neurosurgical resection. On rare occasions, we might test a patient with bilateral amygdala lesions secondary to herpes simplex encephalitis, but their damage would invariably impact other brain structures outside of the amygdala. S. M.

was the first patient we had ever met with bilateral amygdala lesions that appeared to be largely confined to the amygdala.

Dr. Tranel immediately began testing S. M. to illuminate the impairments that could arise from such a circumscribed lesion. The results of her initial neuroimaging and neuropsychological tests were published a few years later (Tranel & Hyman, 1990), in what would be the first in a long line of S. M.-related publications. Hundreds of experiments over the course of nearly three decades of testing have made S. M. one of the best-characterized neuropsychological case studies of all time. The corpus of research built around S. M. has led to a host of discoveries across a broad range of domains (Table 1.1). The implications of this body of work have been far-reaching, impacting not just the fields of neuropsychology and neuroscience, but also philosophy, sociology, law, economics, and anthropology. And of perhaps greatest importance, the field of psychiatry has benefited immensely from this research as the case of S. M. has contributed important clues about the etiology of a number of different conditions, especially along the spectrums of anxiety and autism.

For more details about published research on S. M., the reader is pointed to several review chapters that have been written on this topic (Adolphs & Tranel, 2000; Adolphs & Tranel, 2004; Buchanan, Tranel, & Adolphs, 2009; see Adolphs, Chapter 10, this volume). Two of these chapters (Adolphs & Tranel, 2000; Buchanan et al., 2009) also contain detailed descriptions of S. M.'s neuropsychological profile, which has remained generally stable over the years, and in line with expectations given her educational and occupational background. Most of her test performances are within the normal range on standardized measures of IQ, memory, language, and perception, with some noted weaknesses on tests tapping nonverbal visual memory and phonemic fluency. In recent years, we have found signs of decline in her verbal memory, but not yet near the scope or severity that would be indicative of dementia. Overall, her cognitive functioning remains relatively preserved, and she continues to live independently. In terms of occupational functioning, S. M. has spent the majority of her adult life unemployed and surviving off of government assistance in the form of monthly disability checks. The only exception was a 3-year period during the late 1990s when S. M. worked as a security guard, a job she specifically chose as part of a welfare-to-work program. She claims to have enjoyed working as a security guard but was laid off when her employer closed down the building where she worked.

The case of S. M. provides a compelling example of the functional consequences of living life without an amygdala. The other chapters in this book highlight additional cases with bilateral amygdala damage, providing the most comprehensive picture to date of the various behavioral manifestations that can develop following focal disruption to the core

TABLE 1.1. A List of Peer-Reviewed Publications That Tested Patient S. M.

Domain	Authors (year)	Journal	Citations
Background assessment	Tranel & Hyman (1990)	*Archives of Neurology*	228
	Boes et al. (2011)	*Social Cognitive and Affective Neuroscience*	7
Emotion recognition	Adolphs et al. (1994)	*Nature*	2,103
	Adolphs et al. (1995)	*Journal of Neuroscience*	1,169
	Adolphs et al. (1999b)	*Neuropsychologia*	812
	Adolphs & Tranel (1999)	*Neuropsychologia*	181
	Adolphs et al. (2005a)	*Nature*	1,000
	Atkinson et al. (2007)	*Neuropsychologia*	59
	Gosselin et al. (2007)	*Neuropsychologia*	148
	Spezio et al. (2007)	*Journal of Neuroscience*	142
	Tsuchiya et al. (2009)	*Nature Neuroscience*	137
Emotional memory	Adolphs et al. (1997)	*Learning and Memory*	411
	Adolphs et al. (2005b)	*Nature Neuroscience*	227
	Bechara et al. (1995)	*Science*	1,318
	Bechara et al. (2003)	*Annals of the New York Academy of Sciences*	450
Emotional experience and arousal	Adolphs et al. (1999a)	*Psychological Science*	238
	Feinstein et al. (2011)	*Current Biology*	156
	Feinstein et al. (2013)	*Nature Neuroscience*	79
	Glascher & Adolphs (2003)	*Journal of Neuroscience*	309
	Tranel et al. (2006)	*Cognitive Neuropsychiatry*	69
Neuroeconomics and decision making	Bechara et al. (1999)	*Journal of Neuroscience*	1,640
	De Martino et al. (2010)	*Proceedings of the National Academy of Sciences USA*	178
	Hampton et al. (2007)	*Neuron*	68
	Shiv et al. (2005)	*Psychological Science*	394
Social cognition and behavior	Adolphs et al. (1998)	*Nature*	1,238
	Adolphs et al. (2002)	*Journal of Cognitive Neuroscience*	449
	Birmingham et al. (2011)	*Social Neuroscience*	18
	Heberlein & Adolphs (2004)	*Proceedings of the National Academy of Sciences USA*	137
	Kennedy & Adolphs (2010)	*Neuropsychologia*	49
	Kennedy et al. (2009)	*Nature Neuroscience*	171
	Paul et al. (2010)	*Journal of Neurodevelopmental Disorders*	38
	Wang et al. (2015)	*Social Cognitive and Affective Neuroscience*	8

Note. The studies are broken down into the different domains that were tested. The number of citations was calculated in December of 2015, using *Google Scholar*.

circuitry of the amygdala. When comparing different cases, it is important to recognize that a multitude of factors can fundamentally alter the behavioral manifestations of a lesion, including the etiology and developmental time course of the lesion, the extent of damage, the brain's compensation following the damage, and the unique personality and set of life experiences of each individual lesion case (see Adolphs, Chapter 10, and Patin & Hurlemann, Chapter 11, this volume). S. M.'s amygdala lesion is developmental in nature, likely emerging around the age of 10 and slowly progressing over the course of adolescence and adulthood (Feinstein, Adolphs, Damasio, & Tranel, 2011). Due to the critical involvement of the amygdala in emotional learning, the behavioral presentation of a developmental lesion may differ from that of an adult-onset lesion (Bechara, Damasio, & Damasio, 2003; Hamann et al., 1996), and this certainly appears to be the case for S. M. (e.g., see Figure 1.2). Even when directly comparing S. M. to other developmental lesion cases with the same etiology, there may still be fundamental behavioral differences related to the greater extent of amygdala damage found in S. M.'s brain (see Van Honk et al., Chapter 12, this volume). The borders of S. M.'s lesion appear to extend slightly beyond the amygdala, encroaching on tissue in the anterior entorhinal cortex and adjacent white matter, and in recent years, there is emerging evidence of small additional lesions outside of the medial temporal lobe (Feinstein et al., 2011). It is also worth reiterating that the lesion likely includes fibers of passage within the amygdala—in this respect, when compared to nonhuman animals, S. M.'s lesion is more comparable to aspiration-type lesions rather than ibotenic acid lesions (Meunier, Bachevalier, Murray, Málková, & Mishkin, 1999). The severity of her lesion presentation is consistent with the severity of her clinical phenotype, and both of these factors are likely playing a role in S. M.'s unique behavioral presentation. As previously discussed, UWD is a systemic condition, and it is plausible that certain somatic symptoms (e.g., hoarseness of voice and aging skin) may have affected S. M.'s social behavior independently of her amygdala damage. These points notwithstanding, rare lesion patients, such as S. M., offer the opportunity to elucidate the "neurobiological" definition of concepts such as emotion, fear, and psychiatric disease. This book and its fascinating collection of lesion cases provide an invaluable road map for deciphering the critical behavioral functions of the amygdala.

Exteroceptive Fear

When it comes to survival, no other emotion is as imperative as fear. Across humanity, fear is universally recognized and experienced, and across the animal kingdom, fear-like behaviors such as freezing and withdrawal are

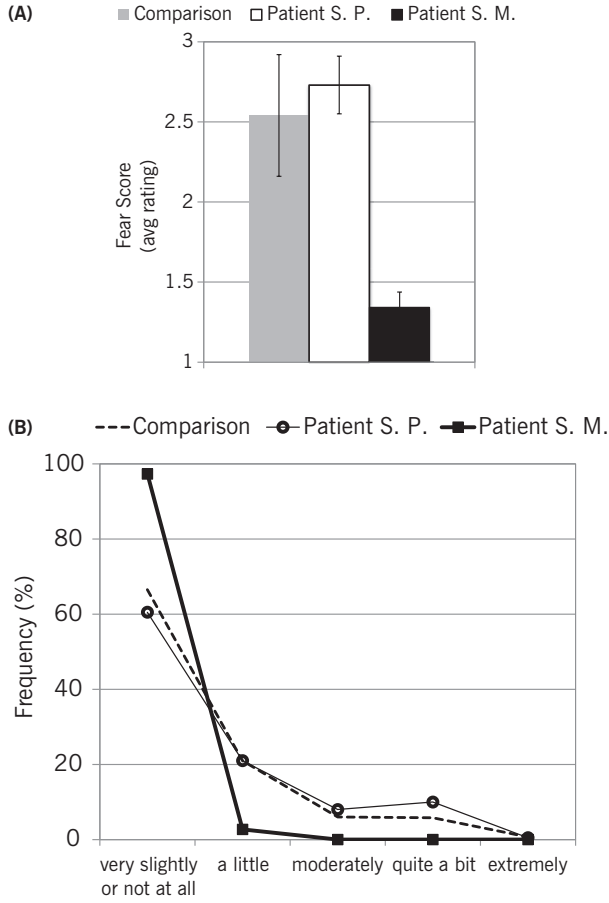

FIGURE 1.2. Fear following developmental versus adult-onset bilateral amygdala damage. S. M. (developmental lesion) reported experiencing considerably less fear than patient S. P. (adult-onset lesion), a woman with bilateral amygdala lesions stemming from a right medial temporal lobectomy (at the age of 48), along with reactive gliosis of unknown extent in her left amygdala (see Todd, Anderson, & Phelps, Chapter 13, this volume). Both patients completed state and trait versions of the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). Data for S. P. and 20 healthy comparison participants were reported in Anderson and Phelps (2002), in which a "fear score" was computed using five PANAS items (afraid, scared, nervous, jittery, and distressed). We computed the same fear score for S. M. (A) Trait fear: Mean trait fear in S. M. and S. P. on a scale ranging from 1 ("very slightly or not at all") to 5 ("extremely"). Means were derived by averaging the scores across multiple administrations of the trait version of the PANAS; S. M. completed seven administrations over a 3-year period, and S. P. completed three administrations over a 1-year period. All error bars represent the standard error of the mean. (B) State fear: Frequency distribution of state fear ratings in S. M. and S. P., reflecting how often each patient reported experiencing different magnitudes of the five fear-related items on the PANAS. S. M. completed the state version of the PANAS multiple times a day over a 3-month period, and S. P. completed it daily over a 30-day period.

ubiquitous (Anderson & Adolphs, 2014). Consequently, fear is the most extensively studied emotion in all of science, and the field of neuroscience is no exception (Adolphs, 2013; Feinstein, 2013). In this regard, one of S. M.'s most seminal contributions has been the remarkable selectivity of her emotional deficits to the realm of "exteroceptive fear," which encompasses all manner of environmental threats conveyed to the brain via the *external senses* of vision, hearing, smell, and touch.

The first discovery came in 1994, when we found that S. M. was unable to recognize the emotion of fear in another person's face (Adolphs, Tranel, Damsio, & Damasio, 1994, 1995; Adolphs et al., 1999b). In contrast, her recognition of other facial expressions was generally intact, with the exception of some difficulty recognizing surprise, an emotion that contains many of the same facial features as fear. Control tests showed that S. M.'s profound impairment in the realm of fear recognition could not be accounted for by a basic perceptual impairment (e.g., she is able to accurately discriminate and recognize the identity of faces) or conceptual impairment (e.g., she understands the concept of fear and has intact knowledge of what the word "fear" means; Adolphs et al., 1994, 1995; Feinstein et al., 2011). Follow-up experiments revealed that a major reason for S. M.'s difficulty in recognizing fear in faces is because she fails to orient her attention to the eyes, which in the case of fear are opened wide with upper eyelids raised— the telltale sign that a person is scared (Adolphs et al., 2005a). Interestingly, S. M.'s fear recognition deficit extends into the social domain, where she is severely impaired at judging the approachability and trustworthiness of other people, often rating the most unsavory characters as both approachable and trustworthy (Adolphs, Tranel, & Damasio, 1998). S. M. also has no sense of personal space and feels no discomfort or unease when other people are standing in close proximity, even during the highly awkward situation of standing nose-to-nose with a total stranger (Kennedy, Gläscher, Tyszka, & Adolphs, 2009). Consistent with lesion work in nonhuman animals, S. M. has a severe impairment in fear conditioning through both visual and auditory channels (Bechara et al., 1995). In contrast, she is able to mount a normal skin conductance response (SCR) to unconditioned stimuli, such as a 100 decibel boat horn (Bechara et al., 1995). On the Iowa Gambling Task, S. M. failed to generate anticipatory SCRs prior to making disadvantageous choices, and she also failed to generate SCRs in response to monetary rewards and punishments (Bechara, Damasio, Damasio, & Lee, 1999), a finding that may partially explain her notable lack of loss aversion when making monetary gambles (De Martino, Camerer, & Adolphs, 2010). Taken together, these studies suggest that S. M. has great difficulty accurately recognizing and processing exteroceptive information that is conducive to survival. She also appears to be impaired in generating the appropriate response to this exteroceptive information, irrespective of whether the response is

physiological (e.g., a conditioned SCR), cognitive (e.g., judging the trustworthiness of a person), or behavioral (e.g., regulating interpersonal distance).

Given S. M.'s diverse array of fear-related deficits detected in the laboratory, we became very interested in learning about how such deficits might manifest in the real world. In 2003, we started an in-depth case study of S. M. that lasted for the better part of a decade. Beyond just exploring her behavior in everyday life, we were also intrigued by the prospect of assessing her emotional experience (Tranel, Gullickson, Koch, & Adolphs, 2006). In particular, we wanted to know whether her amygdala damage had in some way impaired her ability to feel fear. While lesion studies in nonhuman animals have been largely confined to the examination of "threat-induced defensive reactions" (LeDoux, 2013), S. M. provided the unique opportunity to examine fear as a conscious emotional experience. This was an exciting new avenue of research, but it came with a host of challenges. "Feelings," by definition, are subjective, and hidden within the vaults of consciousness. There are no objective indices that can definitively reveal the content of another person's conscious experience of emotion, and currently the only way to validly and reliably determine how someone is feeling is by asking them (Barrett, 2004; Watson, 2000). Unfortunately, self-report has its own set of limitations, the least of which are the inherent demand characteristics of the experiment and the possibility that a person is not accurately portraying how he or she really feels. To date, there have only been two other studies that attempted to measure the subjective experience of emotion in patients with amygdala damage (Sprengelmeyer et al., 1999; Anderson & Phelps, 2002). Both studies relied on a single self-report questionnaire for assessing fear (e.g., Figure 1.2), and neither study directly exposed the patient to any fear-inducing stimuli.

From the outset, we decided to take a more comprehensive and systematic approach to answering the question as to whether or not S. M. was capable of feeling fear (Figure 1.3). Instead of relying on a single measure of self-report, we had S. M. complete a battery of eight different fear measures, multiple times over the course of several years, with questions probing a wide range of different fear experiences from both a state and trait perspective. We also used experience sampling to capture S. M.'s emotional experience in real time as it unfolded in her natural environment. S. M. was provided with a small handheld computer that she took with her everywhere she went over the course of a 3-month period. At three random times each day, an alarm in the computer would ring, prompting S. M. to rate her current emotional state across a set of 50 different emotion terms, covering a whole spectrum of different emotional experiences, including fear. In order to mitigate the risks of relying solely on self-report, we also collected detailed behavioral observations while

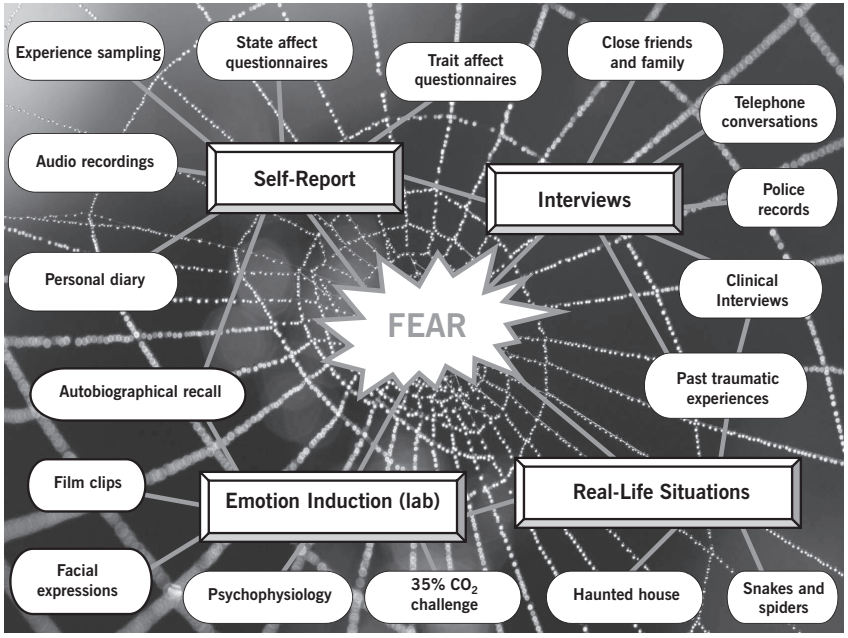

FIGURE 1.3. Assessing the tangled web of fear in S. M. There are a multitude of methods for assessing the expression and experience of fear, both inside and outside the laboratory. This diagram provides an overview of the various methods we utilized in our case study of S. M. Rather than viewing any single method as being conclusive in and of itself, we looked for consistency across methods. This comprehensive approach allows for a more fine-grained analysis of how fear is expressed and experienced in different contexts and time frames, while greatly enhancing the overall ecological validity.

directly exposing S. M. to realistic and ecologically valid inducers of fear, including 10 different horror films, real live snakes and tarantulas, and a world-famous haunted house. Finally, we spent many hours querying S. M. about her past, searching for any experiences that may have induced fear. We also scoured through her personal diary, spoke with close friends and family members, and examined police records. In 2011, the results from this in-depth case study were published in *Current Biology* (Feinstein et al., 2011).

Across the wide range of different tasks and approaches, S. M. consistently experienced a marked absence of fear, even when directly exposed to fear-provoking stimuli. The large selection of horror films all failed to induce fear, yet S. M. had no difficulty expressing or experiencing a range of other emotions when viewing a different set of films, including sadness, happiness, anger, disgust, and surprise. More than just a loss of fear, her

behavior was conspicuously lacking in avoidance, and instead featured an excess of exploratory approach. For example, at the haunted house, S. M. voluntarily anointed herself the leader of our group, excitedly guiding five strangers and two researchers down dark hallways and into scare traps. S. M. would continually run ahead of the group, yelling, "This way guys, follow me!" as she summoned us with a wave of her arm before jetting down another dark passageway. The whole experience felt as if we were being led into battle. Yet, if this were a real battle, our group would not have survived very long. There was no caution or hesitation in S. M.'s approach. She always seemed to take the most direct path into harm's way. When an elaborately dressed actor would suddenly appear from behind a wall to scare us, the rest of the group would jump backwards and scream. S. M. never screamed. She never jumped backwards. She never flinched. The repeated attempts at scaring her all failed, and with the exception of a very loud explosion, she was never startled either. Instead, she would gaze with amusement at the monstrous creatures, smiling or laughing at them, and in one instance, even scaring an actor dressed as Hellraiser when she poked him in the head because she was "curious" as to what the mask would feel like. Throughout the haunted house, she explicitly denied feeling any fear, but did report a high level of excitement and enthusiasm on par with how she remembered feeling while riding a rollercoaster. S. M. has also told us, on a number of occasions, that she really wants to try skydiving. While these observations insinuate a high-level of "sensation seeking," it is worth noting that in everyday life S. M. rarely engages in purposeful risk-taking behavior, perhaps due to her inability to afford such activities.

Based on the results from the case study (Feinstein et al., 2011), it became apparent that S. M.'s experience of fear was lacking. During the 3-months of experience sampling, she rated all of the fear terms at the lowest possible level. Likewise, she reported an impoverished experience of fear across the entire battery of fear measures. In contrast to her paucity of fear as an adult, S. M. remembers experiencing several fearful incidents as a young child, all occurring before the age of 10 and likely before the onset of her amygdala damage (Feinstein et al., 2011). One incident involved a large and vicious Doberman pinscher that trapped her in a corner and caused her to feel "gut-wrenching scared," suggesting that S. M. understands, at an experiential level, what fear is supposed to feel like. As an adult, S. M. denies experiencing any intense states of fear despite the fact that she has faced numerous situations that would be considered fear-inducing or even traumatic in nature. It is evident that she has great difficulty detecting looming threats in her environment and learning to avoid dangerous situations, features of her behavior that have in all likelihood contributed to her high incidence of life-threatening encounters.

Quite strikingly, during the aftermath of a traumatic event, S. M. reports no signs of avoidance, hyperarousal, or emotional reexperiencing. Indeed, S. M. appears to be largely immune to the devastating effects of posttraumatic stress. Interestingly, a group of war veterans who survived penetrating brain injuries during battle that damaged their amygdalae also failed to develop posttraumatic stress disorder (PTSD; Koenigs et al., 2008). Without fear, S. M.'s distress lacks the deep heartfelt intensity endured by most survivors of trauma. Such an interpretation is consistent with a previous study (Tranel et al., 2006), in which two experienced clinical psychologists interviewed S. M. without having any knowledge of her condition. To the psychologists, S. M. came across as a "survivor," as being "resilient" and even "heroic" in the way that she has dealt with adversity in her life. Taken together, these findings suggest that the amygdala is a critical site for triggering a state of fear when an individual encounters threatening stimuli in the external environment. Many different cognitive, autonomic, and behavioral changes comprise a state of fear, and the induction of such a state is required in order to experience a feeling of fear. Thus, we view S. M.'s lack of experienced fear as a direct consequence of her failure to mount a normal fear response to external threats.

Survival in "the Wild"

Far from the fringing forests of Zambia and the ocean shores of Cayo Santiago lies the American Midwest, where S. M. was born and raised, and where she lives to this very day. While certainly not *wild* in the traditional sense of the word, S. M.'s environment has been challenging, to say the least. Given her striking deficits in the realm of exteroceptive fear, we have often wondered how S. M. has managed to survive, especially in light of the fact that she has spent her entire adult life living on her own. When Dr. Kling's amygdalectomized monkeys were let back into the wild, it was only a matter of days, and sometimes weeks, before they met their demise, often related to starvation, social abandonment, assault, or being attacked by a predator (Dicks et al., 1969; Kling et al., 1970). As it turns out, S. M. has faced her fair share of all these predicaments. Below, we discuss each of these situations in more detail. The details were gathered over the course of hundreds of hours of observation and conversation with S. M. across a range of different contexts, including the laboratory, her home, and over the phone.

Food and Money

Living in a poor area of the country and sustaining herself with government assistance, S. M. has repeatedly found herself in need of food.

Interestingly, these dry periods fail to trigger the sort of desperation that one might expect. In a manner reminiscent of amygdalectomized monkeys, S. M. does not seem very motivated to find food during times of hunger, adding further support to the notion that the amygdala plays an important role in the regulation of feeding behavior (Cai, Haubensak, Anthony, & Anderson, 2014). In this context, it is important to emphasize that she is by no means anorexic, and she will gladly eat food if it is easily accessible. However, her food preferences are rather discriminative, mostly limited to sugary treats (e.g., chocolate and artificially sweetened juices and soda) and foods that can be easily chewed and swallowed (e.g., pasta and mashed potatoes). Her lack of motivation for food is primarily evident during those times when she is out of food *and* out of money. During these dry periods, she has gone entire days without eating, and typically only asks for assistance once her hunger has reached rather extreme levels. What's more, many of these episodes of hunger could have easily been prevented had she made wiser decisions on how she spent her money, a likely consequence of her deficit in loss aversion (De Martino et al., 2010). For S. M., money comes and goes very quickly, with little forethought about the consequences. Left on her own, S. M. will habitually spend her money on frivolous items that are clearly not necessary for survival. For example, one month, with only a few dollars remaining, S. M. decided to purchase a "ring back" tone for her phone, an entirely useless feature that allows the caller to hear a song being played instead of the traditional ring tone. Similarly, S. M. will often buy very expensive food for her pets, even at the expense of not being able to eat herself. It is evident that S. M. does not have a good conceptual understanding about the value of money, and despite repeated attempts, she appears incapable of spending her money wisely, perhaps a by-product of her disturbed circuitry in the ventromedial prefrontal cortex (Boes et al., 2011; Hampton, Adolphs, Tyszka, & O'Doherty, 2007). In order to help remedy her repeated financial dilemmas, we have now requested that a payee help manage all of her money. For the most part, this new arrangement has succeeded in ensuring that S. M. always has money available to buy food. Sadly, without this extra help, starvation would not have been outside the realm of possibility.

Social Relationships and Prosocial Behavior

S. M. has never been able to maintain a long-term relationship, intimate or otherwise, and this includes members of her own family. She raised three children as a single mother, but rarely speaks to any of her children (all of whom are now adults). Her first child was conceived at the age of 18 with her first sexual partner, a man who quickly abandoned S. M. as soon as he discovered she was pregnant. In her early 20s, S. M. had an

unstable relationship with an abusive man who was the biological father of her other two children, and who left her while she was pregnant with her last child. In her mid-20s, she was married to a man for less than a year, a marriage that ended in a divorce following a harrowing incident (described later in the chapter). Since the divorce, S. M. has not been in any other serious romantic relationships.

Part of S. M.'s difficulty in maintaining a long-term relationship stems from her overly trusting nature and lack of interpersonal space (Adolphs et al., 1998; Kennedy et al., 2009), leaving her unable to discern when someone is trying to take advantage of her and unable to understand the social etiquette of how to build a relationship slowly over time. Another part stems from S. M.'s personality and her "tendency to be somewhat coquettish and disinhibited" during social interactions (Tranel & Hyman, 1990). For example, during conversations S. M. has a tendency to speak in hypersexual undertones, which can leave the uninitiated feeling somewhat uncomfortable (of note, we have never witnessed overt hypersexual behavior). Sadly, most people, including her own family members, have great difficulty accepting S. M. for who she is (i.e., the way she speaks, the way she looks, and all her behavioral eccentricities).

Over the years, we have witnessed many friendships develop, only to fall apart. The typical pattern goes as follows: (1) When a stranger first meets S. M., it is not uncommon for her to divulge very personal details and discuss intimate topics, leaving the stranger with the impression that he or she is having a conversation with someone they have known for a very long time; (2) if the stranger reciprocates, he or she will quickly be swept up as S. M.'s new best friend, and asked to perform myriad favors, such as helping her with chores, giving her rides, and being willing to chat at all hours of the day; and (3) when the newly anointed friend is not willing to conform to S. M.'s rapid pace and all of her requests, and asks for some space, S. M. has a tendency to take it very personally and the friendship usually dissolves shortly thereafter. S. M.'s lack of a social circle is in line with recent work showing that greater amygdala volume is correlated with a larger social network (Bickart, Wright, Dautoff, Dickerson, & Barrett, 2010), and is also consistent with the reduced social network found in another bilateral amygdala lesion patient, B. G. (Becker et al., 2012; Patin & Hurlemann, Chapter 11). Based on these observations, it appears that one outcome of living life without an amygdala is abandonment and social isolation, conditions that conflict with S. M.'s extraverted nature. In the first article ever written about S. M., it was noted that she "has occasionally reported depressive symptomatology, related to difficult situational exigencies" (Tranel & Hyman, 1990, p. 350). For S. M., there is nothing more difficult than the loneliness of having no social circle and the feeling of being abandoned by the people who you love the most.

This should in no way insinuate that S. M. is not a good friend. In fact, she will do almost anything to help a friend in need. She once helped care for an older adult lady (Miss B.) who lived all by herself and needed some extra help due to her obesity and severe diabetic neuropathy. Every week S. M. would walk several miles to take Miss B. her groceries, help her out around the house, and keep her company. It was obvious that S. M. received great joy knowing that someone else needed her. One evening, as we were speaking to S. M. on the phone, a severe thunderstorm came rolling into her town, with warnings of a possible tornado. The thunder was so loud that we could hear it over the phone, shaking S. M.'s building. A few minutes later, while we were still on the phone, Miss B. called S. M. on her other line and told her that the power had just gone out at her house and she needed help. Before we had time to persuade her otherwise, S. M. was outside in the middle of the storm, walking over to Miss B.'s house. When we spoke to her later that night to make sure she was okay, S. M. told us that the storm was quite intense, with a heavy downpour of rain, strong winds, and streaks of lightning flashing everywhere. It was evident from her voice that she found the whole experience to be quite exciting. Remarkably, she denied feeling scared, even by the loud booms of thunder. The fact that she was voluntarily walking outside during such a vicious storm supports her assertion. When queried, S. M. was well aware of the dangers of being outside but reported being glad to have gone because, when she finally arrived, she found Miss B. huddled in the corner of her home crying. Even S. M. was able to recognize how scared Miss B. was. It took a while to calm her down, but eventually she fell asleep in S. M.'s arms, the fearless holding the fearer. The storm finally passed.

At this juncture, it is worth taking a moment to comment on an important observation: S. M. is *not* a psychopath. Case in point is her selfless and compassionate behavior toward Miss B. And while many psychopaths may indeed have amygdalar dysfunction and a lack of exteroceptive fear (Blair, 2008; Marsh, 2013), S. M. reveals that these factors may not be the causal ingredients driving the psychopathic behavior. Certainly, an outright lesion of the amygdala is not the correct neurological model for psychopathy. Such a model would fail to account for the fact that S. M. appears to have a keen sense of empathy and hates to see others suffer, especially those who are downtrodden and alone. For example, she once saw a homeless man shivering on the sidewalk during the middle of winter and immediately took him to the local Salvation Army and bought him a coat with the little money she had left to spend that month. It is also worth noting that throughout her life, S. M. has never intentionally broken the law or committed any crimes, though she has been the victim of numerous crimes. It turns out, S. M. is actually quite averse to breaking the law, and part of this stems from the fact that she does not like getting in trouble. Some may call this a fear of punishment, but it may actually

have more to do with her personality and compensatory strategies. Perhaps as a consequence of her amygdala damage, she often views rules and laws in a very black-and-white manner, and has trouble seeing shades of gray. She also has a preserved, yet rigid, understanding of basic concepts such as good and bad, and right and wrong; consequently, her behavior is rarely reckless and typically conforms to societal standards. Instances in which she fails to conform usually involve benevolent acts that transcend social barriers. For many years, S. M. attended a church where she was the only white person in a crowd of all black people. Even though there were other churches nearby that catered to a white audience, S. M. actually preferred the black church, and enjoyed the festive nature of the gathering, especially the music and singing. She adamantly denied feeling any sense of discomfort being the only white person in attendance. As S. M. explains, "In my eyes, we're all the same. I don't look at people differently. We all bleed the same color red." This point is made even more poignant by the fact that many of the crimes committed against S. M. involved a perpetrator who was black. Despite these negative encounters, S. M. always viewed them as isolated incidents and has never developed any distrust or racism toward African Americans.

Response to Social Threat

The sacrifice and courage that S. M. displays in the face of her own demise will often come out whenever other people are in danger. S. M. frequently tells a story about a "6 foot 5 neighbor lady" who slapped S. M.'s eldest son when he was a young boy. Without hesitation, S. M. confronted this much larger woman and a pushing match ensued. Things quickly escalated as the neighbor lady's entire family came running outside and surrounded S. M., threatening to attack her as a group. Other neighbors called the police, who quickly arrived and managed to break up the tussle before it escalated further. This was documented in police records that we were able to obtain. These same records helped verify another claim that S. M. has made for many years: Several other neighbors (and their associates) had explicitly threatened to kill S. M. on multiple occasions. Apparently, when S. M.'s son found a small bag of crack cocaine in the backyard, S. M. quickly took the bag to the police and told them exactly which neighbors she thought were dealing the drugs. When the police followed up on S. M.'s tip, unaddressed letters started appearing on S. M.'s doorstep, detailing elaborate plans to kill her if she did not stop speaking to the cops. Such threats did not alter S. M.'s determination to make sure that her kids were not exposed to drugs. When her son found more drugs in the backyard, S. M. immediately went back to the police to file another report. Once again, her motherly instincts prevailed over her own safety.

Around the same period of time when she was receiving all the death threats, S. M. remembers an incident while standing by herself outside her apartment. A large man (whom S. M. claims to have never seen before) suddenly appeared from behind a corridor, holding a gun in his hand. Without saying a word, he walked up to S. M., put the gun to her head, and yelled at the top of his lungs, "BAM!" before running away, never to be seen again. S. M. remembers finding the whole experience "strange" and seemed perplexed as to why someone would do something like that, apparently not connecting the dots between the man with the gun and all the recent death threats she had received. She has no recollection of feeling afraid, even when the gun was put to her head. Later that day, S. M. was back in her apartment and received a knock at her door. It was a local police officer. He sounded concerned and asked S. M. if everything was okay. She replied that she was doing just fine and inquired as to why he was there. The officer, a bit confused at this point, told S. M. that they had received a call from a neighbor who was quite disturbed and reported that she witnessed a man putting a gun to S. M.'s head. S. M. explained to the officer that this did indeed happen, but nothing ever came of it and the man had left the scene.

The striking disconnect between S. M.'s reaction to threats against her own life versus threats against other people's lives warrants more attention and investigation. At the very least, S. M.'s behavior suggests that she has great difficulty responding and appropriately reacting to threats against her own life, while at the same time, reacting quickly—and even somewhat overreacting—to threats that could harm others. Why she would contact the police during the latter situations but not the former is quite perplexing. When queried, S. M. does not have a clear explanation for her behavior. In the absence of such an explanation, it can be inferred that external threats to her own life often fail to induce fear and consequently do not leave much of an impression. On the other hand, external threats to other people's lives, especially loved ones, reflexively engage S. M.'s protective motherly instincts, a social form of threat detection that apparently can be deployed by circuitry outside of the amygdala.

Finally, even though S. M. is not living in the jungle with wild rhesus monkeys, she does live in a fairly dangerous area that harbors human predators. An incident in which a drugged-out man put a knife to her throat and threatened to kill her is a perfect example (Feinstein et al., 2011). There are many other traumatic incidents, some of which paint a rather grim picture of the human race and all its unsavory characters. One incident that really highlights the dangers of living without an amygdala involved a middle-aged man whom S. M. described as "tall and skinny with glasses." One day this stranger pulled up beside S. M. in his aquamarine pickup truck. The man struck up a conversation and told S.

M. that he knew one of her friends and wanted to take her out on a date to shoot some pool. Not surprisingly, S. M. immediately trusted this man and gladly took him up on his offer.

When they arrived at the pool hall, it was closed and would not be open for another hour. They decided to go for a drive through the countryside as they waited for the pool hall to open. The man eventually pulled up to an old abandoned barn and asked S. M. if she wanted to go outside and explore the barn. Interestingly, S. M. reported being hesitant to get out of the pickup. When asked to elaborate, S. M. claims that she was worried that they were on private property and could get in trouble for trespassing (a good example of her black-and-white thinking about rules and laws). Never once did she report feeling threatened by this strange man she had just met or the isolated environment to which he had surreptitiously guided her. After a little more prodding, the man eventually convinced S. M. to get out of the truck and they started walking toward the barn.

As they stepped inside the barn, the man quickly came up from behind S. M. and tackled her to the ground. He proceeded to flip her over and pull at her shirt, exposing her breasts. S. M. started yelling, "Take me home! Take me home!" The man started to unbuckle her belt and tried to remove her pants. S. M. continued yelling, her hoarse voice screeching through the sky. When retrospectively asked how she was feeling at the time, she denied feeling scared, but did report feeling extremely angry. Suddenly a dog appeared at the abandoned barn, attracted by all the commotion. When the man saw the dog, he quickly stood up, perhaps scared that the dog's owner was not far behind. He nonchalantly dusted himself off, asked S. M. if she was all right, and offered to help her up. S. M., still very upset, picked herself up from the ground and again yelled for the man to take her home. She proceeded to get back into the pickup truck on her own, and the man drove her home without saying another word about the events that had just transpired.

Hearing S. M. recount this incident was shocking to everyone in the laboratory. While we fully understood her deficit in the realm of trust and approachability of strangers, here was a clear-cut example of someone who had just attempted to rape her, yet, she got back in the car with him! Why would she do this? Why not run to the nearest farm and ask for help? Why not demand that the man leave without her? What if the man decided to take her to a more isolated location instead of taking her home? These were the questions that echoed through the minds of those with a functioning amygdala. Apparently, none of these thoughts crossed S. M.'s mind. She clearly did not accurately appraise the danger of the situation or the danger of this man. Instead, she thought that if he left her at the abandoned barn, she would have difficulty getting home, since they

were quite far away from any town. While most people presented with this same situation would have preferred being stranded than having to spend another moment with such a savage, S. M. apparently did not feel this way.

On the way back home, S. M. directed the man to her apartment complex, seemingly unconcerned that he would now know where she was living. Upon arriving, the man nonchalantly asked S. M. if she wanted to do something later that night. S. M. said no thanks, got out of the car, and walked up to her apartment. She did not even take the time to remember or write down the number on the man's license plate. As soon as we learned about what had happened, we directed S. M. to immediately call the police. Unfortunately, she had no defining details to provide them. No license plate, no name or model for the pickup, no last name of the perpetrator, just a vague description of some middle-aged man and his aquamarine pickup truck. The police were unable to offer her any help. We implored her to be cautious, since the man knew where she lived, and to run away quickly if she should ever see this man again. S. M. reported feeling *violated*, *worthless*, and *lower than dirt*, and remained upset for several days afterward. These negative feelings, however, were not enough to stop her from reengaging with the world outside. Later that same day, S. M. was back outside on her typical walk, putting herself at great risk of encountering this predator once again.

Survival with the Wild

A recent study that involved collecting human intracranial recordings of amygdala neurons found that cells in the right amygdala have a high rate of response to pictures of animals, even more so than pictures of people (Mormann et al., 2011). Other amygdala neurons seem to be selective for emotional facial expressions such as fear (Wang, Tudusciuc, et al., 2014). Likewise, functional neuroimaging has found significantly higher levels of amygdala activation in response to pictures of threatening animals and people versus pictures of threatening objects, such as guns (Yang, Bellgowan, & Martin, 2012). These data suggest that the amygdala hones in on detecting various forms of life in the animal kingdom (humans, as well as other species), with somewhat of a predilection for animals that are dangerous. Beyond mere detection of animate life, the data from nonhuman animals further suggest that the amygdala plays a critical role in rapidly constructing the defense barriers we erect when confronted with an unfamiliar animal, halting our approach behavior and minimizing interspecies interaction. Consequently, amygdala damage can manifest as a striking lack of avoidance of innately feared stimuli, as borne out by rats with amygdala lesions who approach cats (Blanchard & Blanchard, 1972) or a predator-like robot (Choi & Kim, 2010), or by monkeys with

amygdala lesions that readily approach humans (e.g., Weiskrantz, 1956) or snakes (e.g., Meunier et al., 1999). The conspicuous reduction in avoidance and defense responses when confronted with potentially dangerous animals is one of the most well-replicated findings in nonhuman animals with amygdala lesions (in this volume, see Amaral, Chapter 3; chapter, Kim, Choi, & Lee, Chapter 5; Bachevalier, Sanchez, Raper, Stephens, & Wallen, Chapter 7; Oler, Fox, Shackman, & Kalin, Chapter 8). Since nonhuman animals are unable to report verbally on their internal subjective experience, we became interested in learning how S. M. felt about other animals, especially species that are commonly feared by humans.

To our surprise, S. M. has repeatedly told us that she "hates" snakes. Given the aforementioned findings in nonhuman animals, we were rather bewildered by this revelation. It is possible that S. M.'s snake aversion developed as a child. She remembers an incident when she was very young and out on a hike through the woods with her father. Some loose brush covered a hole in the ground, and when she walked over this brush, it gave way, and she fell several feet into the hole. To S. M.'s dismay, the hole contained a nest of young snakes that quickly started to slither up her legs. She recalls screaming for her father to help and finding the whole experience extremely upsetting. While her amygdala damage likely emerged later in life, the memory for this event remained and probably contributed to her hatred for snakes.

Taking her word at face value, we assumed that S. M. would naturally avoid snakes when confronted with them in real life. Moreover, the fact that S. M. would repeatedly tell us, year after year, how much she disliked snakes, led us to believe that she might even have a mild form of ophidiophobia. In order to examine this possibility further, we arranged for a visit to an exotic pet store containing a large collection of different snakes of various sizes and colors (Feinstein et al., 2011). The store also contained more traditional pets, such as hamsters, birds, and puppies. Upon arrival, we asked S. M. if she wanted to go inside the pet store and check it out. Given her love for animals, she was more than happy to comply. Our goal was simply to observe her behavior around this large collection of animals. We had envisioned that she would probably focus most of her attention on animals she liked, such as the puppies. Since it was an exotic pet store, we also thought she might occasionally look at the snakes from afar, and perhaps she would even go near their housing so we could assess whether her reported level of fear changed at different proximities. As soon as we entered the store, however, we quickly realized that our expectations were way off base. Instead of observing the snakes from afar, S. M. was spontaneously drawn to them and strongly captivated by their presence. Simply looking at them was not enough. She needed to touch them. A store employee took notice and brought out a snake for S. M. to handle. As it wrapped around her hands, S. M. was mesmerized. She started

rubbing the snake's leathery scales while closely inspecting all aspects of its body. The flicking tongue really grabbed her attention and she started gently touching it with her fingertips, spontaneously commenting, "This is so cool!" After 3 minutes of interacting with the snake, she was ready to move on, except now she desperately wanted to "touch" and "poke" the larger and more dangerous snakes, asking the store employee 15 different times if this would be possible, despite the employee repeatedly telling her that the larger snakes were not safe and could potentially bite her. In the past, S. M. has also told us about her aversion to spiders, yet at the exotic pet store, she tried to touch a very large and hairy tarantula and once again had to be stopped because of the high risk of being bitten. S. M.'s compulsive desire to approach snakes and spiders at the pet store is highly reminiscent of the behavior of monkeys with Klüver–Bucy syndrome (Klüver & Bucy, 1939). It is also worth noting that S. M.'s behavior was not merely the result of feeling comfortable in the relatively safe environment of a pet store, since we later learned (from a family member) that S. M. once encountered a very large snake outdoors and behaved in a similar manner (see Supplemental Data in Feinstein et al., 2011).

Throughout the whole experience at the pet store, S. M. was clearly overcome with "curiosity," which is exactly what she would tell us every time we asked why she would want to touch or hold something that she claims to hate. It was as if her amygdala damage had created a disconnect between cognition and behavioral control. Cognitively, she hates snakes, and to this very day she continues to hate them. Yet, while in their presence, she is compelled to touch them. Such a striking dissociation between cognition and behavior highlights the perils of relying solely on self-report, and the importance of observing behavior as it unfolds in the real world. Even though S. M.'s cognitive aversion to snakes is strong, it clearly is not strong enough to win the battle over behavioral control. Is winning this battle perhaps a key function of the amygdala? Each moment, as we navigate an uncertain world with unfettered curiosity and appetitive motivation, the amygdala acts as a powerful opposing force that inhibits our exploratory behavior, provoking both caution and avoidance in the face of danger. Such an explanation is corroborated by the rich set of behavioral observations in nonhuman animals with amygdala lesions (in this volume, see Amaral, Chapter 3; chapter, Kim et al., Chapter 5; Bachevalier et al., Chapter 7; Oler et al., Chapter 8). The case of S. M. further suggests that much of this battle over behavioral control occurs at an unconscious level, far outside the jurisdiction of reason and rational thinking.

One of the most readily observable forms of behavior is avoidance, which serves many functions beyond its critical role in fear. For example, disgust also features a core aspect of behavioral avoidance, and a burgeoning body of functional neuroimaging work indicates that the amygdala

is highly responsive to disgusting stimuli (e.g., Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Stark et al., 2003). It is quite possible that another reason S. M. reports hating snakes is because she cognitively believes they are disgusting (e.g., she has, on occasion, used the word "gross" to describe snakes). She also finds cockroaches to be quite "gross" and "icky"; nevertheless, when S. M. found a cockroach scurrying about her apartment floor, she reported capturing it with her bare hands and systematically pulling off its body parts. Curiosity prevailed once again, and when asked to explain her discrepant behavior, she said, "I wanted to find out what made it tick, what it looked like inside." Viewed in this light, S. M.'s deficits in avoidance may extend beyond the realm of fear and into the domain of disgust. However, the overlap is only partial, for there are a variety of situations and objects that induce disgust in S. M. and prompt behavioral avoidance. Most of these revolve around consumption. For example, when we showed her a short video clip of a person eating dog feces from the film *Pink Flamingos*, she found it to be extremely disgusting (Feinstein et al., 2011). Likewise, there are many different foods and liquids that S. M. finds disgusting (e.g., most vegetables), and as a consequence she refuses to consume them. One morning, shortly after drinking some milk, S. M. became sick to her stomach and started vomiting. For the next week, she refused to drink any milk, even though her neighbor drank out of the same container of milk and showed no signs of illness. This suggests that S. M.'s conditioned aversion to taste is preserved, and further suggests that gustatory stimuli (which stimulate an interoceptive, rather than exteroceptive, sensory channel) are capable of triggering avoidance in the absence of an amygdala. Clearly, more research is needed to explore the boundaries between fear-induced and disgust-induced avoidance in order to provide a more parsimonious explanation of the amygdala's core function.

Interoceptive Fear

After many years of unsuccessful attempts using external threats to scare S. M., we decided to shift course. Unfortunately, almost the entire arsenal of paradigms and techniques currently employed to study fear use exteroceptive stimuli, typically processed through visual and auditory channels. Options for safely triggering internally induced states of fear are far more limited, but one such method that has been well-studied involves the inhalation of an air mixture containing 35% carbon dioxide (CO_2). To put this amount in perspective, we are talking about a quantity of CO_2 that is 875 times greater than that in the air we typically breathe. Given such high concentrations, the subject only takes a single vital capacity inhalation of the mixture, triggering a brief hypercapnic state that is typically resolved

within 30 seconds. During this time period, chemoreceptors in both the central and peripheral nervous system are activated, driving physiological responses, especially breathing. The most commonly reported side effect of this experiment is a profound sense of air hunger that is felt almost immediately after the inhalation and lasts for about a minute. Interestingly, oxygen levels are typically unaffected, so the manipulation is actually triggering an illusion of air hunger. Despite its illusory nature, the feeling is very real and capable of inducing fear, and even panic, in up to one-fourth of healthy individuals who undergo this challenge (Colasanti, Esquivel, Schruers, & Griez, 2012). In patients with a history of panic disorder, the manipulation readily produces full-blown panic attacks that closely parallel those occurring in everyday life (Colasanti et al., 2012; Schruers, Van de Mortel, Overbeek, & Griez, 2004).

The aversive nature of CO_2 appears to be evolutionarily hardwired into our physiological system. For example, *Drosophila* fruit flies have specialized olfactory sensory neurons that are able to detect minute changes in levels of CO_2 in the environment, and rapidly trigger a change in flight pattern in order to avoid that area of space (Suh et al., 2004). Climbing up the evolutionary ladder, it has been shown that the amygdala in mice has the ability to directly detect changes in CO_2 and acidosis through acid-sensing ion channels, leading to CO_2-evoked fear behaviors (Ziemann et al., 2009). Given this finding in mice, in addition to S. M.'s remarkable absence of fear in response to the diverse array of previously discussed exteroceptive threats, and the fact that several prominent theories highlight a central role for the amygdala in the generation of panic (Coplan & Lydiard, 1998; Gorman, Kent, Sullivan, & Coplan, 2000), we hypothesized that S. M.'s bilateral amygdala lesions would reduce her level of CO_2-evoked fear. In collaboration with Dr. John Wemmie at the University of Iowa, we arranged for S. M. to undergo a 35% CO_2 challenge, marking the first time we had ever directly exposed S. M. to an interoceptive threat.

Immediately following the inhalation of 35% CO_2, S. M. began breathing at a rapid pace and gasping for air. Her physiological response to the CO_2 was clearly intact. Approximately 8 seconds following the inhalation, she started waving her right hand frantically near the air mask. By this point, S. M. was clearly in a state of distress. At 14 seconds post-inhalation, S. M. gestured with her right hand toward the mask and exclaimed, "Help me!" The experimenter immediately removed the mask from S. M.'s face. As this was happening, her body became rigid, her toes curled, and her fingers on both hands were flexed toward the ceiling. As soon as the mask was removed, S. M. grabbed the experimenter's hand and in a relieved tone said, "Thank you." The skin on her face was flushed, her nostrils were flared, and her eyes were opened wide. At 30 seconds post-inhalation, S. M. let go of the experimenter's hand and said, "I'm all right." However, she was not all right, at least not yet. Her breathing

remained slightly belabored, and we could hear her on occasion trying to pull extra air in through her nose. Approximately 2 minutes later, one of the experimenters was going through a list of the various symptoms that people might feel during a panic attack. Just as she was asking S. M. about whether she had experienced the sensation of choking, S. M. suddenly stopped answering the questions. She started waving her right arm again as she struggled to communicate. She whispered, "I can't," as her right hand started tapping her throat. We asked if she was okay. S. M. shook her head no and with all her willpower gasped, "I can't breathe."

S. M. had just experienced the first panic attack of her life. The whole episode, from inhalation to her eventual recovery, lasted a total of 5 minutes (considerably longer than most other CO_2-induced panic attacks, which usually last on the order of 1–2 minutes). Every experimenter in the room was shocked. S. M. had actually felt fear. She called it the "worst" fear she had ever felt. In all likelihood, it was probably the first time she had experienced fear since childhood. Her response was unlike anything we had seen before. After many years of attempting to scare S. M., we had finally found her kryptonite: carbon dioxide.

In one breath, we immediately learned that the amygdala could not be the brain's quintessential and sole "fear center." Plasticity of function is certainly a possibility. Without a functioning amygdala, S. M. was still able to experience an intense and prolonged state of fear. If anything, her fear response was actually exaggerated. To test whether this result was reproducible, we collaborated with Dr. René Hurlemann, who identified monozygotic twin sisters (A. M. and B. G.) who both have focal bilateral amygdala lesions secondary to UWD (see Patin & Hurlemann Chapter 11, this volume). The twins were flown to Iowa from their home in Germany and administered the same testing protocol that S. M. had completed. Replicating the finding in S. M., CO_2 triggered panic attacks in both twins (Feinstein et al., 2013). The rate of CO_2-evoked panic attacks in the patients with amygdala lesions was significantly higher than that observed in a matched sample of neurologically intact comparison participants (Figure 1.4). This paradoxical finding suggests that instead of inducing panic, the amygdala is integrally involved in inhibiting panic. Such an inhibitory role might help explain how another patient with an amygdala lesion developed spontaneous panic attacks (Wiest, Lehner-Baumgartner, & Baumgartner, 2006), as well as provide a plausible account for the significant amygdalar atrophy found in patients with panic disorder (Hayano et al., 2009; Massana et al., 2003). In both scenarios, the amygdala pathology could conceivably lead to disinhibition of downstream panic circuits given that the output from the central nucleus of the amygdala is gamma-aminobutyric acid (GABA)ergic (Ciocchi et al., 2010) and projects to brainstem nuclei that have been implicated in producing panic-like behavior (Del-Ben & Graeff, 2009).

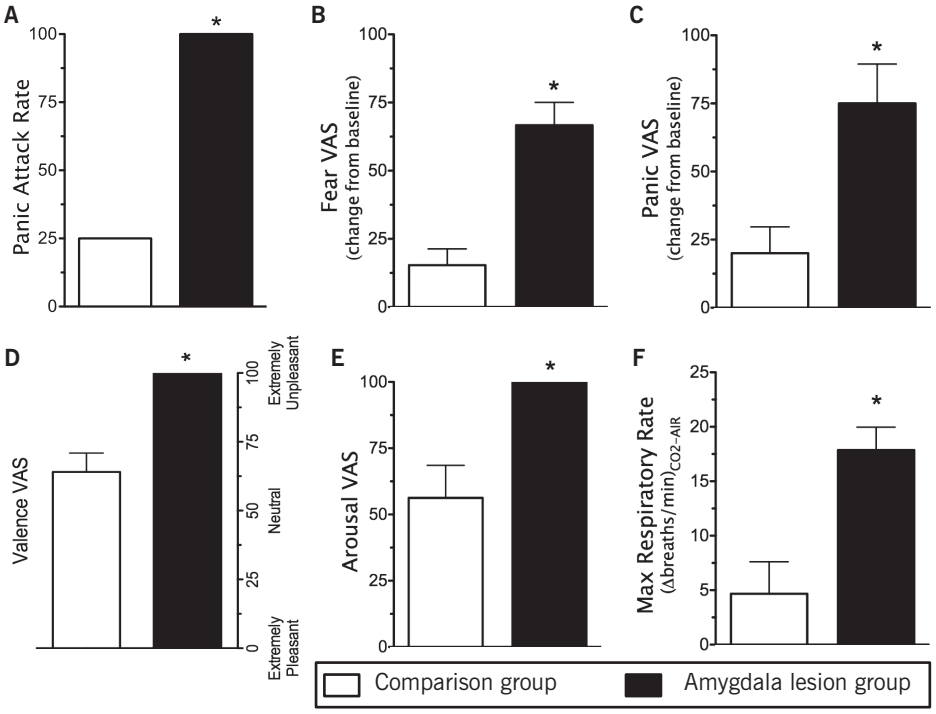

FIGURE 1.4. Results from the CO_2 experiment (Feinstein et al., 2013). A single vital capacity inhalation of 35% CO_2 triggered a panic attack (A) in all of the patients with amygdala lesions but only one-fourth of the comparison subjects. There were no significant differences between the patients with amygdala lesions and those comparison subjects who did panic. However, in relation to the comparison subjects who did not panic, the patients with amygdala lesions reported experiencing significantly higher levels of fear (B), panic (C), unpleasantness (D), and arousal (E). They also exhibited a significantly higher rate of respiration to the CO_2 challenge (F). * $p < .05$; all error bars represent the standard error of the mean. VAS, visual analogue scale.

The results from the CO_2 experiment (Figure 1.4) showed that a single inhalation of air containing 35% CO_2 triggered a panic attack in all of the patients with amygdala lesions, characterized by an intense feeling of suffocation, high levels of self-reported fear and panic, heightened physiological arousal (including hyperventilation and gasping for air), prominent signs of escape behavior, and concomitant thoughts of dying (Feinstein et al., 2013). This latter observation was particularly poignant, since it highlights that the type of fear we evoked was tapping into a very primal and existential system in the brain. Evidently, our fear of death,

and the brain systems that allow this fear to permeate our consciousness, does not require the amygdala.

If not the amygdala, then what other brain regions could be responsible for generating such a primal experience of fear in S. M. and the other patients with amygdala lesions? While a definitive answer to this question will require further research, certain observations from the CO_2 experiment provide some important clues. During debriefing, all of the patients reported that the fear induced by the CO_2 was clearly linked to the feeling of suffocation. This observation appears to support Donald Klein's (1993, p. 306) suffocation false alarm theory of spontaneous panic, which hypothesizes that "a physiologic misinterpretation by a suffocation monitor misfires an evolved suffocation alarm system. This produces sudden respiratory distress followed swiftly by a brief hyperventilation, panic, and the urge to flee. Carbon dioxide hypersensitivity is seen as due to the deranged suffocation alarm monitor." Our data suggest that patients with bilateral amygdala lesions have a deranged suffocation alarm monitor that is hypersensitive to CO_2. An important follow-up question is to elucidate the precise location of this suffocation monitor, since it is the likely source of the fear and panic experienced by S. M. Although it is too early to know for sure, we predict that the suffocation monitor is embedded deep within the circuitry of the brainstem and hypothalamus, inside a cluster of closely connected nuclei that are adept at detecting changes in CO_2 and respiration, and rapidly inducing a state of fear and panic when the changes surpass a certain threshold. The critical nuclei likely include the periaqueductal gray, parabrachial nucleus, nucleus of the solitary tract, retrotrapezoid nucleus, locus coeruleus, raphe nucleus, and the dorsomedial and perifornical nuclei of the hypothalamus (Davenport & Vovk, 2009; Deakin & Graeff, 1991; Guyenet & Abbott, 2013; Grove, Coplan, & Hollander, 1996; Johnson et al., 2011; Nattie, 1999). Additionally, the experience of suffocation likely recruits higher-order brain regions, including the insula and anterior cingulate cortices (Banzett et al., 2000; Evans et al., 2002; Liotti et al., 2001). The truth is, we know very little about how the human brain instantiates fear from interoceptive signals. It will be incumbent on future research to unravel the neural basis of interoceptive fear, and this is currently an active area of investigation in our laboratory.

Interestingly, in S. M., fear was only one part of the experience that was activated by CO_2. After the experiment was over, S. M. told us that during her panic attack she had a flashback to a traumatic event. In the early 1990s, S. M. was married for a short period of time. She soon discovered that her husband was cheating on her. She approached him about the infidelity and asked him to move out of the house. The conversation quickly escalated into a fight that ended with the husband on top of S. M., strangling her. She remembers blacking out for a short period of

time. By that point, he had let her go, left the house, and never returned again. When S. M. recalls this event, she denies ever feeling scared, even at the time of the assault, but she readily admits that she was extremely angry and also devastated that the man she loved would do this to her. The memory of the episode was on her mind for many months and even years after the event had taken place. Eventually, however, she moved on, and rarely ever thought about the event. It is quite remarkable that 16 years later a single inhalation of CO_2 caused S. M. to relive this traumatic memory.

Much of our understanding about the neural basis of emotional memory revolves around the amygdala and the important role that it plays in the consolidation of emotional memory, especially for arousing events (Hamann, 2001; LaBar & Cabeza, 2006). While S. M.'s emotional memory for exteroceptive events (i.e., events she sees, hears, or smells) is generally deficient (Adolphs, Cahill, Schul, & Babinsky, 1997; Adolphs et al., 2005b; Buchanan, Tranel, & Adolphs, 2003), her emotional memory for interoceptive events appears, at least anecdotally, to be much better. The feeling of suffocation while being strangled by her unfaithful husband likely induced a strong state of arousal in S. M. and, in the process, created an indelible memory trace that was reactivated by the closely associated feeling of suffocation induced by CO_2. This suggests that emotional memories for arousing interoceptive events may not require the amygdala. If this is true, then we would expect S. M.'s memory for the CO_2-induced panic attack to also be enhanced. Sure enough, more than 2 years after the CO_2 experiment, we were on the phone with S. M. discussing the possibility of an upcoming research visit. Without ever mentioning anything about the CO_2, S. M. spontaneously remarked, "That test with the gas. I don't want to do it no more. It makes me very uncomfortable. It brought back memories of when my husband strangled me." Not only had she remembered her experience with the CO_2, but she also remembered the memory that was reactivated by the experience. What's more, her preserved emotional memory was accompanied by a preserved avoidance response. She had absolutely no interest in ever inhaling CO_2 again and was averse to the very idea of it. This suggests that emotional memories for arousing interoceptive events can be encoded, consolidated, and retrieved without a functioning amygdala.

Such observations made us wonder whether there are other interoceptive events that S. M. experienced that might have induced states of fear and arousal leading to enhanced emotional memory and preserved avoidance behavior. So far, we have been able to identify two potent examples, both of which involve painful medical procedures related to her disease.

As previously mentioned, S. M. has a rather severe form of UWD, and the calcifications have infiltrated many different systems throughout her

body. Recently, her tear ducts have become calcified, causing a buildup of tears in her eyes. To help correct this, an ophthalmologist placed small artificial tubes in her tear ducts, but these would frequently fall out after a short period of time. Finally, he decided to try a rather invasive procedure to keep the tubes in place by creating a small incision in her nasal bone and threading the tubes through this incision. Apparently no anesthesia was used during the procedure, causing S. M. extreme pain. After the procedure was over, S. M. remembers crying the entire way home. To this day, she still vividly remembers the pain. Eventually the tubes fell out again, but she refused to go back to the doctor even though the excessive tearing caused her to have blurry vision. Further questioning revealed that she was scared he would perform the same painful procedure again, and she did not want to risk having to endure the pain. The situation was eventually resolved when the doctor promised to put her under general anesthesia. Nevertheless, the day before the procedure, S. M. called us, extremely worried about what would happen if the doctor did not follow through on his promise to use anesthesia. Her voice was filled with apprehension, and she said that she had been worried all week long, dreading the procedure. We had never observed such anticipatory anxiety relative to any of the other surgical procedures that she typically undergoes several times a year, and that have been commonplace throughout her life. In this instance, her anxiety was clearly a by-product of the intense interoceptive pain experienced during the original procedure, combined with her preserved emotional memory for the painful experience.

S. M.'s disease also adversely affects her gums and teeth. Several years ago, we noticed that her teeth were falling out. We asked S. M. what her dentist was doing to help maintain her teeth, and she proceeded to tell us that she does not have a dentist and has no interest in seeing one. We started probing deeper to figure out what was behind her resistance to seeing a dentist. Apparently, 15–20 years ago, S. M. reported that she had all four of her wisdom teeth removed, but the dentist failed to use a sufficient amount of anesthesia during the surgery. In S. M.'s own words, "I felt everything. Every pull, every tug, I felt it all. And I couldn't tell him because he had my mouth propped open. And I tried to stop him with my hands and he had the nurse hold my hands down. He said to me that if you do that again, I may slip and I might hurt you. And in the back of my mind I was like you are hurting me now, stop!" The pain was excruciating, and ever since this incident she has been afraid to go back to the dentist. The mere thought of a drill makes her cringe. We did not know it at the time, but we later learned that S. M. had purposefully avoided going to the dentist for over 15 years. She said that she would rather lose her teeth than see another dentist. True to her word, last year S. M. lost her very last tooth.

A Tale of Two Fears

What appears to be emerging is a tale of two very different worlds inside our brain: the internal world of our body, and the external world in which that body lives. Each waking moment, the brain is in constant flux, attempting to pair what is happening on the outside with what is happening on the inside. At the interface between these two worlds lies the amygdala, a critical gatekeeper that is responsible for helping to merge these worlds together so that the next time they collide, the body will be better prepared to cope with the challenges posed by the external environment. The case of S. M. reveals that the amygdala does not provide a two-way street between these disparate worlds. Whereas external threats traverse the amygdala in order to induce a state of fear, internal threats are capable of bypassing the amygdala altogether. The amygdala's role in processing internal threats appears to be more regulatory in nature, inhibiting panic centers in the brainstem and hypothalamus, while scouring the external environment to find a plausible source that can explain, and subsequently predict, the internal disturbance.

Ultimately, the amygdala is not the quintessential source of fear in the brain (Janov, 2013). The neuroanatomical arrangement is such that only the internal fear pathway has direct access to the body, and the amygdala must communicate through this pathway in order for external stimuli to induce a state of fear. Sensory and association cortices required for representing external stimuli are intact in S. M.'s brain, as are the brainstem and hypothalamic circuitry necessary for orchestrating the action program of a fear response. S. M.'s amygdala lesions in effect disconnect these two components, making it improbable, if not impossible, for external sensory representations to trigger full-blown fear responses, leading to S. M.'s profound deficits in the realm of exteroceptive fear. On the other hand, interoceptively conveyed sensory information can directly stimulate the brainstem and hypothalamus, triggering a fear response that culminates in S. M.'s conscious experience of fear and panic. In comparison to exteroceptively-induced fear, it can be argued that interoceptive fear is more central to survival; consequently, the neural circuitry responsible for its induction may be more resilient to brain injury.

In the end, the life of S. M. has been a struggle from the very beginning. From an abusive upbringing to constant ridicule as a child, through failed relationships, and poverty, and pain, and death threats, and near-death experiences, S. M. has lived through it all. She has experienced a lifetime of adversity, with many more trials and tribulations likely to come. What is remarkable is that throughout this struggle, S. M. has maintained her composure and positive outlook on life, a steadfast resilience that endures to this day (see Box 1.1). In essence, the horrors of life

BOX 1.1. A Selection of Quotes from S. M. Obtained from Diary Entries, Interviews, and Conversations

"I struggle with this question all the time. What is my purpose? What is my purpose in life? I truly have no clue."

"I have no idea why I keep on going. Why haven't I just given up? Tossed in the towel?"

"I have no place to go, no one to go to, no money in my pocket. The old saying goes 'history repeats itself.' It's true!"

"I'm now getting evicted. Well here I am, the story of my life. All by myself, no one to turn to. No money. I'm back to square one. But hey, I will be just fine. I ain't going down without a good fight!"

"I'm the type of lady that can and will handle anything that comes my way! I can stand on my own two feet. I can and will survive."

"I try to be a tough woman. I try to take the whole world on by myself . . . I ain't going down without a fight."

"As you know, I have been through a lot! I will always keep a positive attitude, and will always have a smile no matter how hard life is!"

"I'm sitting here. It's a beautiful day, sunny, warm as can be. I haven't been outside yet. And I'm so lonesome that I could just cry. I am. I swear to God, I am."

"In my lifetime I hardly ever had any close friends. Friends to me are just like family members. I always get close to them and it's like one minute they're there, and the next minute they're nowhere to be found."

"The way I look at life, I was a loner when I was growing up. I didn't have many friends. I was always picked on. I was always by myself. I'm still alone now. . . . I don't want to be alone for the rest of my life."

"And this condition I have, with my skin and everything, kind of puts me down. Seems like every single day I get up in the mornings, I look in the mirror and I look 10, 15 years older than I am. And that kind of brings me down, too. I mean, I'm 43 and I look like I'm 55 or 60. . . . Seriously, I look like I'm an old lady!"

"I just wish, pray, that someone would come up with a cure for this."

"My life has been nothing but a lot of hurt, pain, and hateful people. My life has also been joy, love, and most of all, survival. I am thankful for my life and what kind of woman it made me. I am strong, very hard-headed, stubborn, very loving, caring, very passionate. But most of all, I am very thankful for having a good heart."

(continued)

Diary question: What have your life experiences taught you about what it means to survive?

S. M.: *It has taught me to be able to stand on my own two feet and take all the punches that life throws and still be able to stand and to keep right on going. It taught me to be strong, never give up. It taught me that I can not count on anyone but myself to take care of business. My life experiences are what made me the woman I am today. To be honest, loving, caring, understanding, nonjudgmental, to accept any situation that comes my way. Most of all, this may sound strange, but it also taught me never to hate!*

Experimenter: Your son is now a soldier in Afghanistan, right? Are you worried about him?

S. M.: *Yes, I am.*

Experimenter: What are you worried about?

S. M.: *I am worried about him being hurt, having bad things happening to him. Someone can be holding a gun to my son right now.*

Experimenter: There's something interesting there. You basically say that if someone held a gun to you, you wouldn't be afraid. But if someone did that to your son then you would be afraid?

S. M.: *I am not afraid. I just don't want that for him. What you need to understand is that I am worried, but not afraid.*

Experimenter: What do you think is the difference between "being worried" about something and "being afraid" of something?

S. M.: *"Afraid" means being frightened. Being scared. And "worried" means not wanting something to happen. I have always been worried about things, but I am never afraid. If I could stand between my son and the bullet, I would do that because I am not afraid.*

seem unable to penetrate her emotional core and stamp their traumatic imprint. Like Dr. Kling's amygdalectomized monkeys, S. M. repeatedly finds herself in precarious circumstances. Unlike Dr. Kling's monkeys, S. M. has somehow managed to stay alive all of these years. Whether this reveals something important about the evolution of the human race or the necessity of fear for survival in modern society is open for debate. What is not debatable is that we owe S. M. a tremendous debt of gratitude for her unwavering support of brain research and all of the incredible insights she has provided to the scientific community. As the science of

fear advances to new levels of understanding, the case of S. M. lives on, her star shining brightly in the night sky, helping to lead the way.

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