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Slow To Warm Up: Delayed Neural Habituation To Faces And Risk For Social Phobia

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Abstract

Social phobia is a chronic and disabling anxiety disorder that affects approximately 1 in 10 people in their lifetime. Individuals with social phobia experience intense anxiety and fear in situations where they are exposed to unfamiliar people or possible scrutiny by others, leading to social discomfort and isolation. Neuroimaging studies have revealed that novel faces consistently elicit heightened amygdalar and hippocampal activity in social phobia patients. Heightened amygdala activity to novel faces is also associated with inhibited temperament, a strong risk factor for social phobia, suggesting that heightened neural activity to social novelty may be a biological marker of risk. Preliminary findings suggest that slow habituation to novelty may underlie the heightened neural activity seen in inhibited individuals and patients with social phobia, with this prolonged neural response contributing to feelings of unfamiliarity, memory impairments, and increased social fear.

Introduction

Anxiety disorders are the most commonly occurring class of psychiatric disorders, with approximately 1 in 4 people affected by one or more anxiety disorders within their lifetime[1]. Due to their prevalence, the economic cost associated with anxiety disorders is estimated at a staggering $42 billion annually[2]. Social phobia is the second most common type of anxiety disorder[1] and a significant contributor to disability and economic burden[3]. Social phobia, also known as social anxiety disorder, is characterized by a persistent, intense, and chronic fear of being watched or judged by others that interferes with work, school, and other activities[4]. Individuals with social phobia are typically thought of as shy and quiet, and may show physical discomfort (blushing, lack of eye contact) when interacting with others. Although some individuals with social phobia desire the company of others, they often avoid social situations due to their fear of being judged. The burden of social phobia is often underestimated[5] because individuals with social phobia often do not seek treatment. However, impairments associated with social phobia can range from mild to severe. Individuals with mild social phobia often have fears of public speaking; however, less than 5% of individuals with social phobia meet criteria for the diagnosis based exclusively on public speaking fears[6-8]. Instead, the vast majority of individuals with social phobia experience significant fears in *most* social situations, resulting in reduced educational attainment[9;10], low occupational and financial status[10-12], and reduced quality of life[3;11-13]. Social phobia has a typical onset in adolescence[1;2;8;12;14], is highly persistent throughout the entire life course[2], and has high comorbidity with other psychiatric illness[5;12;15;16].

Understanding risk factors related to the development of social phobia could ultimately have important implications for prevention and treatment. The etiology of social phobia appears to be dependent on multiple factors, including neurobiological and developmental risk factors. This review characterizes the most prominent neurobiological findings in social phobia, and the neurobiological and developmental factors most strongly linked to risk for social phobia.

Neurobiology of social phobia

Individuals with social phobia experience intense fear of evaluation in most social situations. Social stimuli which are only mildly aversive or threatening to most people—such as seeing a negative facial expression—can cause emotional distress and anxiety in social phobia patients[17]. Accordingly, a majority of studies[18] have used mildly threatening/aversive social stimuli—such as angry, fearful, or critical faces, or anticipation of public speaking—to probe for altered neural function in social phobia. These studies have identified the amygdala and the hippocampus as two prominent brain regions which show abnormal activity in social phobia.

The amygdala is critically important in the detection of environmental threat[19] and in the expression of fear and anxiety[20;21]. Monkeys with amygdala lesions show a striking lack of fear to environmental and social threat[22;23], and human patients with bilateral amygdala damage have difficulty recognizing fearful expressions[24]. Consistent with the role of the amygdala in threat detection, functional neuroimaging studies have found increased amygdala activity in

social phobia patients in response to various types of social threat, such as viewing of threatening faces[25-27] or anticipation of public speaking[28;29]. The degree of amygdala activity in social phobia patients is correlated with the severity of social anxiety symptoms, but not trait anxiety symptoms, indicating that the amount of amygdala activity in response to social threat may be a relatively specific marker of social phobia severity[25]. Following successful anxiety treatment, social phobia patients show reduced amygdala activity in response to social threat[30;31], indicating that heightened amygdala activity is crucial in the expression of anxiety symptoms. These findings clearly support the role of the amygdala in the detection of social threat, and indicate that hyperactivity of the amygdala in response to negative or threatening social stimuli may at least partially underlie social phobia symptoms.

Interestingly, neutral faces also elicit increased amygdala activity in social phobia patients relative to controls[32;33], although to a lesser extent than threatening faces. Neutral expressions are more emotionally ambiguous than other facial expressions[34], and there is preliminary evidence that individuals with social phobia tend to view neutral expressions as slightly threatening[35], perhaps due to their ambiguity. Therefore, increased amygdala activity to neutral faces could reflect a difference in perception of social threat. Alternatively, increased amygdala activity to neutral faces may reflect generally heightened face or novelty processing in social phobia. The amygdala has a well-defined role in face detection and contains neurons which preferentially respond to faces regardless of emotional valence[36;37]. Some studies have demonstrated heightened amygdala activity to happy faces in social phobia patients[38;39], supporting the notion that social phobia patients may show heightened amygdala activity to all faces, regardless of valence. The amygdala is also critically involved in novelty detection and contains neurons which respond only to the first presentation of a stimulus[36;37;40]. Because social phobia studies often don't control for novelty effects, abnormal novelty processing cannot be ruled out as a contributor to increased amygdala activity. Therefore, it is possible that the amygdala is hyperactive not only to social threat, but also social novelty.

One region which may modulate the amygdala during social threat and social novelty processing is the hippocampus. The hippocampus provides contextual information to the amygdala through dense, reciprocal connections[41], and has been associated with the overgeneralization of anxiety[42-44]. Neural processing of the surrounding environment appears to involve a complex interaction between the amygdala and the hippocampus, with the amygdala influencing memory-related plasticity in the hippocampus[45], and the hippocampus playing a modulatory role over the amygdala during negative face viewing[46;47]. In social phobia patients relative to controls, social threat is associated with increased activity in the hippocampus and parahippocampal gyrus[27;48;49], and attenuated hippocampal activity following successful social anxiety treatment[31]. Similar to the amygdala, the hippocampus and entorhinal cortex play a role in both face detection and novelty detection[36;40], responding most strongly to the first presentation of a face regardless of valence[50]. Therefore, it is possible that increased hippocampal activity to face stimuli in social phobia patients may be at least partially related to hyperactive processing of faces or novelty. No previous studies have specifically examined hippocampal activity in response to neutral faces in social phobia, so it is unknown whether the hippocampus, similarly to the amygdala, shows increased activity to neutral social images. However, these findings suggest that the hippocampus not only participates in face and novelty detection, but also plays an important modulatory role over the amygdala during social threat detection and may be critical in the expression of anxiety in social phobia.

While amygdalar and hippocampal function are important in the neurobiology of social phobia, much less is known about whether these regions contribute to risk for the disorder. If amygdalar and hippocampal function are disrupted early in the progression of the disorder—prior to the onset of significant anxiety symptoms—these regions may serve as early biological markers of risk and help guide early prevention and treatment. Some preliminary evidence suggests that this may be the case; for example, amygdala dysfunction has been found in individuals with inhibited temperament[51-53], a group at significantly increased risk for development of social phobia.

Inhibited temperament as a risk factor for social phobia

While the lifetime prevalence of social phobia in the general population is estimated to be 12%[1], approximately 40% of individuals with inhibited temperament will develop social phobia in their lifetime[54-56]. Because of this substantially increased risk, investigation of the neurobiology underlying inhibited temperament may provide valuable insight into neural risk factors for social phobia. Temperament refers to stable, biologically-based individual differences in emotion, cognition, and behavior that are measureable during the first years of life[57]. Inhibited temperament is the predisposition to react to environmental novelty, such as new people, places, and events, as potentially threatening[58;59]. Approximately 15% of individuals are born with an

inhibited temperament[60], which biases them to react to novelty with fear and wariness. Inhibited children are thought of as "slow to warm up" in new social situations[61] and often withdraw from unfamiliar peers[62]. Investigation of the neurobiology underlying inhibited temperament may provide valuable insight into a specific risk pathway for social phobia.

Because inhibited temperament is associated with avoidance of novelty, often new people, several studies have investigated neural responses to social novelty in inhibited temperament. A seminal study by Schwartz and colleagues used neutral face stimuli to explore amygdala novelty processing in individuals with inhibited temperament. In this study, young adults who had been identified as inhibited at 2 years of age had heightened amygdala activity to novel faces compared to uninhibited individuals, but showed similar amygdala activity as uninhibited individuals to familiar faces[51]. In a later study, Blackford and colleagues showed that inhibited individuals, compared to uninhibited individuals, also have a faster and longer amygdala response to novel neutral faces[52]. These studies indicate that novelty processing in inhibited individuals is associated with exaggerated amygdala activity, which may drive the behavioral avoidance of novelty exhibited by these individuals. Although the study by Schwartz and colleagues included a small number of inhibited individuals who also had social phobia, there were no significant effects of diagnosis on amygdala reactivity to novelty[51]. Because social phobia patients and individuals with inhibited temperament showed similar amygdala response to novelty, Schwartz and colleagues proposed that amygdala hyperactivity in social phobia patients may be influenced by, or perhaps due to, differences in novelty processing that are similar to differences seen in individuals with inhibited temperament[51].

Although social threat tasks are commonly used in social phobia studies, these tasks are infrequently used in studies of inhibited temperament. Only two studies to date have investigated amygdala activity in response to threatening social stimuli in inhibited individuals, and these studies have yielded ambiguous findings. In the first study, Perez-Edgar and colleagues found that inhibited individuals showed increased amygdala activity, relative to controls, in response to threatening faces[65]. However, this increased amygdala activity was found when subjects were required to attend to the emotion of the face, but was not found during passive viewing of threat faces. In contrast, a passive viewing study by Clauss and colleagues found that inhibited individuals showed greater amygdala activity than uninhibited individuals when threatening faces were expected, but not when threatening faces were unexpected[66]. These studies indicate that amygdala activity is increased in individuals with inhibited temperament in response to threatening faces, although attention and expectation may each play a modulatory role. Because both studies were relatively small, further exploration of amygdala response to threatening faces is warranted.

The hippocampus has received much less attention than the amygdala in human studies of inhibited temperament. However, animal lesion studies have demonstrated an important hippocampal role in behavioral inhibition and social interaction. Rats with ventral hippocampal lesions show decreased behavioral inhibition in both novel and potentially dangerous environments, and engage in more social interaction than non-lesioned controls[67], consistent with an anxiolytic effect. Similarly, non-human primates with hippocampal lesions show increased exploration of novel objects and significantly fewer fear behaviors than controls when interacting with novel objects[68]. Additional findings in non-human primates indicate that increased hippocampal function during exposure to a novel environment is predictive of behavioral inhibition[69] and is a key neural signature of anxious temperament[70]. Importantly, hippocampal lesions produce slightly different behavioral phenotypes than amygdala lesions, indicating that the hippocampus has a unique role in the production of anxiety-related behaviors[67;68]. These findings suggest that the hippocampus may play an important role in the neurobiology of inhibited temperament, although investigation of hippocampal function in humans is needed.

In summary, the amygdala and hippocampus show heightened activity in response to novel faces in healthy individuals[71], consistent with their role in both face detection and novelty detection. However, individuals with inhibited temperament show abnormally heightened amygdala activity in response to novel faces[51;53;72], suggesting that abnormally heightened amygdala activity may contribute to increased fear or avoidance of novelty. The mechanisms underlying abnormally heightened amygdala activity and avoidance of novelty in inhibited temperament are not well understood, although altered habituation has been proposed to play a key role[53;72].

Habituation to novelty in inhibited temperament

At its simplest, habituation represents a decreased response to repeated presentations of a stimulus[73]. Novelty detection is a critical first step in the evaluation of potential threats (or rewards) in the environment. However, humans must continually process vast amounts of incoming sensory

information. Therefore, rapid habituation to novel stimuli which are neither threatening nor rewarding is crucial for effective navigation of our constantly changing environment. Neuronal habituation signals safety and familiarity[36;37;74-76], while a failure to rapidly habituate to novelty may trigger feelings of unfamiliarity[36;37;74-76], potentially leading to increased fear and anxiety in novel situations. Although habituation is a fundamental process, individual differences in habituation appear as early as infancy[77;78], potentially providing a neural mechanism for the increased reactivity to novelty observed in behaviorally inhibited infants.

The amygdala and hippocampus are both critically involved in the detection of novelty[36;37;40;50;51;74;75;79-81] and rapidly habituate to repeated exposure[36;37;40;50;74;75;79;81] in healthy individuals. Interestingly, both of these regions show slow habituation to novelty in individuals with inhibited temperament[53;72]. Blackford and colleagues showed that during initial viewing of novel, neutral faces, uninhibited and inhibited individuals had a similar increase in amygdalar and hippocampal activity; however, with repeated presentations of the same neutral faces, uninhibited individuals showed a quick decline to baseline, while inhibited individuals showed sustained amygdalar and hippocampal response after approximately 1 minute of face viewing (Figure 1)[72]. Single-unit recording studies have shown that habituation usually occurs rapidly, with the greatest decrease in response observed between the first and second stimulus repetition[36;37], providing a critical neuronal code for familiarity[36;37;74-76]. Additionally, slow habituation of the amygdala to novel faces, similar to that observed in inhibited temperament, has been associated with more severe social impairment in autism[82]. Therefore, prolonged neural response to novelty is likely to contribute to decreased feelings of familiarity in novel situations[36;37;74-76], and may result in anxiety and uncertainty in novel situations and increased novelty avoidance in inhibited individuals. Preliminary findings in social phobia are less clear. In a single study which investigated habituation in social phobia, social phobia patients showed an altered pattern of amygdala habituation to novel emotional faces, although group differences in the rate of habituation were not found[83]. However, social phobia patients in this study were required to make a gender selection for each face, while habituation studies in inhibited temperament have used passive viewing of faces. Task demands may significantly alter amygdala activity[84-86].

Delayed habituation is associated with reduced ability to discriminate between novel and recently-seen faces[74] in healthy adults, suggesting that altered habituation may affect conscious memory. Habituation is one of

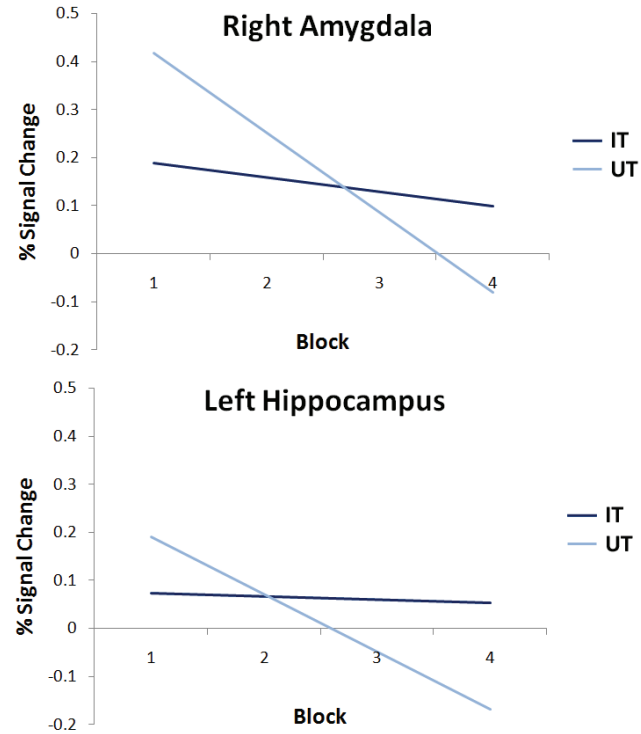

Figure 1. Linear regression of blood-oxygen-level dependent activity by region. Individuals with uninhibited temperament (UT) show a linear decrease in amygdala and hippocampal activity across repeated blocks of neutral faces, indicating habituation to face stimuli. In contrast, individuals with inhibited temperament (IT) do not show habituation of neural activity over repeated blocks of neutral faces. Note: blocks consist of repeated presentations of face stimuli. Each block of face stimuli is 18 seconds long.

the simplest forms of learning and memory in the brain and has been demonstrated in higher order processing regions involved in recognition memory, such as the amygdala and hippocampus[87;88]. This has led to speculation that habituation in the amygdala and hippocampus may be a critical component of short-term recognition memory[74]. This notion is supported by several lines of evidence in both healthy and clinical populations. In healthy individuals, poor working memory for emotional faces is associated with increased amygdala activity during the encoding of emotional faces[89], suggesting that abnormally elevated amygdala activity may disrupt or impair memory formation. Slow habituation in the amygdala, hippocampus, parahippocampal cortex, and perirhinal cortex has also been correlated with poor recognition and episodic memory in patients with Alzheimer's disease[90]. Similarly, slow habituation in the medial temporal lobe has been reported in schizophrenia[91], a psychiatric

disorder associated with memory impairments[92]. Behavioral studies have shown memory impairments for recently familiarized faces in inhibited temperament[93] and social phobia[94], although no studies to date have examined habituation in relation to memory impairments in either of these groups. Although normal amygdala[95] and hippocampal[96] activity is associated with memory improvement in healthy individuals, these findings suggest that abnormally prolonged amygdala and hippocampal activity may negatively affect short-term memory for social stimuli.

Conclusions

Preliminary evidence suggests that the increased amygdala and hippocampal responses to novelty in inhibited individuals may reflect slowed neural habituation in these brain regions. Slow amygdala and hippocampal habituation may have several consequences including increased wariness of novelty, increased fear and anxiety, and reduced declarative memory function in inhibited individuals, contributing to risk for development of social phobia. Future studies should systematically investigate habituation rate in inhibited temperament and social phobia in relation to novelty avoidance, state-based anxiety, and memory ability, in order to understand how habituation contributes to each of these factors.

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