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Volumetric Associations Between Amygdala, Nucleus Accumbens, and Socially Anxious Tendencies in Healthy Women

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Abstract—Socially anxious individuals report higher social fears and feelings of distress in interpersonal interactions. Structural neuroimaging studies indicate brain morphological abnormalities in patients with social anxiety disorder (SAD), but findings are heterogeneous and partially discrepant. Studies on structural correlates of socially anxious tendencies in participants without clinical diagnoses are scarce. Using structural magnetic resonance imaging, the present study examined the relationship between social interaction anxiety and gray matter (GM) volume in 38 healthy women. The amygdala and nucleus accumbens (NAcc) were defined as a priori regions of interest. Moreover, exploratory whole-brain analyses were conducted. Higher levels of social anxiety significantly predicted increased GM volume in the right amygdala [$k = 262$ voxels, voxel-level threshold at $p < .05$ (uncorrected), with a cluster-corrected significance level of $p = 0.05$ calculated by Monte Carlo Simulations] and bilateral NAcc [left: $k = 52$ voxels, right: $k = 49$ voxels; at $p < .05$ (corrected for search volume)]. These relationships remained significant when controlling for a potential influence of trait anxiety. Additionally, socially anxious tendencies were associated with an enlarged striatum [i.e., putamen and caudate; left: $k = 567$ voxels, right: $k = 539$ voxels; at $p < .001$ (uncorrected)]. Our findings indicate that higher social interaction anxiety in healthy individuals is related to amygdalar and striatal volumetric increases. These brain regions are known to be involved in social perception, anxiety, and the avoidance of harm. Future studies may clarify whether the observed morphological alterations constitute a structural vulnerability factor for SAD.

Key words: social anxiety, magnetic resonance imaging, MRI, voxel-based morphometry.

INTRODUCTION

Social anxiety is characterized by a fear of being negatively judged or rejected by others in anticipated or actual social situations (Leary and Kowalski, 1995). The experience of anxiety and discomfort in a variety of social situations, such as during job interviews or public speaking, is quite common and occurs normally across the population (Leary and Kowalski, 1995; Rapee and Spence, 2004). Social anxiety can be considered as a personality trait and individuals differ broadly in their socially anxious tendencies (Leary and Kowalski, 1995). When excessive social fear, feelings of distress in social situations, as well as maladaptive avoidant behaviors lead to functional impairments in daily life, individuals may be diagnosed with social anxiety disorder (SAD, or social phobia, American Psychiatric Association, 2013). With a lifetime prevalence of 11–12% SAD is a relatively common psychiatric disorder (Kessler et al., 2005, 2012), affecting women more often than men (MacKenzie and Fowler, 2013; Jacobi et al., 2014; Kessler et al., 2012).

A growing body of functional neuroimaging research provided consistent evidence for an amygdalar and insular hyper-responsiveness to socially related stimuli in SAD patients, when compared to healthy controls (see Brühl et al., 2014a for a meta-analysis). Structural imaging studies in this field are scarce and revealed discrepant results (see Brühl et al., 2014a for a systematic overview). In the fusiform gyrus, several studies documented greater GM volumes in patients (Frick et al., 2014a; Talati et al., 2013; Tückel et al., 2015), but there is also evidence for reduced cortical thickness in a small sample (Syal et al., 2012). In occipital cortices, volumetric increases have been reported (Frick et al., 2014a; Talati et al., 2013). Moreover, abnormalities in parietal cortices

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Abbreviations: GM, gray matter; NAcc, nucleus accumbens; SAD, social anxiety disorder; SIAS, Social Interaction Anxiety Scale; STAI, State-Trait Anxiety Inventory.

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have been demonstrated, with several studies reporting volumetric increases or cortical thickening (Brühl et al., 2014b; Irle et al., 2014; Talati et al., 2013; Tückel et al., 2015; Zhao et al., 2017), and fewer studies reporting volumetric decreases or cortical thinning (Meng et al., 2014; Syal et al., 2012). In the temporal cortices, increases in thickness or volume have been observed (Brühl et al., 2014b; Frick et al., 2013; Tückel et al., 2015; Zhao et al., 2017), but also decreases (Liao et al., 2011; Talati et al., 2013; Syal et al., 2012). In the orbitofrontal cortex, three studies indicate decreased GM volumes or cortical thinning (Talati et al., 2013; Syal et al., 2012; Zhao et al., 2017). In other regions of the frontal cortex, increases (Brühl et al., 2014b; Irle et al., 2014; Liao et al., 2011) as well as decreases (Syal et al., 2014; Zhao et al., 2017) have been observed. These inconsistent findings may be explained by varying sample sizes, different methodological approaches, and a potential influence of comorbidity, medication, and other psychopathological variables. For example, findings from larger samples ($N > 20$ patients; Brühl et al., 2014b; Frick et al., 2014a; Irle et al., 2014; Talati et al., 2013; Tükel et al., 2015; Zhao et al., 2017) rather point to volumetric increases or thickening in occipital and parietal cortices, and the fusiform gyrus in SAD patients relative to healthy controls. Previous heterogeneous results point out the importance of further research and the conduction of meta-analyses. It has been shown that multivariate pattern recognition methods could successfully discriminate male SAD patients from healthy controls based on GM volume information (Frick et al., 2014b). Correct classifications required volumetric information from the whole brain, since a restriction to the fear circuit (i.e., amygdala, insula, hippocampus, and anterior cingulate gyrus) yielded no satisfactory accuracy. Hence, these findings indicate brain structural abnormalities in male SAD patients, which are rather diffusely distributed and not limited to limbic regions.

Regarding subcortical regions some studies indicate volumetric decreases in the amygdala and hippocampus in SAD relative to healthy controls (Irle et al., 2010; Meng et al., 2013), whereas other researchers failed to find group differences in these brain regions (e.g., Bas-Hoogendam et al., 2017; Brühl et al., 2014b; Syal et al., 2012). Moreover, evidence for an increased density of gray matter (GM) in the amygdala and hippocampus in clinical and subclinical SAD has emerged (Machado-de-Sousa et al., 2014). One study reported volume reductions in the putamen in SAD patients (Zhao et al., 2017), whereas other studies found no alterations in this region (e.g., Potts et al., 1994). In contrast, results obtained from a recent multi-center study with a notably large sample point to GM increases in the right putamen in SAD patients (Bas-Hoogendam et al., 2017).

Previous heterogeneous findings for morphological abnormalities in SAD might be due to gender differences, as has been reported by Irle et al. (2010), or by a potential influence of illness duration on GM atrophy (Machado-de-Sousa et al., 2014; Meng et al., 2013). Machado-de-Sousa et al. (2014) proposed that early stages of SAD may go along with an increased limbic GM density, and subsequent volumetric decreases might be induced by persistent exposure to stressful situations.

Only few studies tried to illuminate brain structural correlates of anxious tendencies or social anxiety in individuals without a history of psychiatric disorders. Findings in healthy subjects with high trait anxiety, a more general disposition to experience anxiety and respond fearfully to a variety of unspecific threats (Spielberger et al., 1983), indicate volume increases in the amygdala (Baur et al., 2012) and nucleus accumbens (NAcc) (Kühn et al., 2011). Anxious temperament in children appears to be associated with an enlarged amygdala (Qin et al., 2014). Furthermore, loneliness seems to mediate a relationship between higher amygdalar volume and feelings of distress in social situations (Tian et al., 2016). A previous study showed volumetric increases in the amygdala and caudate in predominantly healthy adults with behaviorally inhibited temperament, compared to uninhibited adults (Clauss et al., 2014). Inhibited temperament is characterized by shyness, fear, and withdrawal in novel (social) situations and constitutes an important risk factor for developing SADs (see Clauss and Blackford, 2012 for a meta-analysis). In general, the amygdala is known to be a key component in the anxiety network (Tovote et al., 2015), plays a crucial role in the perception and elaboration of emotionally salient social stimuli (Adolphs, 2010), and in enhancing vigilance and guiding attention toward these stimuli (Davis and Whalen, 2001; Phelps and LeDoux, 2005). Therefore, it is not surprising that research on the neural substrates of anxiety and its disorders focused on this brain structure. As a part of the ventral striatum, the NAcc is a key node of the reward circuitry and plays an important role in reward-related approach and avoidance behavior (Haber and Knutson, 2010). However, there is also growing evidence for the involvement of the NAcc in anticipating and actively avoiding potential harm (Jensen et al., 2003; Kohls et al., 2013; Levita et al., 2012). Since social anxiety is characterized by an irrational fear of being socially harmed and an avoidance of social situations, this brain region could also be of particular interest when identifying neurobiological underpinnings of this condition.

In the present study, structural magnetic resonance imaging scans were obtained from young, healthy adults with varying degrees of social interaction anxiety. We aimed to examine the relationship between socially anxious tendencies and GM volume in the amygdala and NAcc. Women appear to be affected by SAD nearly twice as often as men, particularly during adolescence and early adulthood (American Psychiatric Association, 2013). In a large community sample, women reported more fears of being criticized or embarrassed and scored higher in social anxiety measures, when compared to men (Caballo et al., 2014). There is preliminary evidence for gender differences in brain morphological alterations, with male patients, but not female patients, showing reduced amygdalar size compared to healthy controls (Irle et al., 2010). Hence, only women were recruited for this study to increase the chances of detecting relation-

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