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EXPLORING THE SOCIALLY ANXIOUS BRAIN

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ABSTRACT

Social anxiety disorder (SAD) is a prevalent psychiatric condition, which causes considerable suffering. The disorder has for long been studied in neuroscience, although the clinical impact of research results have so far been insignificant. In the first part of this essay, the basic understanding of SAD within cognitive neuroscience is provided. Studies using functional magnetic resonance imaging (fMRI) have revealed that SAD is primarily related to dysfunctions in, and between, threat processing, emotional regulatory, attentional and perceptual neural systems - implicating regions such as the amygdala, insula, prefrontal, parietal and occipital lobes in the disorder. To this background follows a presentation and discussion about more recent research on SAD using a neuroimaging method known as functional connectivity. Here, I find that the functional connectivity research, although problematic in many regards, extends the cognitive neuroscientific view on SAD. This by suggesting that the disorder is related to abnormalities in functional connectivity between several of the above-mentioned regions and within brain networks such as the default mode network. Finally, I explore the potential of functional connectivity as a tool for the diagnosis of SAD and for predicting individual patients' treatment responses. Studies on these topics, while sparse, indicate that functional connectivity measures can make both accurate classifications of SAD and predictions of treatment outcomes on the level of individuals. However, there is not sufficient empirical evidence to suggest that functional connectivity measures are superior to other neuroimaging measures in these contexts. Moreover, there are substantial challenges that need to be surmounted before neuroimaging measures can have clinical viability.

Keywords: social anxiety disorder, social phobia, resting-state functional connectivity, neurodiagnostics, treatment outcome prediction

CONTENTS

1. INTRODUCTION

Everyone is likely to be nervous about social situations at times, in preparation for an important presentation, before a date, or at a party. For some this social nervousness is replaced by an intense social anxiety, fear and distress which seeps its way into almost every social interaction, weighing them down as if they wore shackles attached to an iron ball. These people endure the social reality, which most of us find joy in, with excruciating agony.

On online forums like Social Anxiety Support and Reddit, thousands of users share their experiences of living with social anxiety. One user responds, to the question "what is it like to have social anxiety disorder?", with the following:

"It's like being scared, constantly. Physically, it's like the feeling of accidentally skipping a stair while going down the stairs, but imagine that feeling while doing everything in life... Imagine coming out of every conversation, but instead of having a nice time, imagine your most embarrassing experiences and make that feeling every experience of your life. 'Does this person like me? Was I being too loud? What if she secretly hates me and she's just putting up with me to be nice? What if what I said sounded stupid? What if everyone thought I was being obnoxious? What if they actually don't want to be friends with me? What if I was being too much? What if they secretly make fun of me behind their back?...' It's a lot of constantly worrying, panicking over tiny things that really don't even matter... I've had to leave in the middle of classes, parties, various social events because of my anxiety. It's such a bad way to live life…" (What is it like to have social anxiety disorder?, 2016)

Someone else adds:

"It's like having a monster live inside of your head...This fear wears you down until you give into it before it starts—you stay home all the time, stop answering calls, don't even want to comment on social media in case someone pokes fun at what you have to say. You don't even want to go to the grocery store because people might make eye contact with you, or you'll have to say 3 words to the cashier. You order things online because the thought of going outside makes your heart race with fear."

Social anxiety disorder (SAD) is a sickness of the mind which is estimated to affect 12.5% of the population at some point during their lives (Bruce & Heimberg, 2014; Stangier, 2016). Since the disorder was first recognized as such back in the 70's (Månsson, 2016), the scientific fields studying psychiatric disorders have progressed quite a bit. Neuroscientists,

with the advancements of neuroimaging techniques, have in recent years with an increasing precision become able to study the neurobiological underpinnings of various mental illnesses. Unfortunately, it does not seem as if neuroscience has contributed much to the understanding of psychiatric disorders - at least not in practical terms. In the latest revision of *Diagnostics and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013), few signs of influence from the over 15 000 publications of neuroimaging findings of psychiatric disorders made in the last 19 years are visible (Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015). This implies that, despite significant efforts and resources put into neuropsychiatric research, findings have not been clinically relevant.

What is more, psychiatric disorders are a leading cause of disability in the world (Whiteford et al., 2013). Societal costs, as a consequence, are high. In the year 2010, the total societal cost for anxiety disorders (ADs; of which SAD is the second most common) is estimated to have exceeded 74 billion € in Europe (Gustavsson et al., 2011). Which makes ADs the third most costly group of mental disorder - falling behind only psychotic disorders (e.g. schizophrenia) and mood disorders (e.g. clinical depression). Additionally, research shows that having a mental disorder increases one's likelihood of being affected by physical conditions. It is also believed that having SAD can cause individuals to develop other more severe psychological ailments, such as major depression or substance use disorder (Månsson et al., 2015). Thus, there are clear economic incentives from a societal standpoint to treat and cure individuals suffering from SAD. Unfortunately, the currently available treatment options for SAD aren't as effective as one could hope (Hofmann, 2013; Stein & Stein, 2008).

Albeit neuroscientific research on SAD may not yet have generated findings of clinical importance, methodological and technological advancements have raised hopes that such contributions may come in the near future. In particular, a relatively recently developed method which studies how subjects' brain regions interact (see section 2.2.2. for an explanation) has been argued to have great potential for better understanding brain function and the neural basis of psychological dysfunction (Biswal, 2012; Murphy, Birn, & Bandettini, 2013). Moreover, by combining neuroimaging methods, such as the one mentioned above, with advanced computer software, researchers hope to be able to both identify individuals with SAD and predict their responses to treatments (e.g. Gabrieli et al., 2015; Woo, Chang, Lindquist, & Wager, 2017).

1.1. AIM & STRUCTURE

In this thesis, I primarily aim to present and discuss research findings of functional brain connectomics in SAD in addition to reviewing how and whether such research has contributed to headway in understanding the neurobiological basis of SAD. Furthermore, the potential application of functional connectivity in diagnostics and SAD treatment prediction are considered in a discussion, where I aim to answer if the method is viable for identifying neurobiological markers of SAD on a single-subject level to the degree that could merit clinical use of functional neuroimaging. Is it likewise conceivable that measures of functional connectivity will be useful for predicting individual patients' treatment outcomes, and so contribute to a step forward in the pursuit of treatment optimization?

To discuss and answer these questions, I start off by presenting a background on the pathology of SAD, the relevant fundamental aspects of functional magnetic resonance imaging (fMRI) and functional connectivity - in that order. After that, the cognitive neuroscience of SAD is overviewed from the perspective of experimental fMRI research. Only after this do I move on to presenting functional connectivity research on SAD, from which I eventually segue over to discussing functional connectivity as a single-subject neurodiagnostic and treatment predictive tool. Throughout, I somewhat emphasize resting-state (RS) functional connectivity research since SAD is more explored using this approach, decidedly so in diagnostic and predictive contexts.

2. BACKGROUND

2.1. THE PATHOLOGY OF SOCIAL ANXIETY

2.1.1. THE DEFINITION OF FEAR AND ANXIETY

There are different views in the scientific community on the definition of *anxiety*. Many definitions relate anxiety to *fear* and distinguish the two by defining fear as an immediate response to a threat while anxiety is a sustained fear (Lebow & Chen, 2016). By others, fear has been conceptualized as the emotional response to a direct and immediate threat, whereas anxiety is regarded as that lingering, aching feeling that occurs in anticipation of spatially or temporarily distant or uncertain threats (LeDoux & Pine, 2016).

Of course, how we define concepts dictate how they are used and by extension, how they are operationalized in science. Therefore, even though most have an intuition about the

meaning of these words, which to a large degree overlap, reaching consensus on clear conceptual definitions of 'fear' and 'anxiety' is an important challenge for neuroscientists to tackle, imperative for understanding the neurobiology of these emotional states and disorders rooted in fear and anxiety.

2.1.2. DIAGNOSTIC FEATURES

As a clinical condition, SAD falls under the umbrella category of ADs (Craske & Stein, 2016). Other disorders which are classified as ADs include but are not limited to panic disorder, specific phobias (spider phobia for example) and generalized anxiety disorder (GAD). The common element in all of these disorders is a persistently out-of-proportion fearful, anxious, or avoidant response to perceived threats, which can be both external (e.g. meeting new people) or internal (e.g. unusual body sensations).

Although the pathological aspects of social anxiety were outlined by French psychiatrists already in the early 1900's, it wasn't until the 70's that social anxiety (then called social phobia) was identified as a distinct disorder (Månsson, 2016).

In the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association [APA], 2013) SAD is described as a highly prevalent, chronic mental disorder which is characterized by excessive fear and anxiety during, after or in anticipation of social interactions. Central to the disorder is an excessive distress in relation to social situations, which is either endured or causes avoidance. Nevertheless, the anxiety impairs the affected individual significantly in their social and occupational life (APA, 2013). The sufferer's fear and anxiety are especially oriented around being scrutinized or negatively evaluated by others, possibly as a consequence of her anxious behaviors (APA, 2013). Importantly, anxiety should not be able to be better explained by other psychiatric or somatic conditions (e.g., agoraphobia, panic disorder, obesity) and be a lasting condition over the course of at least six months to be classified as SAD.

While fearing negative evaluation by others is a central symptom in SAD, the APA (2013) added to the DSM-5 that social anxiety might also be about fear of offending others and fear of rejection. The expanded definition may in part be due to the cultural differences that have been found to influence social anxiety. Whereas social anxiety in Western cultures is often rooted in fear of embarrassing oneself, in East Asian societies a fear of offending others appears to be a more common characteristic (APA, 2013; Pannekoek et al., 2013). Another

criteria for SAD is that social anxiety must be out of proportion to the social situation or context. In previous versions of the DSM, it was up to the patient herself to determine whether this was the case or not, in the DSM-5, this has been changed. It is now the clinician that judges if the patient's social fear is excessive or not.

According to the DSM-5, there is, apart from the generalized SAD that has been described above, a *performance only* subtype (APA, 2013). This subtype applies to individuals who only have marked social fear in relation to a specific type of performance. Often individuals with performance fears are most impaired in their professional lives, but not in other social settings. An example would be a teacher who has excessive fear and anxiety related to public speaking.

2.1.3. PSYCHOLOGY

Cognitive models of SAD suggest that negative beliefs about the self are a hallmark of social anxiety (Gilboa-Schechtman et al., 2017; Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009). These negative self-beliefs are further theorized to manifest in socially anxious individuals' tendencies to interpret social cues as signs of disapproval and rejection, which evoke excessive negative emotional and behavioral reactions. Moreover, it has recently become evident that individuals with SAD consistently judge themselves to be of lower social ranking than other people (Gilboa-Schechtman et al., 2017).

Some researchers have suggested that people with SAD have a heightened intrinsic focus on and concern about, others' views about them (Clark & Wells, 1995; Fenigstein, Scheier, & Buss, 1975; Vleeming & Engelse, 1981). Further, a study conducted by Wells and Papageorgiou (1999) indicated that individuals with SAD are biased towards remembering social (but not non-social situations) from an observer's perspective. There are some also studies showing that socially anxious individuals tend to direct their attention inward (on themselves) under situations of social stress (Mansell, Clark, & Ehlers, 2003) and that, for individuals with socially anxious tendencies, focusing on oneself during social situations increases anxiety both and during after an interaction (Gaydukevych & Kocovski, 2012; Zou, Hudson, & Rapee, 2007).

Individuals with SAD have a tendency to engage in various strategies (both behaviors and mental processes) to cope with and avoid their anxiety (Taylor & Alden, 2010; Wells et al., 1995). These so-called safety behaviors include avoiding others' attention and eye contact

so as to not feel negatively evaluated, or memorizing speech in advance to avoid not knowing what to say during an interaction (Kim, 2005). However, engaging in safety behaviors is regarded as being detrimental to the individual: while safety behaviors may prevent discomfort when applied, they simultaneously serve to preserve erroneous assumptions that the sufferer has. Therefore, safety behaviors are considered to be a factor which maintains SAD (Clark & Wells, 1995). In favor of this view, evidence shows that deliberate disengagement from using safety behaviors significantly decreases social anxiety (Kim, 2005).

2.1.4. PREVALENCE

Collectively, ADs are the most common mental health conditions in the world: one in 14 people across the entire planet is estimated to be affected at any given time and one in nine any given year (Craske & Stein, 2016). Among ADs, SAD is the second most common disorder second to the specific phobias. According to estimates, 12.5% of the population suffer from SAD at some point in their life (Bruce & Heimberg, 2014; Stangier, 2016) and around 0.5-2% of the European population develop the disorder yearly (APA, 2013). In Sweden, prevalence seems to be somewhat higher - one source reports that SAD can be found in 15% of the Swedish general population (Furmark et al., 1999) and nearly 1/6th of Swedish university students (Tillfors & Furmark, 2007). In early studies on social phobia, prevalence rates were much lower in the general population. While it is possible that SAD has become an increasingly widespread mental disorder, Månsson (2016) regards the increase in SAD prevalence to rather be a consequence of changes in DSM criteria and developments in study methodology.

Of note, SAD appears more frequently among women than in men (APA, 2013; Beesdo et al., 2007). The APA (2013) write that the disorder is 1.5-2.2 times more prevalent in women than in men and Furmark et al. (1999) report that SAD appears in 18% of females and 10% of males. Månsson (2016) cites one paper from the early 90's where it was suggested that close to 70% of individuals with social phobia were females. It also appears that SAD is more prevalent in some subpopulations than others; the APA (2013) report that, in the U.S., relative to non-Hispanic whites, Native Americans are more likely to have SAD - whereas other groups (African Americans for instance) are affected to a lesser extent.

2.1.5. RISK FACTORS, DEVELOPMENT & REMISSION

Researchers have identified several risk factors that predispose individuals to develop SAD. For one, having a family member with SAD increases one's likelihood of being affected at least two-fold (APA, 2013; Tillfors, Furmark, Ekselius, & Fredrikson, 2001). The disorder is also suggested to have a strong genetic component and to be heritable to 65% (Beatty, Heisel, Hall, Levine, & La France, 2002). Furthermore, psychological traits such as the tendency to be withdrawn, shy or avoidant of new situations due to distress (known as behavioral inhibition) predispose individuals to SAD and are thought to be well-grounded in genetics (APA, 2013).

For many, pathological social anxiety develops in pre- or early puberty, between the ages eight and 15 (APA, 2013). The disorder can often start to take hold after particularly embarrassing incidents, prolonged ostracization or bullying. However, this need not be the case - onset can happen slowly and subtly. Only in rare cases does the disorder bloom later in life, then the onset may often occur in connection with particularly stressful or life-changing events.

Some research suggests that a considerable proportion (30%) of those that are affected by SAD spontaneously recover within a year and 50% over multiple years (APA, 2013). For 60% of individuals that are affected, it may take many years before symptoms retract. In a recent review, the estimated rates of (partial and full) spontaneous remission are reported to vary from 3% to 93% depending on the type of study (e.g. during what times span, retrospective or prospective). The vast variation in remission rates led the authors to speculate that there may exist different course types of SAD - spanning from short-lasting to persistent and chronic (Vriends, Bolt, & Kunz, 2014).

2.1.6. COMORBIDITY

Very often SAD precedes other, severe psychological disorders (Månsson et al., 2015) like depression or substance use disorder (APA, 2013). APA (2013) suggested that the development of these additional mental disorders may be consequences of prolonged social isolation due to avoidance or self-medication to cope with social fears. What is more, suicide attempts are nearly six times as common among individuals with clinical social anxiety compared to healthy individuals (Schneier, Johnson, Hornig, Liebowitz, & Weissman, 1992).

Depression is a common comorbidity among individuals with SAD and having SAD makes one twice as likely to become depressed (Beesdo et al., 2007). Not only does SAD often precede depression, research shows that it can also make depressive symptoms more severe. It has similarly been reported that almost half of individuals with SAD co-suffer from alcohol abuse and dependence in the United States and that 22.3% suffer from drug use disorders (Grant et al., 2005).

An increasing number of studies have also related psychiatric illness with physiological diseases, such as hypertension (Licht, de Geus, van Dyck, & Penninx, 2009; Penninx, Milaneschi, Lamers, & Vogelzangs, 2013). Preliminary results additionally indicate that SAD and other ADs are associated with accelerated aging (Verhoeven et al., 2015).

2.1.7. TREATMENT

Despite the agony and social impairment that living with SAD can inflict upon a person, it is uncommon that individuals seek treatment in Western societies. Only about half of those that have SAD ever reach out for professional help and often after 15-20 years of illness (APA, 2013). Out of the available treatment options for SAD, cognitive behavioral therapy (CBT) is the best followed by psychotropic intervention using selective serotonin reuptake inhibitors (SSRIs), according to a recent extensive meta-analysis of intervention effectivity in SAD (Mayo-Wilson et al., 2014). Although both CBT and SSRI treatment is generally effective and significantly more so than placebo, treatment responses for individual patients vary. For 30-50% of patients undergoing CBT, treatment is not adequately efficient (Hofmann, 2013; Klumpp, Fitzgerald, Angstadt, Post & Phan, 2013). Another source reports that 50% do not respond to either SSRI or CBT (Stein & Stein, 2008). Of those that do respond to SSRI, positive effects seem to wane after the drug is discontinued (Mayo-Wilson et al., 2014). In 25% of those that do continue with medication, relapse is still likely to occur after 6 months.

A substantial amount of misery is caused by SAD. The disorder affects a large percentage of people and is associated with high costs for society. Although severity and longevity of the disorder vary a lot, so do the effects of treatment. Therefore, there is a great incentive to learn more about the biology of SAD, explore various methods for increasing effectivity of diagnosis as well as treatment. One way to approach these issues is through the lens of neuroscience, where neuroimaging has proven to be a valuable tool in outlining

neuropathological elements of SAD and putative potential in diagnostics and prediction of treatment response.

2.2. FUNCTIONAL MAGNETIC RESONANCE IMAGING

Having access to oxygen is essential for most life forms on Earth. In human cells, diatomic oxygen molecules partake in several fundamental processes. In order to supply bodily cells - including neurons - with oxygen, the blood carries oxygen molecules bound to the protein hemoglobin. When blood subsequently leaves a cell, the oxygen has detached itself from the hemoglobin molecules. Oxygen-carrying hemoglobin and non-oxygenated hemoglobin have different magnetic properties - this magnetic difference is capitalized on in the neuroimaging technique known as functional magnetic resonance imaging (fMRI) (Murphy et al., 2013).

In fMRI, the MRI instrument is adjusted to detect the magnetic signal of oxygenated blood, commonly called blood oxygenation level dependent signals (BOLD for short). As such, fMRI detects regions of the brain where the concentration is increased relative to the rest of the brain and measures this increase. Murphy et al. (2013) explain that since neural activity is largely driven by oxygen, BOLD signals provide an indication of neural activity in the brain tissue based on how much oxygenated blood is supplied to a region of interest.

The method is highly susceptible to noise and therefore requires the use of sophisticated analytical tools for data to be meaningful. The temporal resolution of fMRI is also quite poor in comparison to other neuroimaging techniques. However, because of its ability to measure brain activity with a high spatial resolution, fMRI has been an important tool in exploring the brain and its subregions' functions over the years.

2.2.1. EXPERIMENTAL FUNCTIONAL MAGNETIC RESONANCE IMAGING

A vast majority of fMRI studies investigate the neural activity as elicited by some task or stimuli that the observer employs through various experimental paradigms. Similar trends can be found in neuroscience using other instruments for measuring brain activity, such as EEG.

Through the use of task-based fMRI paradigms, research has been able to isolate specific regions and networks which are functionally relevant for the performance of various tasks, based on the activation pattern elicited by the task. Two paradigmatic study

methodologies are *event-related* and *block designed* fMRI. In block designs, experimental conditions (tasks or stimuli) are arranged in separate blocks, lasting a certain period, which are presented alternatingly (Amaro & Barker, 2006). Blocks are distinguished by the cognitive process(es) that they invoke and are alternated continuously to maintain the subject's engagement in the experiment. Event-related fMRI contrastively involves presenting conditions one at a time, separated by periods of inactivity. Depending on what kind of experimental design that is applied, the nature of the hemodynamic response may vary in experiments.

The endeavor to understand the brain's responses to behavioral and perceptual tasks has overall been successful in generating knowledge about brain function. However, the large focus on evoked brain responses has in much amounted to scientific neglect of the brain's intrinsic and spontaneous activity.

2.2.2. THE BRAIN'S INTRINSIC ACTIVITY & FUNCTIONAL CONNECTIVITY

For the average human, the brain accounts for 2% of her total body weight. Despite the brain's mass being relatively insignificant for a person's weight, at rest, it accounts for a whole 20% of the body's total energy consumption (Clarke & Sokoloff, 1999). This indicates that metabolic activity is continuously ongoing in the resting brain to a significant degree. In recent years, the neuronal activity that is intrinsic to the brain - that is, the activity that is not explicitly caused by stimulation from the outside world or conscious mental processes has gained increasing attention within the neuroscientific community.

That the brain is constantly sparkling with neuronal activity in the absence of deliberate stimulation was discovered already in 1929 by Hans Berger, the man responsible for inventing electroencephalography (EEG). Though for long this intrinsic activity of the brain was largely overlooked. It was regarded as being insignificant noise and therefore averaged out in both fMRI and EEG research (Fox & Raichle, 2007; Raichle, 2015). This was until 1995 when Biswal, Yetkin, Haughton, and Hyde (1995) made a groundbreaking discovery about the brain's activity at rest.

While initially being concerned with understanding how noise signals (stemming from cardiac and respiratory activity) varied between rest and task conditions, Biswal et al. (1995) instead found that low-frequency (<0.1 Hz) fluctuating activity in the two hemispheres of the somatomotor cortex displayed significantly correlated activity at rest. This

finding was groundbreaking in that it suggested that BOLD signals that were previously believed to be noise to be done away with could actually be meaningful brain activity. Why? Because the two regions displaying correlated BOLD activity (left and right somatomotor cortex) have similar functional properties, hence the observation that they are synchronously activated implied they are engaged in continuous connective interactions.

Biswal et al.'s (1995) findings in the somatomotor cortex of resting subjects have since been replicated numerous times (see for example Fox, Snyder, Zacks, & Raichle, 2006; Fox, Snyder, Vincent, & Raichle, 2007). What is more, research has revealed that a great number of other brain regions display correlated activity during rest (Smith et al., 2009) and that patterns of intrinsic activity are reliably stable across and within individuals over time (Chen et al., 2015; Guo et al., 2012; Zuo & Xing, 2014). Though it has been likewise noted that RS activity can be significantly modulated by learning (Albert, Robertson, Miall, & Hall, 2009; Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009), moods (Harrison et al., 2008), emotions (Lamke, Gaebler, Rahman, Daniels, & Do, 2014) and other subjective states (Carhart-Harris et al., 2012).

Regions that display correlated activity during rest have been categorized into several different functional connectivity networks, so-called resting-state networks (RSNs) – which are characterized by the property of brain areas within a network showing high levels of correlated intrinsic brain activity with one another, but weak, no or negative (Fox et al., 2006; Fox & Raichle, 2007) correlations with other regions (which belong to other networks). These RSNs have subsequently been observed to correspond, at large, to same networks of brain regions which are seen to be activated by various tasks and stimuli in fMRI experiments (Smith et al., 2009). Interestingly, the brain's spontaneous activity as organized into RSNs continues, though slightly modulated, during task performance (Fox & Raichle, 2007). The intrinsic activity of the brains also to a degree continuous across mental and conscious states, awareness levels (indeed even during anesthesia) and sleep (Deco, Jirsa, & McIntosh, 2011) - meaning that it has functions beyond psychology and consciousness.

The term functional connectivity can be used to describe the correlated interregional BOLD activity in both task-based and RS-fMRI studies, which can be confusing (Fox & Raichle, 2007). However, since RS functional connectivity persists during tasks, some have questioned whether these two types of functional connectivity measure the same thing.

Although functional connectivity is to some extent necessarily dictated and constrained by the structural connectivity (anatomical connections) of the brain, research has shown that the existence of one does not infer the other and that there can be functional connectivity between regions that are not directly anatomically linked (Honey et al., 2009).

Studying brain's intrinsic activity and the functional connectivity between various regions has become increasingly popular and is today one of the largest and fastest growing fields of research within the branch of neuroscience that uses fMRI (Friston, 2011). RS functional connectivity allows researchers to map and understand how regions and networks across the entire brain interact continuously (see the Human Connectome Project: humanconnectomeproject.org) while avoiding task-related confounding factors and certain assumptions about neural activity that are required in task-based designs (Fox & Greicius, 2010). The relative simplicity of RS functional connectivity methodology compared to task-based fMRI is one of its main strengths. Nevertheless, RS functional connectivity has its intricacies.

A myriad of methods and variations are available for the processing and analysis functional connectivity data. Each of these is based on some specific assumptions about brain activity and result in separate functional connectivity measures (Margulies et al., 2010). Two of the most common approaches are independent component analysis (ICA) and seed-based analysis. In the seed-based approach, one or several regions of interest are identified *a priori*. During subsequent scanning, the BOLD signal in the chosen area(s) is compared to activity measured in other voxels (arbitrary three-dimensional points in the brain) to find correlations between these and the seed region. Many favor this method due to its relative simplicity, directness, and accuracy (Fox & Raichle, 2007). However, one of its limitations is that researchers' biases might heavily influence the *a priori* selection of seed regions and further contribute to biased results. In order to curtail this problem, ICA may be used instead (Margulies et al., 2010). This technique constitutes an analysis of whole-brain BOLD data sets which do not require predefined regions of interest. Instead, the BOLD data is decomposed into statistically maximal independent components (Fox & Raichle, 2007), making ICA especially effective for identifying and mapping the spatial distribution of functional connectivity networks (Margulies et al., 2010). Another benefit of ICA is that it differentiates between various sources of BOLD signals (e.g. noise from network activity)

easily. Though a drawback is that the method is based on the questionable assumption that the signal properties in a given functional network are unique and independent.

Knowledge about the general patterns of neural activation and interaction can potentially be highly relevant for all fields of research concerned with the human brain. In the context of clinical research, being able to study widespread regions and functional connectivity within networks, between networks, as well as locally within regions allows understanding pathology at the level of functional brain organization - rather than through over or under-activation of specific regions (MacNamara, DiGangi, & Phan, 2016). Some also view the goal of organizing the brain into functional networks as a potential revolution in how psychiatric disorders are classified, shifting focus from a symptom-fixated perspective to an intersubjective network-based one (Sylvester et al., 2012). Despite the usefulness of studying brain connectomics at rest, task-based functional connectivity can be an important complementary approach when functional connectivity is used to study specific conditions, states or mental phenomena which relate to cues from the external environment, like social anxiety.

In the two previous section, a background on what is known about the pathological aspects of SAD was given. Thereafter, the fMRI instrument was introduced as a tool for brain exploration. Two main methodological approaches used in fMRI research - experimental fMRI and functional connectivity- were also discussed. In next section (3.), neuroscientific research on SAD using mainly experimental fMRI will be presented, in addition to some theoretical perspectives on the results of such research.

3. COGNITIVE NEUROSCIENCE OF SOCIAL ANXIETY DISORDER

There is a large body of research within the cognitive neurosciences on the neurobiology of SAD and the disorder has been studied in as many ways as there are methods available in the field. Many studies use neuroimaging techniques such as fMRI to compare the brains of individuals with SAD to those of healthy persons. Based on this research, several extensive meta-analyses and reviews have been written in the last decade (e.g. Brühl, Delsignore, Komossa, & Weidt, 2014; Cremers & Roelofs, 2016; Etkin & Wager, 2007; Freitas-Ferrari et al., 2010). These sources provide the basis for the following summary of what is known about SAD in cognitive neuroscience.

In the field, SAD is conceptualized as a pathology that is mainly associated with aberrancies in neural system involved in the processing of threat as well as generating and regulating emotional experience and responses (see for example Etkin, 2009). Therefore, I will briefly overview the neural underpinnings of these processes before delving deeper into SAD-specific research.

3.1. THE NEURAL BASIS OF FEAR AND ANXIETY

The amygdala is well established as a key brain region for the processing of negative emotion and fear or of threatful stimuli in both human and nonhuman animals (Etkin, 2009; Tovote, Fadok, & Lüthi, 2015). Anatomically, the amygdala is housed in the medial temporal pole on either side of the brain (Bear, Connors, & Paradiso, 2016). It is almond-shaped and composed of several cytoarchitecturally distinct substructures, which are regarded as having functional differences.

The amygdala receives input from a large variety of sources - from several subcortical structures and all five of the cortical lobes. The amygdala's basolateral nuclei receive direct input from the sensory systems in addition to the anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (VMPFC) – which are involved in cognitive, attentional and emotional processes (Etkin, 2009). The amygdala, in turn, has efferent connectivity back to the VMPFC as well as with deeply seated brain areas involved in autonomic regulation and behavioral responses – which indicates that the amygdala is important also for physiological expressions of fear and anxiety.

Human subjects that have received electrical stimulation to their amygdala have reported feeling fear or anxiety (Etkin, 2009). The amygdala also activates when healthy subjects are presented with threats and even more so in anxiety patients (LeDoux & Pine, 2016). Etkin (2009) reports that the amygdala lights up in response to anxiety-provoking stimuli that is processed both within and outside of awareness. He describes one study where the magnitude of activity in the basolateral amygdala in response to unconsciously processed fearful faces corresponded to participant's pre-test self-reports of anxiety.

Patients with amygdala lesions, on the other hand, have severe deficits in their ability to label facial expression of negative emotion and to form fear-based memories (Etkin, 2009). Their physiological reactions to threats are similarly dysfunctional and substantially weaker than normal (LeDoux & Pine, 2016). However, these patients are still able to experience fear,

panic, and anxiety subjectively. This last observation suggests that the systems responsible for physiological and subjective threat response do not correspond (LeDoux & Pine, 2016).

LeDoux & Pine (2016) argue that the neural system responsible for creating bodily reactions of fear and anxiety is distinct from the system that produces the phenomenology of fear and anxiety. Their view is supported by evidence that there are discrepancies between subjective reports of fear and anxiety with measures of behavioral and physiological reactions: in studies where threats are present subliminally to subjects, the amygdala is still activated and contributes to bodily threat responses - even if the subjects report no feelings of fear and anxiety (LeDoux & Pine, 2016). This has been observed not the least in patients who cannot consciously experience visual stimuli presented in parts of their visual field. Such patients exhibit increased amygdala activity as well as behavioral reactions to threatful stimuli even though they are not aware of the stimuli nor report feeling fear. Hence, the common theory - that there exists a core fear circuitry from which both subjective and behavioral responses to threat stimuli are produced - is likely erroneous.

Additionally, LeDoux & Pine (2016) point out that researchers have often used the words *'fear'* and *'anxiety'* to refer to physiological and behavioral responses of both nonhuman and human subjects, which may have contributed to a tacit belief that there is only one system for threat response. They contend instead that *'fear'* and *'anxiety'* should only be used in reference to subjective experiences, whereas their behavioral and physiological counterparts should be called *'defensive'*. Based on this distinction they further describe a basic model of defensive circuitry and fear and anxiety circuit.

According to their model (LeDoux & Pine, 2016), the defensive circuit involves sensory data being processed by the amygdala which produces an immediate defensive reaction (freezing) and feeds information forward to the striatum - from which a defensive action such as avoidance is produced. Thus, the amygdala is likely to only contribute to subjective fear and anxiety indirectly by detecting and creating initial responses to threats. The feelings themselves, fear and anxiety, are postulated to arise out of a cortical network including the prefrontal cortex (PFC), insula and posterior parietal area, which receive inputs from both sensory systems and the defensive circuit.

In this cortical network, the insula, in particular, has been demonstrated to be of relevance for fear and anxiety. The insular cortex can be found folded in the lateral sulcus (the fissure which separates the temporal, frontal and parietal lobes) on either side of the

brain. The general view implicates the insula in autonomic regulation, monitoring and awareness of bodily states and sensation, tactile perception (Freitas-Ferrari et al., 2010; LeDoux & Pine, 2016), emotional processes and to some extent even social cognition (Kolb, Whishaw, & Teskey, 2016). The area is strongly connected to the amygdala, as well as to many of the same subcortical regions (Etkin, 2009). Although the insula's function in negative emotional processing is much less explored than the amygdala's, it frequently activates in unison with the amygdala in experiments, particularly so during emotional processing tasks (Brühl et al., 2014) and there is substantial evidence of its importance in fear and anxiety. For instance, the insula together with the amygdala show increased activity in fear conditioned healthy individuals when they are exposed to the conditioned stimuli (Etkin, 2009). That both fear conditioning and various forms of anxiety are associated with hyperactivation in amygdala and insula not only supports the notion that fear and anxiety are closely related emotions but further implies that a key component in AD pathology is associated with an overly active or reactive fear system (Etkin & Wager, 2007) – making them highly relevant targets in the study of SAD neurobiology.

LeDoux and Pine's (2016) two system-framework is certainly well-motivated based on the evidence they raise against the traditional fear circuitry view. However, it is controversial and not sufficiently elaborate - especially with regards to the cortical network that they propose. Moreover, their framework specifically outlines neural systems for threat processing, fear, and anxiety, even though it is still unclear whether all emotions are generated by the same systems or if different emotions are produced differently in the brain.

Ochsner, Silvers, and Buhle (2012) present a general account of emotional generation, which in the present context serves as an alternative LeDoux and Pine's (2016) framework. Ochsner et al. (2012) suggest that emotions are generated principally in four stages. In the initial two stages, stimuli (either internal or external) are encoded and attended to based on the situational context. Thereafter, the significance and value of the stimuli are assessed. The fourth and final stage consists of translating the appraisal into emotional experience, behavior and autonomic responses. According to Ochsner et al. (2012), these last two stages describe processes occurring predominantly in the amygdala, ventral striatum, VMPFC, and insula.

3.2. THE NEURAL BASIS OF EMOTIONAL REGULATION

Besides deficits in emotional generation and reaction, many psychiatric disorders are linked to deficits in emotional regulation. According to Jazaieri, Morrison, Goldin, and Gross (2015), *emotion regulation* refers to the cognitive effort made by a person to influence and control their current emotional states, how they are experienced and expressed. Others use a broader definition of the term and include both conscious and autonomic processes (Hartley & Phelps, 2010; Ochsner et al., 2012). The process of regulating emotion has been shown to be dysfunctional in many ADs, SAD included. Individuals with SAD are observed to have difficulties with multiple types of emotion regulation, some of which are reviewed in Jazaieri et al. (2015).

One emotional regulation strategy with which SAD patients struggle is characterized by changing one's emotional response by reinterpreting the stimuli causing the emotional reaction (Ray, McRae, Ochsner, & Gross, 2010). In the context of social anxiety, a situation where this strategy could be usefully applied is when one is anxious about attending a meeting, as an example. In this scenario, reinterpreting the meeting as something good by actively thinking of and focusing on how attending it is beneficial and positive, consequently downregulating the anxious feeling, would constitute a successful application of the strategy. This specific strategy is known as (cognitive) reappraisal and is a hallmark of CBT (Jazaieri et al., 2015).

In neuroimaging studies, emotional regulation has been related to activity in several prefrontal regions (Brühl et al., 2014) such as the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), ACC, dorsomedial prefrontal cortex (DMPFC), and VMPFC (Etkin, 2009; Ochsner et al., 2012), which are also key to the brain's executive functioning. These regions are thought to mediate activity in amygdala through direct or indirect recurrent connections (Etkin, 2009; Hartley & Phelps, 2010).

To summarize, the previous two sections outline two neurofunctional systems. The first system, where the amygdala and insula are central is thought to be crucial for fear and anxiety. The second system had an emotional regulatory function and involved PFC regions. Regions in these two systems largely overlap with the areas that have been observed to activate abnormally in experiments on SAD; this will become more evident in the next section.

3.3. THE NEURAL BASIS OF SOCIAL ANXIETY

3.3.1. EXPERIMENTAL FUNCTIONAL MAGNETIC RESONANCE IMAGING FINDINGS

The neural substrates of SADs have been extensively studied using fMRI. A majority of studies have focused on BOLD activity responses to stimuli used specifically to trigger SAD fears and symptoms (Brühl et al., 2014; Fouche, van Der Wee, Roelofs, & Stein, 2012). Often in these studies, subjects are presented with emotional facial expressions or exposed to social criticism and violations. In a typical experimental task, participants are asked to, by pressing buttons, determine the emotional expression of a presented face. At other times, BOLD activity is measured during self-related thoughts in anticipation of public speaking or similar. Occasionally, researchers may use cognitive, social or emotional tasks that do not specifically provoke SAD fears, such as computerized trust games or reward anticipation tasks (Brühl et al., 2014).

As noted by Månsson (2016), fMRI experiments on SAD exist in primarily two types. In the first type, researchers study automatic processing of and reactions to, threat stimuli. Contrastively, when the aim is instead to study how subjects' brains perform a certain operation during stimulation, another design is used. This latter approach could constitute presenting a subject with a threatful face and asking them to reappraise it to neutrality or positivity. In this scenario, the neural activity of interest is related to the reappraising process, the *extended action* after stimuli presentation, rather than the immediate neural reaction to a stimulus (Månsson, 2016). These two different approaches will lead to different BOLD activity outcomes. Reactive experiments are likely to record activity in sensory and threat-responding regions, whereas extended action ones will find activity in cognitive and emotional processing areas. Therefore, considering that these methodological differences exist is important when regarding aggregated results from meta-analyses, where they tend to go unnoticed.

The across-the-board most robust finding in all fMRI research on SAD and other ADs is hyperreactivity of patients' bilateral amygdala and insular cortices to stimuli (Etkin, 2009; Etkin, 2012; Fouche et al., 2012; Brühl et al., 2014). The types of stimuli that evoke this marked overt activity in the amygdalae and insular cortices of clinical compared to healthy individuals vary depending on the AD. Though SAD is unique in that it is especially facial expression-stimuli that evoke such responses (Blair et al., 2008). It is not only in response to

negative or threatening emotional faces that the amygdala and insula activate in SAD but to neutral faces as well. Of relevance, SAD individuals have a biased perception of facial expressions and are more prone to interpret neutral faces as negative and threatening (Birbaumer et al., 1998; Freitas-Ferrari et al., 2010).

In a meta-analysis which included over 30 task-based fMRI studies of SAD published between 2009 and 2014, Brühl et al. (2014) further reported that the bilateral medial prefrontal cortex (MPFC) and VLPFC, ACC and parietal cortex are often engaged by tasks in SAD patients compared to healthy control subjects (HCS). Some studies consistently showed activations in the hippocampus, fusiform gyrus – which have both been hypothesized to have their respective roles in ADs (Etkin, 2012). Moreover, activations in patients' DLPFC, VMPFC, thalamus and occipital lobes and are also recurring. These results are on a general level well in line with what previous meta-analyses of SAD research have reported (Etkin & Wager, 2007; Freitas-Ferrari et al., 2010).

Furthermore, by pooling data from studies included in their own meta-analysis with those in Etkin and Wager's seminal (2007) analysis, Brühl et al. (2014) found activity in the amygdala, insula, MPFC, DLPFC, and occipitotemporal cortex. The frequency with which activity in the above-mentioned structures has been observed, and the variety of tasks, suggests that they are important neurobiological components of SAD. This is emphasized in some studies, where social anxiety severity has been correlated with regional BOLD activity. Most often, results show that the more a person's amygdala is activated by stimuli, the more severe their social anxiety is (Brühl et al., 2014).

3.3.2. NEUROCOGNITIVE MODELS OF SOCIAL ANXIETY

Based on these experimental fMRI findings, neurocognitive models of SAD have been proposed aiming to explain the functional role and contribution of the brain regions shown to be involved in SAD and relate them to symptomatology (Etkin & Wager, 2007). These models seek to explain the role of brain regions and networks in SAD from the broader perspective what is known about their function from affective and cognitive research. However, a crucial limitation in SAD neuroimaging research is understanding whether the observed activation differences reflect manifestations of pathology or compensatory responses (Freitas-Ferrari et al., 2010).

As expected, the amygdala and insula are core regions in models of social and other ADs (Brühl et al., 2014; Cremers & Roelofs, 2016; Etkin, 2009; Etkin & Wager, 2007; Grupe & Nitschke, 2013). Etkin (2009) proposes that in SAD, a limbic network, in which the amygdala and insula are central, processes sensory information and generates physiological and subjective, affective responses to the stimulus - it registers and reacts. Information about the emotional stimulus is then relayed to anterior brain areas, which monitor and evaluate it further, making it available to conscious perception. These areas feedback into the limbic system and regulate the emotional response through inhibition or activation.

In a previous section (3.2.) it was mentioned that multiple prefrontal regions associated with SAD are involved in emotional regulation and cognitive control. From this perspective, there are a number of possible ways to interpret increased activity in these areas in SAD studies (Brühl et al., 2014). For example, the data can be taken to indicate that SAD patients are attempting to regulate their negative emotions in response to the stimuli, but that the regulatory activity does not reach the amygdala (due to a hypothesized disturbed connectivity) or is not effective in regulating the amygdala. Another interpretation is that the hyperactive amygdala drives prefrontal activity. Regardless, at the essence of neurocognitive views of SAD are a hyperreactivity to social information in the threat processing system (amygdala and insula mainly) coupled with aberrant functioning in PFC regions important for generating evaluating and regulating emotional content.

Recently, areas of the parietal and occipital region have been implicated in the top-down control of attention (Brühl et al., 2014). However, since these areas have increased activity in SAD, even though patients exhibit deficits in controlling and directing attention away from negative stimuli, Brühl et al. (2014) hypothesize that they may have a disrupted connectivity with amygdalar circuitry, making heightened efforts to regulate attention futile.

The fusiform gyrus, located in the occipital lobe, critically supports facial processing. Thus, according to Brühl et al.'s (2014) model of SAD, the elevated fusiform gyrus activity might reflect the sensitivity to facial expressions of SAD patients. However, the same area is also implicated in emotional responses to scenes, which might mean that fusiform reactivity in SAD reflects an overreactive emotional system in patients.

Beyond the view presented here, which focused on SAD, there are recent theoretical works which provide important contributions to the cognitive neuroscience of anxiety at large (see for example Grupe & Nitschke, 2013).

While task-based fMRI has certainly so far been the most used method to probe the socially anxious brain, in recent years several newer imaging approaches have been used to study SAD.

3.3.3. ANATOMICAL ALTERATIONS

Understanding how anatomical structures and connections are altered or dysfunctional in SAD patient populations could provide important insight into the symptoms and mechanisms of the disorder. However, as of yet, most studies have been either weak in power or provided results that are inconsistent with other studies - making it difficult to draw any warranted conclusions based on the available research (Brühl et al., 2014). From this follows that the research presented in this section will be only indicative and not well established.

A recurring observation in SAD patient's left hemispheres are decreases in microstructural integrity of a white matter tract that connects ventral prefrontal and anterior cingulate regions with medial temporal lobe structures such as amygdala and hippocampus (Grupe & Nitschke, 2013; Brühl et al., 2014). Abnormalities in the same white matter structure have also been found in patients suffering from GAD and in individuals high in trait anxiety (Grupe & Nitschke, 2013). As previously noted, both VMPFC and ACC are primary structures in emotional regulation (Grupe & Nitschke, 2013). Moreover, the VMPFC appears important in reward (Etkin, 2009), arousal (Lebow & Chen, 2016), decision-making processes, assigning value and cost of future events (Grupe & Nitschke, 2013). A disrupted connectivity between the amygdala and these ventro-frontal regions could underlie pathological emotional regulation, arousal to social contexts, social decision-making and reward from social behavior associated with SAD.

A recent study found a structural irregularity in another white matter fiber connecting occipitotemporal areas with the PFC in SAD patients (Tükel et al., 2017). The researcher also found that fibers connecting occipital areas like the fusiform gyrus to amygdala on the right side were deviant. Interestingly, the severity of anxiety in patients correlated with the measure of reduced integrity in these two fiber tracts. Aberrant functioning in connections going from occipital parts to the PFC, and from the fusiform gyrus to amygdala, might be related to pathological facial processing in SAD, since communications between these regions are important for facial processing (Tükel et al., 2017). More support for abnormal facial processing in SAD comes from a study on gray matter volume in patient’s brains. The

study, which used a generous sample of 48 SAD patients, found that they had significant enlargements in multiple visuals regions implicated in the evaluation of emotional faces (Frick et al., 2014a). Moreover, Frick et al. (2014a) speculate that SAD symptoms like heightened self-consciousness and attention to negative facial expressions might increase neural activity in these regions and contributes to increased gray matter volume in them.

In summation, current neuroanatomical works on SAD modestly suggest that there are structural abnormalities in amygdalar-VMPFC white matter connectivity and occipital facial processing regions.

4. FUNCTIONAL CONNECTIVITY IN SOCIAL ANXIETY DISORDER

Research on functional connectivity changes associated with SAD pathology is, despite a large number of studies, in an early phase. One primary problem is that a multiplicity of methods and analytical approaches are applied in functional connectivity studies of SAD (Cremers & Roelofs, 2016; Brühl et al., 2014). Therefore most results are not replicated or supported by similar research. Moreover, there are many inconsistencies in findings (Brühl et al., 2014), which urges caution when integrating functional connectivity results with the wider cognitive neuroscience of SAD. These inconsistencies are related to the functional connections shown to be significantly changed in SAD patients compared to controls. For those connections that do appear to be abnormal in SAD, the research is often equivocal as to whether they are stronger or weaker than in healthy persons.

Additionally, the clinical significance of increases or decreases in functional connectivity (irrespective of measure) is so far not ascertained (MacNamara et al., 2016). Just the same, what negative (anti-correlated) functional connectivity values signify is very much a subject of debate (Chen, Chen, Xie, & Li, 2011). Therefore, interpreting neuroscientific results from a psychological perspective is difficult. Succinctly put, research is far distant from being able to answer how functional connectivity manifest itself in behavior or phenomenology of patients.

Regardless, changes in functional connectivity do seem to be relevant for SAD since 1) many studies find differences from healthy individuals and 2) often these differences in functional connectivity results correlate with measures of patients' questionnaire-assessed disorder severity (Ding et al., 2011; Liao et al., 2010a; Liao et al., 2010b; Qiu et al., 2011).

Furthermore, the findings of disturbances in connectivity between various regions are increasingly providing an understanding of SAD as a disorder which is associated with widespread alterations in brain organization.

The previously mentioned extensive meta-analysis by Brühl et al. (2014) included an analysis of a majority of the currently available exploratory studies where both task-based and RS functional connectivity was assessed in SAD. These studies found differences in functional connectivity between numerous and widespread brain regions in SAD patients. Results were very mixed and if comparable, many times incongruent. Nonetheless, Brühl et al. (2014) were able to point out some general tendencies in functional connectivity, especially between those areas that have been associated with SAD in experimental fMRI (see section 2.3).They integrate the aggregated results from their meta-analysis into their model of SAD neurocircuitry, which is an extension of a model outlined by Etkin and Wager (2007), described in section 3.3.2. Their extended model presents a schematic outline of brain connectivity alterations between several different regions (see Fig 1.), which are overactive in SAD. The following section will discuss results in as far as they have been theoretically linked to SAD pathology by Brühl et al. (2014).

4.1. META-ANALYTICAL FUNCTIONAL CONNECTIVITY FINDINGS

Brühl et al.'s (2014) meta-analysis reveals a tendency of results to show increased amygdala-PFC connectivity, which according to the authors could reflect an increased bottom-up influence of the amygdala on higher cognitive and emotional processing regions. Elsewhere, it is suggested that stronger functional connectivity between these two regions might reflect a bias towards threat-related processing, hypervigilance to threat and exaggerated threat responses (Ding et al., 2011; Liao et al., 2010b).

Regions in the occipital lobe have been found to have increased functional connectivity with amygdala as well as with the PFC in studies (Brühl et al., 2014). The occipital lobe is dominated by visual processing areas. Therefore, increased connectivity of regions in this area with the amygdala might underlie the increased sensitivity to social visual stimuli of especially negative emotional valence that is so characteristic of SAD in imaging research (Liao et al., 2010b). Similarly, it is proposed that increased communication between the occipital cortex and PFC in SAD also indicates a mechanism underlying abnormal social visual processing in SAD. Ding et al. (2011) suggest that disrupted fronto-occipital

connectivity may be specifically related to SAD deficits in assessing threatfulness of facial expressions.

Furthermore, both the PFC, occipital cortex, and amygdala appear to have decreased functional connectivity with the parietal lobe in SAD patients (Brühl et al., 2014). In particular, the evidence suggests that among the affected parietal regions are precuneus and posterior cingulate cortex (PCC). These two regions appear to be central hubs of the entire brain. Thus, significant disruptions in connectivity with them could come with considerable consequences for brain function. Additionally, the precuneus and PCC are centrally involved in several self-related processes (see section 3.1.1.), emotional regulation, top-down attention (particularly visual) and working memory. Aberrant fronto-parietal connectivity may, therefore, lead to deficits in controlling attention away from aversive emotions and stimuli in SAD. Brühl et al. (2014) write that "... parietal hyperactivation in SAD together with the disconnection of these parietal regions from other circuits … could possibly reflect heightened [unsuccessful; my note] efforts to regulate the increased bottom-up activation coming from the amygdalo-insular circuit. This is evidenced by the increased activation found in studies investigating emotion regulation in SAD." (p. 274). Decreased fronto-parietal connectivity was noted be common for many ADs in a review where the authors also linked reduced functional connectivity in the circuit to top-down attentional deficits (Sylvester et al., 2012).

Several studies additionally indicate that there are disruptions in functional connectivity between PFC regions among individuals with SAD (Brühl et al., 2014). It is plausible that reduced connectivity between these areas relates to disturbed emotional regulation in SAD (Brühl et al., 2014). To further investigate this hypothesis, frontal functional connectivity could be investigated during an emotional regulation task. Furthermore, if SAD-related deficits in emotional regulation are addressed through CBT, post-treatment measures of functional connectivity in the PFC should be increased and correlate with treatment response. Ding et al. (2011) speculate that frontal connectivity disruptions could be associated with defective social cognition in SAD since PFC regions have been related to understanding the social environment and other's mental states.

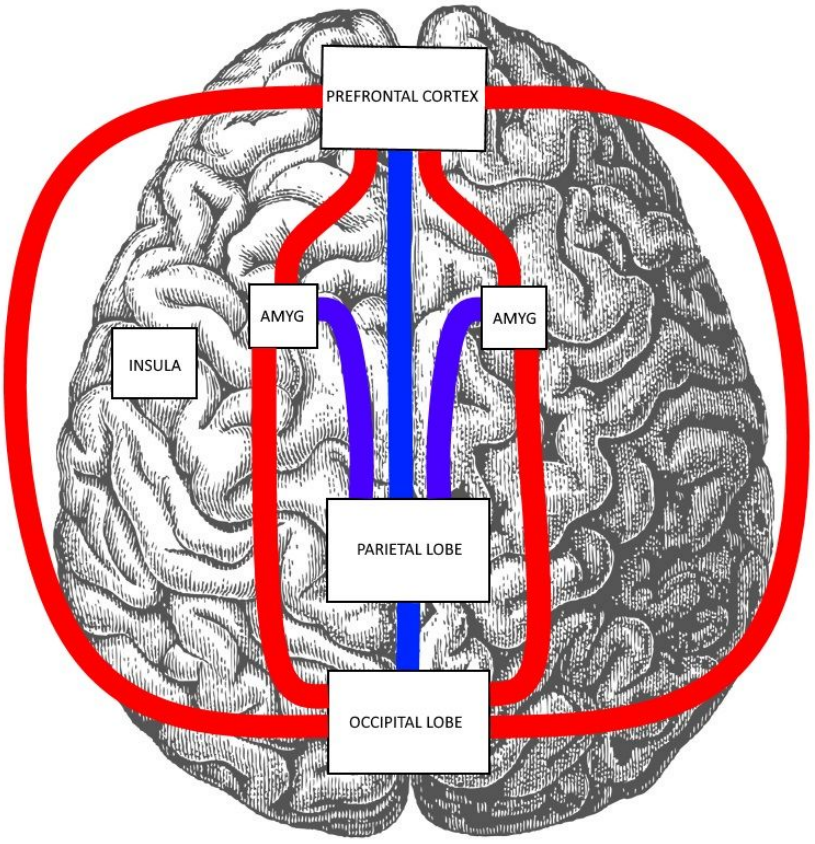

FIGURE 1. Each box represents an area observed to be hyperactive in fMRI experiments on individuals with SAD. AMYG=Amygdala. The red lines represent functional connections which are strengthened among individual with SAD relative to controls. Oppositely, blue lines represent decreases in functional connectivity in SAD patients. Adapted from Brühl, Delsignore, Komossa, & Weidt (2014).

Beyond the SAD-related functional connectivity changes raised here, studies included in the meta-analysis by Brühl et al. (2014) find many more. One group of researchers observed individuals with SAD had significantly altered functional connectivity in seven out of eight RSNs that they investigated (Liao et al., 2010a). Although network connectivity sparsely is addressed SAD research, the research has provided evidence of SAD-related aberrancy in particularly one of the seven networks.

4.2. FUNCTIONAL CONNECTIVITY OF THE DEFAULT MODE NETWORK

The default mode network (DMN) is a network of brain regions first identified as such when researchers observed that several brain areas were deactivated in concert across a wide variety of tasks (Raichle, 2015). Instead, the DMN is active at rest or in the absence of extrinsic stimulation (Northoff, Qin, & Nakao, 2010). Central constituents of the network are precuneus, PCC and MPFC (Fransson, 2005). Activity in these and the wider DMN, have been linked to a large number of self-related mental functions such as episodic memory,

self-referential thought, mind-wandering, self-reflection, emotional regulation (Brühl et al., 2014; Kucyi & Davis, 2015) and recently to several forms of social cognition (Li, Mai, & Liu, 2014). Moreover, alterations in DMN functioning have been implicated in a variety of brain and mental disorders such as Alzheimer's disease, depression (Raichle, 2015), chronic pain (Kucyi & Davis, 2015), autism (Washington et al., 2014) and ADHD (Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2016) to name a few.

Given the functions of the DMN and SAD symptomatology, it is not difficult to imagine that SAD may be related to atypical functioning in the DMN. Indeed, task-based fMRI has shown that AD and SAD patients do not exhibit the same activity decreases in the DMN regions as do HCS (Zhao et al., 2007; Gentili et al., 2009). Gentili et al. (2009) found this in patients' PCCs and precunei during a facial viewing experiment. Recently, several studies have found functional connectivity differences in the DMNs of individuals suffering from SAD and other ADs (MacNamara et al., 2016).

Liao et al. (2010a) found differences that patients with SAD had significantly decreased RS functional connectivity of the precuneus with the rest of the DMN. Similarly, in another study observed whole brain decreases in RS functional connectivity of the precuneus and angular gyrus in SAD were observed (Liu et al., 2015). Liao et al. (2010a) additionally found strengthened connectivity of the DMPFC to the rest of the DMN in patients. In a following study, Liao et al. (2011) used the MPFC as a seed region and found strengthened functional connectivity of the MPFC with PCC/precuneus, superior frontal gyrus as well as bilateral angular gyrus. Connectivity of thalamus and amygdala and several subcortical regions linked to emotion was detected to be increased to PCC and precuneus (Anteraper et al., 2014). However, reduced PCC/precuneal - amygdala RS functional connectivity has also been found in one study (Hahn et al., 2011). Most recently, Zhu et al. (2017) found weakened RS functional connectivity in multiple connections involving default mode regions including the precuneus, PCC, angular gyrus, middle temporal gyrus and medial as well as superior frontal gyrus. Furthermore, it has been found that there is reduced local synchronization of spontaneous BOLD activity (regional homogeneity) within the MPFC, ACC and angular gyrus of SAD patients (Qiu et al., 2011).

While there are studies in which SAD-related differences in DMN functional connectivity could not be found (Pannekoek et al., 2013), these results show, despite some inconsistencies, quite clearly that the DMN in SAD is altered and decreased in its functional

connectivity with both internal and external regions. Decreased DMN functional connectivity does not appear to be unique for SAD but also occur in other ADs (Sylvester et al., 2012) and individuals with obsessive-compulsive and post-traumatic stress disorder (PTSD) - two disorders that share many commonalities with SAD (MacNamara et al., 2016). Moreover, decreased PCC – angular gyrus functional connectivity, and reduced amygdala functional connectivity with DMN regions was also related to a high tendency to avoid or withdraw from new people and social situations (Blackford et al., 2014). There is evidence that decreased DMN functional connectivity is linked to deficits emotional regulatory abilities of both AD patients and individuals high in trait anxiety (Sylvester et al., 2012).

4.3. FUNCTIONAL CONNECTIVITY IN OTHER NETWORKS

Apart from differences in the DMN, Liao et al. (2010a) also found changes in networks related to attentional and executive control as well as in visual network, auditory network and somatomotor network in SAD patients. Connectivity disruptions in the executive control network were also observed by Geiger et al., (2016), which supports the notion of difficulties in top-down fear and anxiety regulation in SAD. Geiger et al. (2016) additionally observed that an executive control region in the VMPFC was more strongly connected with the amygdala and that connectivity strength was positively correlated with patients' Liebowitz Social Anxiety Scale (LSAS) test scores. This result suggests that the amygdala may have an excessive bottom-up effect on this region or deficits of the VMPFC in downregulating the amygdala.

Activity in a brain system known as the salience network to a large degree correlates with the extent to which external stimuli capture attention (Kucyi & Davis, 2015). In some studies of both task and RS functional connectivity, researchers have noticed alterations in the salience network of individuals suffering from SAD (MacNamara et al., 2016). Pannekoek et al. (2013) found that a central salience network region was more strongly connected with the precuneus in patients. They speculated, given that the precuneus has functions related to self-reflection, that increased salience connectivity to it might underlie increased awareness of the self, that is associated with SAD. Similar increases in RS functional connectivity between DMN and salience network have been noted in patients suffering from PTSD (MacNamara et al., 2016).

Manning et al. (2015) investigated RS functional connectivity with seed regions placed in both the ventral striatal nucleus accumbens (NAcc) and in the VMPFC, which are both central to the brain's reward system. The NAcc is associated with reward anticipation, whereas VMPFC is involved in attributing rewards value. Regardless of which seed was used, the connectivity between these two areas was markedly reduced in SAD patients. Both the NAcc and VMPFC also showed reduced connectivity with multiple other PFC regions associated with decision-making and rather increased activity with parietal regions involved in punishment processing. It is suggested that these findings could potentially be linked to diminished experiences of reward from social interactions and increased avoidance of social punishment in individuals with SAD (Manning et al., 2015). However, psychological data supporting this hypothesis is lacking.

The research presented in this section suggests that SAD is related to functional connectivity aberrancies involving widespread brain regions, between several networks and regions which have previously been associated with SAD pathology using other forms of neuroimaging. In this regard, the functional connectivity research well complements the neurocognitive understanding of SAD pathology as outlined in previously (in section 3.3.2.), showing how increased emotional response to social cues could be related to increased functional connectivity between the amygdala, PFC and occipital lobes. Moreover, deficits in emotional regulation seem to be linked with chiefly reduced prefrontal and DMN connectivity. Likewise, reduced connectivity of the parietal lobe with the amygdala, PFC, and occipital lobe appear related to deficits in top-down attentional processes. Preliminary results also suggest that SAD is associated with aberrancies in functional connectivity involving additional networks and regions, such as the salience network, reward system and executive control network.

In the subsequent two sections, the focus will be put on presenting research where RS functional connectivity is used to classify individuals with SAD and predict how they will respond to treatments.

4.4. FUNCTIONAL CONNECTIVITY FOR DIAGNOSTIC PURPOSES

Through the use of RS functional connectivity, three studies have examined how well functional connectivity measures fare when used to classify individual subjects as having SAD or not. Briefly, distinctions of the type discussed in this and the subsequent section (4.5)

are typically made by the application of machine learning algorithms. These artificial intelligences are trained to make inferences about individuals by comparing available information pertaining specific individuals with the entire set of (in this case, neuroimaging) data at their disposal (Orrù, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012). In the few published studies where such methods were used, classifications have obtained quite positive results – showing that functional connectivity measures can be used to distinguish between healthy individuals and those with psychopathology with a high accuracy.

In the context, the diagnostic accuracy of a model is reported as a mean of the proportion of true positive classifications (sensitivity) and the proportion of true negative classifications (specificity) made. Furthermore, the accuracy can for now only be reported as a fraction or percentage relative to the classification of a person having or not having SAD through conventional means of diagnosis (assumed to be 1 or 100%). Currently, this entails observations and an interview made by a clinician in combination with questionnaire results (Åkerlund, 2006). This approach is based on guidelines provided in the DSM-5 (APA, 2013) or similar sources. How accurate such clinical evaluations are for assessing SAD is hard to tell, has not been studied enough. Though one study shows that the inter-rater reliability of clinical interviews for ADs in children is very high (Lyneham, Abbott, & Rapee, 2007).

Through analysis of regional homogeneity data gathered from 40 SAD patients and 40 HCS, Zhang et al. (2015) found differences in multiple regions – mainly in frontal, temporal and occipital lobes of SAD patients. Each participant's fMRI data was input into a machine learning software which was then able to categorize individuals as having SAD or being healthy based on regional homogeneity information with an accuracy of 76%.

This categorization was made through something known as leave-one-out cross-validation – where the data from a single subject of each group is excluded from the model and then used to test the capability of the model (based on all other scans) to distinguish between the two left out subjects (one has SAD, the other is healthy; Orrù et al., 2012). This is repeated until each individual has been categorized and further contrasted to the actual group-belonging of every participant to determine accuracy.

In another study, Liu et al. (2015) instead measured whole brain functional connectivity and used this data for classification. Another big difference from Zhang et al. (2015) is that they include only half the number of participants, 20 with SAD and 20 controls. Group differences were found mostly in the cerebellum, DMN, visual, auditory and

somatosensory networks. More importantly, classification of subjects was made with an 82.5% accuracy. In a third study, it is reported that the researchers, using functional connectivity, were able to discriminate between socially anxious and HCS (n=82) with a remarkably high accuracy of 98.8% (Zhu et al., 2017). Together these three studies provide promising results and give high hopes for the future use of RS functional connectivity as a neuromarker in SAD. Though RS functional connectivity is not unique in its application as a neuromarker.

By using experimental fMRI, Frick et al. (2014b) achieved a predictive accuracy of 72.6% for classifications made on the basis of BOLD activity limited to threat processing regions. In the same study, whole brain gray matter volume was also assessed. On the basis of gray matter data, an even higher accuracy (84.5%) for classifications was acquired.

The current research suggests that RS functional connectivity has good potential for use in neurodiagnostics of SAD. However, that current evidence speaks in favor of RS functional connectivity does not provide grounds for concluding that it, rather than any other fMRI/MRI-based brain measurement, is better suited for neurodiagnostic use. Rather, it may be said that the machine learning technologies that researchers employ are proving to be effective for classification when trained on neuroimaging data. Moreover, several challenges persist for future studies in the field.

For one, current studies have only been carried out using a small number of participants which limits the generalizability of their results. To more definitely demonstrate the predictive capacity of models based on neuroimaging data, studies with larger sample sizes are required - preferably using data gathered at multiple research centers to increase the reliability of results.

Presently, researchers have also only been able to distinguish between individuals with SAD and healthy controls with the use of these models. Being able to make accurate discriminations between individuals with SAD and other ADs, or between individuals with SAD who have different comorbidities, would be a step forward in proving the generalizability of a model - since individuals with SAD more likely seek help when they are affected by additional psychiatric illness (Wittchen, Stein, & Kessler, 1999) and persons in general that pursue a psychiatric diagnosis are potentially affected by *some* mental illness.

It has previously been contended that neuroimaging methods will not be able to provide accurate distinctions between psychiatric disorders on the level of individuals

(Gillihan & Parens, 2011). This account is partially made on the basis of the argument that various mental disorders as described by the DSM, are a collection of dimensional symptoms (they can appear in different intensities for individuals). This is, in contrast, to say, physiological diseases like Human Immunodeficiency Virus (HIV), which are categorical in nature - you either have them, or you don't. Furthermore, there are considerable overlaps in the neural correlates and symptoms of many psychiatric disorder (see for example Etkin & Wager, 2007; MacNamara et al., 2016). A third problem, according to Gillihan and Parens (2011) that a given disorder is likely to be heterogeneous, meaning that it can be caused by different factors and manifest itself differently in different individuals. As such, they argue neurodiagnostics should not be expected to be useful for making DSM diagnoses.

Although Gillihan and Parens (2011) raise important concerns, the implications of their conclusion are unclear. It certainly should not dissuade further research, since it is only through actual empirical investigation that it can be satisfactorily decided whether or not neurodiagnostics will be useful for diagnosis of DSM disorders. As demonstrated here, the preliminary evidence does appear to speak against their stance. Also, the fact that accurate neurally based discriminations have been made between patients suffering from two highly similar neurodegenerative diseases (Focke et al., 2011) supports the notion that neurodiagnostic models will soon be able to distinguish also between similar psychiatric disorders. Furthermore, dimensional psychological properties, such as personality traits, are increasingly being understood neuroscientifically (Sampaio, Soares, Coutinho, Sousa, & Gonçalves, 2014). Similar progress in understanding the neural basis disorders and their symptoms could lead to an expanse of DSM criteria from observed behaviors and subjective experience to the inclusion of a neurobiological perspective.

However, even if the neuroscientific research were to comprehensively show that diagnosis made on the basis of neuroimaging can be accurately made in clinical situations, several logistical and practical problems remain about the cost and resources required for actual clinical implementation of neurodiagnostics (Orrù et al., 2012).

4.5. PREDICTING TREATMENT RESPONSE WITH FUNCTIONAL CONNECTIVITY

At the moment, no scientific inquiries into the methods used for SAD diagnosis have suggested that the current convention is flawed. This does not imply that the clinical

evaluation is perfect, but rather that studying it is, for now, uncharted territory. Conversely, what pertains SAD treatment, a significant body of research shows that the available treatments aren't very effective (see section 2.7). This has motivated research into predicting treatment responses in patients. In this field, a central question to tackle is whether neuroimaging can provide a better predictive power (of treatment response) than solely behavioral measures of the disorder or any other measure available (Gabrieli et al., 2015)

The term *'prediction*' can in some cases be used in reference to correlational relationships, which can either be contemporaneous (e.g. your height and your weight) or separated in time (e.g. self-control as a child and career success, Gabrieli et al., 2015). For our purposes in the present context, 'prediction' will be used in reference to the ability of a general model to make accurate claims based on information that the model is performing the classification on.

Presently, most predictionomic studies are not focused on making these kinds of predictions, but rather about assessing the neurobiological effects of CBT and contrasted participant's BOLD responses to stimuli before and after completing a therapy program. These have generally found that activity in areas that are typically hyperreactive during experiments in SAD (especially amygdala) is normalized immediately after effective treatment (Månsson, 2016). However, in a longitudinal study on the neural effects of successful CBT treatment, Månsson et al. (2017) demonstrated that the attenuation of amygdalar BOLD response does not persist in the long-term. In several studies, posttreatment changes have also been correlated with reductions in disorder severity.

Yuan et al. (2016) associated RS functional connectivity changes after effective treatment with CBT with decreased and normalized connectivity of the amygdala with the DMPFC and ACC. Though in a study of SSRI effects, changes in amygdala connectivity were not observed after treatment. Instead, Doruyter et al. (2016) observed that effective pharmacotherapy correlated with increased connectivity of the ACC with the fusiform gyrus, precuneus and middle temporal gyrus. Interestingly, in the study, functional connectivity between these areas was not significantly different from controls at baseline.

While neither of the two above studies investigates how pre-treatment functional connectivity relates to treatment outcome, this is done by Klumpp, Keutmann, Fitzgerald, Shankman & Phan (2014). According to their results, stronger RS functional connectivity between the amygdala and MPFC/ACC prior to treatment is significantly correlated with

patients' improvement after CBT. Based on these results the authors (Klumpp et al., 2014) suggest that functional connectivity between the amygdala and prefrontal areas might serve well as predictors of CBT treatment response in SAD. Currently though, only one study so far has explored functional connectivity measures as predictors of treatment outcome.

Whitfield-Gabrieli et al. (2015) conducted a study in which they evaluated whether measures of brain connectivity (both functional and structural) could predict treatment response in SAD to CBT better than the traditional measures could. For 38 patients, they carried out pre-treatment measurements of white matter structural connectivity as well as RS functional connectivity.

Traditionally, the only available measure used to predict treatment response in SAD is through scores on a standardized social anxiety assessment questionnaire such as the LSAS (Liebowitz Social Anxiety Scale, as discussed in section 4.3.). This type of measurement, although useful for assessing disorder severity, is exceptionally weak when it comes to accounting for individual variance in treatment outcome. However, Whitfield-Gabrieli et al. (2015) showed that the addition of structural and functional brain measures to this standard measurement markedly increased the researcher's ability to account for individual variability in treatment response from a measly 12% based on questionnaire results alone, to 33% with RS functional connectivity measurements added, to a whole 60% when all three measurements were combined (Whitfield-Gabrieli et al., 2015). Additionally, using these four modes of data (two functional connectivity measures, one structural and one behavioral measure) the researchers' model could categorize individuals into two groups based on whether they were judged to be likely or less likely to benefit (where benefiting equals having reduced one's LSAS score by 50% or more) from CBT with 80% accuracy.

These results can be contrasted to predictive accuracy obtained using experimental fMRI. Doehrmann et al. (2013) analyzed BOLD activity in patients during an emotional faces task which was conducted before treatment (CBT) initiation. BOLD activity patterns in two brain regions correlated to patient's treatment outcomes and could in combination with pretreatment LSAS scores account for 40% of outcome variance (the change in LSAS score posttreatment). Alone, LSAS scores could only predict 12% of outcomes. In another experimental fMRI study, Månsson et al. (2015) predicted individual patients' long-term outcomes to Internet-delivered CBT with an accuracy of 92% based on BOLD responses in the ACC. A third source reports being able to predict posttreatment LSAS changes of

individuals with SAD to 27% based on behavioral measures combined demographic characteristics and 50% when these were combined with fMRI data recorded during exposure to self-referential criticism (Isacsson & Kolbeinsson, 2016).

Compared to neuroimaging methods, other means of predicting treatment responses haven't produced as quite as positive results. In two genetic studies, none of the studied gene variants correlated with patients' CBT treatment outcomes (Andersson et al., 2013; Hedman et al., 2012). Instead, it was found that other factors, such as heredity of SAD, comorbidity and disorder severity could be modeled to predict treatment outcome to 50%.

Many of the same points that were raised in the previous section about neurodiagnostics can be reiterated here. The current research provides good grounds for assuming that neuroimaging-based treatment response predictions could be successfully made in the future. However, no current study provides results that would indicate that RS functional connectivity measures as opposed to anatomical, or experimental fMRI would be particularly useful for predicting treatment responses. Just like diagnostic models of SAD, predictions of treatment outcomes have not yet been applied to out-of-sample subjects in any current study. Rather, studies often only include subjects, both healthy and disorderly that fulfill very specific criteria (Woo et al., 2017) - decreases generalizability of results.

Therefore, although neuroimaging has so far shown to have high potential utility in clinical prediction, actual implementation in practice is far away. Aside from this, there are a number of problems that would need to be addressed before brain scans can be clinically useful.

Even if there existed a model with which one could predict how likely an individual patient is to benefit from CBT treatment there is a crucial lack of evidence on what other, if any, treatment option is likely to be better for that patient (Gabrieli et al., 2015). For treatment optimization to be possible, data of this sort is essential. On the plus side, although studies of what treatments are likely to be effective for non-responders to another treatment have not been conducted yet, there is no reason why brain measures would not elucidate variations among patients that are relevant for this sort of understanding.

5. DISCUSSION

The subject matters of this thesis have been discussed continuously throughout the text. However, these discussions have not been sufficiently comprehensive in elucidating research problems, limitations and potential future directions of research. In this section, such things will be discussed more thoroughly. Finally, the main conclusions of the thesis will be presented. For the sake of clarity, I will first provide a summary of the essay up until this point.

5.1. SUMMARY

The main concern of this essay was to present how SAD is understood within cognitive neuroscience. After the initial background section, experimental fMRI findings in brains of individuals with SAD were presented. Here it was found that the amygdala, insula, several subregions of the PFC, parietal lobes and occipital areas were overactive in the socially anxious brain. These results were then contextualized in terms of neurocognitive models of SAD pathology. In doing so, it was found SAD is currently most prominently linked with abnormalities in the brain's threat processing system, which is overreactive to social cues, leading individuals with SAD to have more dramatic negative emotional responses to them. The disorder is also linked with deficits in emotional regulation, top-down attention and oversensitivity in facial processing.

Furthermore, I sought out to investigate how research using functional connectivity related to the larger body of work on SAD, which has been primarily concerned with experimental fMRI findings. To this end, the results of one large meta-analysis on functional connectivity research in SAD were summarized. The meta-analysis suggests that there are functional connectivity changes in individuals with SAD which mainly involve the PFC, parietal lobes, occipital lobes and the amygdala. Beyond those results included in the meta-analysis, overviewing RS functional connectivity research showed that SAD is associated with abnormalities in several RSNs, particularly the DMN and seemingly also in the executive control, reward and salience network. Some theoretical perspectives on the relation between observed functional connectivity differences and SAD pathology were also introduced. It was generally found that the functional connectivity research has expanded and complemented the neurocognitive views on SAD that have been developed on the basis of

experimental fMRI data by showing that there are differences in how brain areas communicate related to the disorder.

A third aim was to answer whether there is empirical evidence suggesting that RS functional connectivity measures are viable and preferable (over other neuroimaging measures) for neuromarkers of SAD useful for diagnosis or predicting treatment outcome. Therefore, in the last two sections, research on neurodiagnostics and treatment prediction in SAD was presented with a focus on RS functional connectivity. It was found here that RS functional connectivity measures are able to classify and predict treatment outcomes for single subjects with a relatively high accuracy. In three studies classification could be made with an accuracy in the ranges of 70-90% and in one study functional connectivity measures could predict treatment outcome to 33% alone. While these applications of functional connectivity could potentially reach the point of actual clinical implementation, research is at an early stage and logistical problems about introducing neuroimaging to the clinical setting lie ahead.

5.2. PROBLEMS & LIMITATIONS

In a recently published meta-analysis of 537 experimental fMRI studies on mental disorder, Sprooten et al., (2017) raise an important problem in psychiatric neuroimaging research. As it turns out, task-based activity patterns were highly similar across the five DSM-5 categories of mental disorder, of which ADs were one, that was included in the analysis. In other words, there are large transdiagnostic similarities in brain areas implicated in mental disorders. This means that the fMRI results that have been obtained concerning SAD (and many other disorders) are not very specific for SAD itself - but rather reflect dysfunctions in a neural network which is overlapping between many mental disorders. Hence, fMRI results associated with SAD are insufficient for accounting for disorder-specific elements of pathology, which in extension undermines the validity of the neurocognitive models of SAD presented in this essay. The meta-analysis additionally showed that an overreliance on region of interest analysis - a method which is common place in fMRI - has led to an over-representation of amygdalar hyperreactivity in psychiatric research (Sprooten et al., 2017). Meaning that the amygdala's role in SAD pathology might very well be overstated.

With regards to connectivity research (section 4.), the purpose of this thesis was to focus on functional connectivity research. Though a significant portion of the text includes research findings from strictly RS functional connectivity research. The main motivation for doing so is that research on the RS is overrepresented within functional connectivity research.

Furthermore, in this essay, some explanations of how functional connectivity differences relate to psychopathology and integrate findings into general models of SAD are introduced. Though functional connectivity findings appear to integrate well with ideas about SAD neuropathology, they are not always in line with other empirical evidence - for example, Brühl et al. (2014) suggest that functional connectivity between amygdala and PFC are increased in SAD, while white matter studies (see section 3.3.3.) suggest decreased connectivity between them. It is also important to stress that neuropsychological explanations of functional connectivity data are speculatory since little is actually known about how functional connectivity relates to either brain function or psychology (Buckner, Krienen, & Yeo, 2013; Northoff, Duncan, & Hayes, 2010).

Research using functional connectivity, whether in the RS or during tasks, currently lacks a "gold standard of analysis" (Brühl et al., 2014) and there are multiple measures available which might be interpreted quite differently (Margulies et al., 2010). Another problem common for studies is small sample sizes, which are often limited to 10-20 individuals with SAD and a similar number of HCS. Small sample sizes lead to low statistical power and reliability of results - a problem that plagues all of neuroscience (Button et al., 2013). In SAD research, smaller sample sizes may be a consequence of researchers using quite strict criteria for including subjects in studies (Brühl et al., 2014) in order to avoid confounding factors and produce significant results. While doing so may be crucial for being able to make progress in studying a phenomenon such as SAD, it also lowers the generalizability of research results.

To assess the predictive accuracy of neuroimaging-based models for diagnosis and treatment prediction, all studies discussed here use leave-one-out cross-validation. While this method is widely used for such purposes, it has been shown to have some statistical flaws (Kohavi, 1995; Zhu et al., 2017). For this reason, future studies could benefit from testing the models on an entirely independent sample - doing so would also increase the generalizability of model.

5.3. FUTURE DIRECTIONS

The previous section outlined several challenges and limitations to the current neuroscientific research on SAD. In future neuroimaging studies, scientists may benefit from attempting to study brain differences between SAD and other ADs to better understand both the common neural basis and differences of anxiety-related pathology. The field could potentially benefit much from projects where imaging findings from several disorders are compared and integrated into a general neurobiological description of pathological fear and anxiety. To some degree, such works already exist with regards to experimental fMRI (see Etkin & Wager, 2007; Etkin, 2009; Etkin, 2012; Grupe & Nitschke, 2013; LeDoux & Pine, 2016 for examples). In functional connectivity, at least three such reviews (MacNamara et al., 2016; Peterson, Thome, Frewen, & Lanius, 2014; Sylvester et al., 2012) have been published quite recently. Though MacNamara et al. (2016) note that there is a lack of aggregate evidence to draw any conclusions about commonalities and differences in AD-related functional connectivity aberrancies. In the future, comparing functional connectivity differences could potentially aid researchers in understanding how functional connectivity relates to pathology and symptoms.

To achieve such an understanding, research results need to become more reliable. Therefore, as several authors suggest, researchers using RS functional connectivity to study SAD should make a habit out of reporting at least one standard measure of connectivity to increase comparability between studies (Brühl et al., 2014; MacNamara et al., 2016). Beyond standardized analytical approaches, more replications and larger sample sizes will increase the reliability of study findings.

By studying functional connectivity changes longitudinally, researchers may also begin to understand whether connectivity changes related to pathology are predisposing individuals to SAD, or if they are a consequence of prolonged social anxiety. Combining both task-based and RS functional connectivity approaches in the same study might further understanding of the clinical relevance of aberrant functional connectivity since different results have been obtained between the two approaches (MacNamara et al., 2016; Prater, Hosanagar, Klumpp, Angstadt, & Phan, 2013). What concerns diagnostic and predictive efforts using RS functional connectivity, the preliminary results are promising. Addressing

points raised in previous sections might bring us closer to realizing the clinical utility of neuroimaging.

While it was found that RS functional connectivity is not evidently superior to any other brain measure for diagnostic and predictive purposes, some authors have expressed theoretical arguments that speak in favor of using RS functional connectivity for such uses. For one, RS designs require substantially less of participants than experimental approaches (Peterson et al., 2014). It may be difficult for subjects to respond appropriately in tasks due to their disorder and stimuli may trigger symptoms that can interfere with the highly sensitive fMRI measurement. Other benefits of using RS functional connectivity is that study protocols are much simpler than those used in experimental fMRI (Peterson et al., 2014; Woo et al., 2017) - allowing for researchers and less trained personnel, to perform scans easier, at a faster rate and with more subjects than otherwise. Using simpler scans protocols additionally allows researchers, with smaller chances of confounding, to collaborate across sites to perform multicenter studies (Lueken et al., 2016).

Others suggest that combining multimodal measures, as done by Whitfield-Gabrieli et al. (2015) among others, could lead to quick progress in the development of biomarkers of mental disorder and treatment predictors (Lueken et al., 2016). It should also be noted that even if neuroimaging measures currently appear promising as biomarkers and predictors, it is impossible to know if other measures, genetic, behavioral or other will emerge as superior to neuroimaging in the future.

5.4. CONCLUSION

In conclusion, this thesis shows that experimental fMRI and RS functional connectivity studies have revealed several alterations in the socially anxious brain. These alterations are found in areas related to emotional generation and regulation, visual processing, attention and, most prominently the brain's threat processing network. Based on mainly experimental findings, theoretical works link these brain alterations to pathological elements in SAD. These theories or models describe, in a very general sense, the neurobiological mechanisms for the disorder. Furthermore, evidence from functional connectivity research has complemented and expanded these models by indicating how communication between brain regions implicated in SAD reflect pathology - despite numerous problems.

Moreover, research shows that neuroimaging and functional connectivity could potentially reach the point of being able to make sufficiently accurate classifications and predictions to warrant clinical applications. Currently, the few studies that are available on the subject show quite promising results. However, functional connectivity results aren't necessarily proving to be superior to other neuroimaging measures for elucidating neuromarkers - irrespective of measure, predictive or classificatory accuracies are overall similar. Importantly, there are substantial challenges need to be surmounted before clinical use of neuroimaging is viable. Thus, while neuroimaging in SAD has not yet had any clinical impact to speak of yet, it is foreseeable that it will in the near future.

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