Psychiatry Research: Neuroimaging 251 (2016) 34–44

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Resting functional connectivity in social anxiety disorder and the effect of pharmacotherapy

Alexander Doruyter [a,*], Christine Lochner [b], Gerhard P. Jordaan [c], Dan J. Stein [d], Patrick Dupont [e], James M. Warwick [a]

[a] Division of Nuclear Medicine, Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa
[b] US/UCT MRC Unit for Stress and Anxiety Disorders, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
[c] Department of Psychiatry, Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa
[d] US/UCT MRC Unit for Stress and Anxiety Disorders, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
[e] Laboratory for Cognitive Neurology and Medical Imaging Centre, KU Leuven, Leuven, Belgium

ARTICLE INFO

Article history:
Received 2 November 2015
Received in revised form
11 February 2016
Accepted 14 April 2016
Available online 16 April 2016

Keywords:
Anterior cingulate
Pharmacologic effects
Phobia, social
SPECT

ABSTRACT

Neuroimaging research has reported differences in resting-state functional connectivity (RFC) between social anxiety disorder (SAD) patients and healthy controls (HCs). Limited research has examined the effect of treatment on RFC in SAD. We performed a study to identify differences in RFC between SAD and HC groups, and to investigate the effect of pharmacotherapy on RFC in SAD. Seed-based RFC analysis was performed on technetium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO) SPECT scans using a cross-subject approach in SPM-12. Seeds were chosen to represent regions in a recently published network model of SAD. A second-level regression analysis was performed to further characterize the underlying relationships identified in the group contrasts. Twenty-three SAD participants were included, of which 18 underwent follow-up measures after an 8-week course of citalopram or moclobemide. Fifteen healthy control (HC) scans were included. SAD participants at baseline demonstrated several significant connectivity disturbances consistent with the existing network model as well as one previously unreported finding (increased connectivity between cerebellum and posterior cingulate cortex). After therapy, the SAD group demonstrated significant increases in connectivity with dorsal anterior cingulate cortex which may explain therapy-induced modifications in how SAD sufferers interpret emotions in others and improvements in self-related and emotional processing.

1. Introduction

Social Anxiety Disorder (SAD) is characterized by excessive fear of social interactions and of scrutiny by others in which sufferers fear negative evaluation (American Psychiatric Association and DSM-5 Task Force, 2013). The disorder is common (Kessler et al., 2005; Stein et al., 2010) and frequently results in significant disability (Wittchen and Beloch, 1996). There is a growing interest in both anatomical and functional neuroimaging as means to investigate the biology of SAD.

Recent neuroimaging research has established differences in resting-state functional networks in SAD sufferers compared to healthy controls. Ding et al. (2011), using brain parcellation and calculating a correlation matrix of all regions, reported increased connectivity in frontal regions and decreased connectivity between several frontal and occipital regions. Liao et al. (2010b) used a seed-based method with amygdalar seeds and found evidence for disrupted connectivity between amygdala and distributed cortical regions, including default mode network (DMN) nodes. Amygdalar connectivity disruptions using seed-based techniques have also been described by Hahn et al. (2011), Prater et al. (2013) and Pannekoek et al. (2013). The latter study also found dorsal attention network but not DMN disturbances. Arnold-Anteraper et al. used seed-based methods and reported connectivity disturbances in subcortical networks (Arnold-Anteraper et al., 2014). Liao et al. (2011) have used regions of gray matter volume reduction as seeds, including a medial prefrontal cortex seed which showed aberrant connectivity with several DMN regions. Independent component analysis (ICA) was used by Liao et al. (2010a) who reported disturbances in several components including increased connectivity in the self-referential network and decreased connectivity in the DMN. Qiu et al. (2011) used regional homogeneity (ReHo) analysis and reported several ReHo abnormalities including reductions in DMN components. Finally, Liu et al. (2014) used graph theory to identify disrupted

* Correspondence to: Division of Nuclear Medicine, Slenbosch University and Tygerberg Hospital, Francie van Zijl Drive, Tygerberg 7505, Western Cape, South Africa.
E-mail address: doruyter@sun.ac.za (A. Doruyter).

http://dx.doi.org/10.1016/j.pscychresns.2016.04.009
0925-4927/

cortical hubs in right fusiform gyrus and bilateral precuneus.

Given the heterogeneity in analysis techniques and number of (occasionally inconsistent) connectivity disturbances reported in resting-state experiments, a recent neuroimaging review and meta-analysis of connectivity findings in SAD by Brühl and colleagues is particularly valuable (Brühl et al., 2014). In their paper, the authors proposed a network model of SAD that provides a useful basis for generating hypotheses in SAD connectivity research. The model builds on preclinical work in that it implicates several structures of the previously described "fear-circuit" (LeDoux, 2000) and proposes that SAD sufferers have disrupted connectivity between widely-distributed, functionally distinct regions of the brain. It is important to note however that this model is based on both resting-state and paradigm-driven activation and connectivity data. While many of the regions in this model have also been implicated in resting state studies in SAD, the applicability of this model to "baseline" mental processing (resting state), and to anxiety-provoking socially-focused experimental paradigms is still uncertain. The investigation of resting-state functional connectivity (RFC) is important since it contextualizes and refines our understanding of localized activation or deactivation (and connectivity) in paradigm-driven functional neuroimaging experiments (Greicius et al., 2003), as well as network models such as that proposed by Brühl.

A limited amount of RFC research has been conducted in SAD, and has exclusively been acquired using functional magnetic resonance imaging (fMRI). The high temporal resolution of this modality is eminently suited to functional connectivity research since it is possible to detect spatially distinct, temporally-correlated voxels or voxel clusters from a relatively short total scan duration. It is also possible to perform functional correlation analyses during the same time period, using positron emission tomography (PET) or single photon emission tomography (SPECT). Here a cross-subject approach is used to determine whether the signal intensity in remote brain regions are correlated across participants. Such a cross-subject approach has been used in prior PET, SPECT, and fMRI experiments, e.g. (Blumenfeld et al., 2004; Di and Biswal, 2012; Lee et al., 2008; Zhang et al., 2014). There are two main rationales supporting the use of PET and/or SPECT in connectivity research: Firstly, despite its many advantages, fMRI is prone to susceptibility artefacts which make it more difficult to study specific brain regions potentially significant to psychiatric studies such as the orbitofrontal and inferior and medial temporal cortices (Stenger et al., 2000). SPECT and PET do not suffer from this problem. Secondly, the BOLD signal obtained in fMRI depends on a combination of several physiological factors (cerebral blood flow; cerebral blood volume concentration of deoxyhaemoglobin) and serves as an indirect measure (Steinbrink et al., 2006); whereas it may be argued that the signal obtained using perfusion SPECT or PET is more physiological, as a 'pure' perfusion measure. PET and SPECT are thus complementary to fMRI in functional brain imaging.

In terms of behavioural correlates; in understanding the mechanisms by which drugs exert their effects; and as a biomarker of treatment effect, the translational relevance of disturbances in RFC in SAD remains largely speculative. There is evidence to suggest that the DMN plays a role in social cognition (Laird et al., 2011; Mars et al., 2012; Schilbach et al., 2008), and that this network may be disordered in SAD (Gentili et al., 2009; Liao et al., 2010a; Liu et al., 2013). In depression, the DMN's role in maladaptive rumination (also a feature of social anxiety disorder) has previously been reported (Hamilton et al., 2011). This is noteworthy given the frequent comorbidity of depression and SAD (Merikangas and Angst, 1995). Very limited research has been conducted that examines the effect of treatment on RFC in SAD. Giménez and colleagues reported attenuation of connectivity in four components (using independent component analysis) using resting state fMRI in SAD patients treated with an 8-week course of paroxetine (a selective serotonin reuptake inhibitor - SSRI) (Giménez et al., 2014). That group reported attenuation (with therapy) in the DMN (produced in right thalamus); in a posterior insula component (produced in right insula as well as perigenual regions); in an anterior paralimbic component (produced in subgenual ACC); and in a fronto-parietal component (in left insula). No studies have been performed in SAD that test the effect of pharmacotherapy on seed-based RFC. Such analyses in healthy volunteers and in depressed patients have reported changes in RFC with therapy (McCabe et al., 2011; van Wingen et al., 2014; Wang et al., 2015; Yang et al., 2014).

The objective of this study was to compare RFC in HCs and in SAD participants at baseline and to investigate the impact of pharmacotherapy on RFC in the SAD group. We hypothesized RFC differences between SAD and HCs would correspond to the existing network model of SAD proposed by Brühl and that pharmacotherapy effects would be consistent with normalization of connectivity disturbances predicted by the model. All participants in this study were included in a prior study conducted by our institution (Warwick et al., 2006).

2. Methods

2.1. Participants

The study was approved by the health research ethics committee of Stellenbosch University (Ref # S14/08/159).

2.1.1. SAD participants

SAD participants had to meet DSM-IV criteria for SAD. They were screened using the Structured Clinical Interview for the Diagnosis of Axis-I disorders (SCID) (First et al., 1996). Left-handed participants as well as those with other primary (dominant) psychiatric disorders or significant medical illnesses/neurological conditions were excluded. Co-morbid anxiety spectrum disorders were not an exclusion criterion if these were considered secondary in terms of temporal course and severity. Highest level of education was recorded for all participants. Technically inadequate scans were excluded. Data for all SAD participants were used in a previous research study by our institution.

2.1.2. Healthy controls

Healthy control participants underwent a psychiatric screening interview using the Mini International Neuropsychiatric Interview (v4.4) (Sheehan et al., 1998), physical examination and MRI scan prior to inclusion. Participants were excluded if they were left-handed, had any psychiatric diagnoses or significant medical/neurological conditions. Highest level of education was recorded in all participants.

Group matching was assessed using appropriate statistical tests, with significance threshold of $p < 0.05$: a two-tailed Welch's *t*-test was used to detect differences in mean age; a Pearson's Chi-square test was used to detect differences in gender proportions; and a Freeman-Halton extension of the Fisher exact test was used to detect differences in highest level of education.

2.2. Pharmacotherapy

After baseline measures, SAD participants received an 8-week course of pharmacotherapy with either moclobemide or citalopram (open label). No randomization was applied to assign which medication would be prescribed (the citalopram and moclobemide sub-groups originally consisted of independent datasets from