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Altered neural correlates of affective processing after internet-delivered cognitive behavior therapy for social anxiety disorder

Kristoffer N.T. Månsson [a,*], Per Carlbring [b], Andreas Frick [c], Jonas Engman [c], Carl-Johan Olsson [d,e], Owe Bodlund [f], Tomas Furmark [c], Gerhard Andersson [a,g]

[a] Department of Behavioural Sciences and Learning, Psychology, Linköping University, Linköping, Sweden
[b] Department of Psychology, Stockholm University, Stockholm, Sweden
[c] Department of Psychology, Uppsala University, Uppsala, Sweden
[d] Centre for Population Studies, Ageing and Living Conditions, Umeå University, Umeå, Sweden
[e] Umeå Centre for Functional Brain Imaging (UFBI), Umeå University, Umeå, Sweden
[f] Department of Clinical Sciences, Division of Psychiatry, Umeå University, Umeå, Sweden
[g] Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Randomized controlled trials have yielded promising results for internet-delivered cognitive behavior therapy (iCBT) for patients with social anxiety disorder (SAD). The present study investigated anxiety-related neural changes after iCBT for SAD. The amygdala is a critical hub in the neural fear network, receptive to change using emotion regulation strategies and a putative target for iCBT. Twenty-two subjects were included in pre- and post-treatment functional magnetic resonance imaging at 3T assessing neural changes during an affective face processing task. Treatment outcome was assessed using social anxiety self-reports and the Clinical Global Impression-Improvement (CGI-I) scale. ICBT yielded better outcome than ABM (66% vs. 25% CGI-I responders). A significant differential activation of the left amygdala was found with relatively decreased reactivity after iCBT. Changes in the amygdala were related to a behavioral measure of social anxiety. Functional connectivity analysis in the iCBT group showed that the amygdala attenuation was associated with increased activity in the medial orbitofrontal cortex and decreased activity in the right ventrolateral and dorsolateral (dlPFC) cortices. Treatment-induced neural changes with iCBT were consistent with previously reported studies on regular CBT and emotion regulation in general.

1. Introduction

Social anxiety disorder (SAD), also referred to as social phobia, is a debilitating psychiatric condition characterized by excessive and persistent fear and concerns about embarrassment and humiliation from others (American Psychiatric Association, 2000). It is a common condition with a lifetime prevalence of around 13% (Fehm et al., 2005; Kessler et al., 2005). SAD often precedes other complications such as depression (Beesdo et al., 2007), alcohol and drug use disorders (Grant et al., 2005), and it is associated with considerable societal costs (François et al., 2010). Many sufferers do not seek treatment (Baldwin and Buis, 2004) despite that effective pharmacological (Ravindran and Stein, 2010) and psychological (Acarturk et al., 2009) treatment exists.

Internet-delivered cognitive behavior therapy (iCBT) has been demonstrated to be efficacious in at least fifteen controlled trials of SAD (Andersson et al., 2012). Effectiveness studies conducted in clinical settings have also provided evidence for this treatment approach (Hedman et al., 2011a). Effect sizes over the short term have been moderate to large (Andersson et al., 2006; Carlbring et al., 2007; Furmark et al., 2009), and treatment gains have been maintained at long-term follow-ups (Carlbring et al., 2009; Hedman et al., 2011b). The treatment is evidence-based, standardized and relatively easy to set-up, making it suitable for functional brain imaging research.

Moreover, there is an extensive literature on attentional biases in emotional disorders (MacLeod et al., 1986), suggesting that altering this bias reduces anxiety (MacLeod and Mathews, 2012). Faster response towards threat-relevant information in relation to neutral stimuli is regarded as a bias. In attention bias modification

* Correspondence to: Linköping University, IBL, Psychology, SE-581 83 Linköping, Sweden. Tel.: +46 70 585082; fax: +46 13 282145.
E-mail addresses: kristoffer.nt.mansson@liu.se, nt.kristoffer@gmail.com (K.N.T. Månsson).

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(ABM) the participant learns to redirect attention away from threats, such as facial expressions of fear or disgust. ABM have been suggested to share a therapeutic mechanism with CBT (MacLeod and Mathews, 2012). In a study by Schmidt et al. (2009), 72% of the participants in the treatment group as compared to 11% in the control condition, no longer met the criteria for SAD following ABM. These results were maintained at a 4-month follow-up assessment. Two meta-analyses have demonstrated small to medium effect sizes of ABM for anxiety disorders (Hakamata et al., 2010; Hallion and Ruscio, 2011). However, these promising results have not yet been replicated when the same treatment has been delivered via the internet when comparing to placebo conditions (Boettcher et al., 2011; Carlbring et al., 2012; Neubauer et al., 2013). Therefore, in the present study, we used the internet-delivered ABM as a control treatment.

Studying brain mechanisms and associated behavioral changes after treatment could further enhance knowledge about the maintenance of SAD and improve the specificity of interventions. The most consistent finding in neuroimaging studies of SAD is that the disorder is associated with exaggerated activity in the amygdala (Freitas-Ferrari et al., 2010). The amygdala is part of a fear circuit involved in detecting threat signals and coordinating autonomic responses (LeDoux, 2000). In addition, the prefrontal cortex acts in concert with subcortical regions involved in emotional expressions (Barbas et al., 2003), and is crucial for emotion regulation (Hartley and Phelps, 2009; Ochsner and Gross, 2005), extinction learning (Phelps et al., 2004) and resolving emotional conflicts (Etkin et al., 2006). Prior studies have highlighted the orbitofrontal (OFC), ventromedial (vmPFC) and rostral anterior cingulate (rACC) cortices to be involved in regulation of emotional responses (Etkin et al., 2011; Hartley and Phelps, 2009; Milad et al., 2007; Milad and Rauch, 2007). Prefrontal regions may be directly or indirectly connected to the amygdala, and are able to exert inhibitory influences. Regions within the OFC and ACC have the densest connections to the amygdala, accounting for about half of all the prefrontal projecting neurons (Ghashghaei et al., 2007). Hence, it is of particular interest to study if these regions are involved in therapeutic change by psychological interventions.

Viewing emotionally valenced faces has been shown to reliably activate the amygdala in patients with SAD (Lira Yoon et al., 2007; Stein et al., 2002; Straube et al., 2004), and severity of symptoms predicts the amygdala activation to negative faces (Evans et al., 2008; Goldin et al., 2009a; Phan et al., 2006). Affective face processing tasks have also been used as predictors for outcome of CBT for SAD (Doehrmann et al., 2013; Klumpp et al., 2013), and the pharmacological treatment of anxiety (Whalen et al., 2008). A neuroimaging study of SAD by Furmark et al. (2002) reported that responders to CBT delivered in group, and to selective serotonin reuptake inhibitors (SSRIs) both resulted in decreased anxiety-related reactivity in the amygdala after treatment. Phan et al. (2013) also noted reduced amygdala reactivity to fearful faces after SSRI treatment although this was not related to social anxiety symptom improvement.

The present study aimed to investigate neural changes, measured during an emotional face processing task (Hariri et al., 2002), following internet-delivered CBT for SAD in comparison to an active control condition using ABM. We used functional magnetic resonance imaging (fMRI) before and after the treatments to explore therapeutic effects on functional neural responses. We hypothesized that a positive treatment outcome would be associated with attenuated amygdala reactivity. Within iCBT we also investigated concomitant activation changes of the prefrontal cortex that might exert regulatory effects on the amygdala. We expected to find increased activity in prefrontal regions (e.g. dlPFC, mOFC, rACC, vmPFC) in relation to decreases in amygdala.

2. Materials and methods

2.1. Subjects

The study was approved by the local ethics committee. The screening and inclusion procedures were similar to our previous randomized controlled trials (RCTs) of iCBT and ABM (Andersson et al., 2012; Andersson et al., 2006; Carlbring et al., 2012; Furmark et al., 2009). Subjects were recruited via media advertisements and a total of 131 individuals reported interest on a webpage and answered all self-report questionnaires for social anxiety and depression. Also, magnetic resonance safety criteria were assessed. The subjects had to be at least 18 years of age, have no neurological disorder, no other current psychological treatment, and if on pharmacotherapy (e.g. SSRIs), the dose had to be stable during the treatment. Applicants fulfilling the initial screening criteria ($n=44$) were interviewed via telephone using the structured clinical interview for DSM-IV (SCID; First et al., 1997) for presence of SAD and major depressive disorder (MDD). This study was registered at clinicaltrials.gov (identifier NCT01312571).

Twenty-six subjects having SAD as primary diagnosis and no current MDD were initially included but twenty-four subjects completed self-report measures and clinical assessment at post treatment, i.e. two subjects withdrew from the study. Brain imaging data from 22 subjects were analyzed, i.e. four were excluded due to withdrawal or corrupt fMRI data (see Fig. 1). Five iCBT subjects and four in the ABM group had ongoing SSRI treatment during the study. A majority of the subjects met the criteria for the generalized subtype of SAD ($n=22$, 85%). All subjects were right handed by self-report and gave written informed consent prior to participation. Demographic data are presented in Table 1.

2.2. Clinical assessment

The Liebowitz Social Anxiety Scale – self-report version (LSAS-SR; Baker et al., 2002; Liebowitz, 1987) was the main outcome measure for SAD symptoms. LSAS-SR has been reported to have good psychometric properties (Baker et al., 2002). The Social Phobia Screening Questionnaire (SPSQ; Furmark et al., 1999) is a measure used for diagnostic screening and was administrated prior to the SCID. In addition, the Social Phobia Scale (SPS) and Social Interaction and Anxiety Scale (SIAS; Mattick and Clarke, 1998) were used as secondary outcome measures. In screening of depressive symptoms the Montgomery Åsberg Depression Rating Scale, self-report version (MADRS-S; Svanborg and Åsberg, 1994) was used. All self-report measures were administered over the internet, a procedure that has good established psychometric properties (Hedman et al., 2010). An experienced clinical psychologist, independent and blind to the experimental conditions, estimated global improvement at post treatment, using the Clinical Global Impression-Improvement scale (CGI-I; Zaider et al., 2003). Patient who were classified as much or very much improved on the CGI-I were considered to be treatment responders. In addition, the subjects verbally reported fear and distress on a continuous 0–100 (min–max) scale in conjunction with the fMRI task.

2.3. General procedure

During brain imaging data acquisition, an emotional face processing task was used (Hariri et al., 2002). Two other tasks were administered but are not reported here. Subjects were randomized to either iCBT or ABM by a blinded external researcher using an independent third-party online true random-number service (www.random.org). Information regarding the assigned treatment was placed in a sealed envelope, distributed to the subject after the pretreatment brain imaging session. After treatment, clinical outcome measures were acquired prior to the last imaging session. A second treatment phase started after this session (cross-over design, data not reported).

2.4. Treatments

The iCBT for SAD used in this study has been evaluated in several RCTs (Andersson et al., 2012; Andersson et al., 2006; Carlbring et al., 2007; Furmark et al., 2009). The guided internet-delivered treatment protocol contains a 9-week intervention supported by a clinician. The treatment is based upon the model by Clark and Wells (1995) and includes cognitive components, exposure instructions, and relapse prevention. Each week the therapist introduces a new module containing information, work sheets and homework assignments. In total there were nine modules. For more information about the iCBT, see Andersson et al. (2006).

The ABM was also delivered via the internet, over a period of 4 weeks, with exercises implemented twice a week, totaling eight sessions. Male and female disgust faces or neutral expressions and fixation crosses ("+") were presented during 500 ms on the participants´ own computer screen. Then a probe (letter E or F) replaced the neutral facial expression. The subject was instructed to respond to the probe as fast as possible. Training sessions consisted of 160 trials. With the exception of reminders via e-mail or SMS, the research group had no other contact