Behavioural Brain Research 318 (2017) 45–51

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Structural but not functional neuroplasticity one year after effective cognitive behaviour therapy for social anxiety disorder

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HIGHLIGHTS

- Long-term amygdala gray matter volume reduction corresponds to less social anxiety.
- In contrast, amygdala response alterations are not present at 1-year follow-up.
- Decreased anxiety cannot solely be explained by attenuated neural activation.
- The interplay between amygdala volume and function might be a treatment mechanism.

ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form 4 November 2016
Accepted 8 November 2016
Available online 9 November 2016

Keywords:
Amygdala
Neuroplasticity
Long-term
Social anxiety disorder
Cognitive behavior therapy

ABSTRACT

Effective psychiatric treatments ameliorate excessive anxiety and induce neuroplasticity immediately after the intervention, indicating that emotional components in the human brain are rapidly adapTable Still, the interplay between structural and functional neuroplasticity is poorly understood, and studies of treatment-induced long-term neuroplasticity are rare. Functional and structural magnetic resonance imaging (using 3 T MRI) was performed in 13 subjects with social anxiety disorder on 3 occasions over 1 year. All subjects underwent 9 weeks of Internet-delivered cognitive behaviour therapy in a randomized cross-over design and independent assessors used the Clinically Global Impression-Improvement (CGI-I) scale to determine treatment response. Gray matter (GM) volume, assessed with voxel-based morphometry, and functional blood-oxygen level-dependent (BOLD) responsivity to self-referential criticism were compared between treatment responders and non-responders using 2 × 2 (group × time; pretreatment to follow-up) ANOVA. At 1-year follow-up, 7 (54%) subjects were classified as CGI-I responders. Left amygdala GM volume was more reduced in responders relative to non-responders from pretreatment to 1-year follow-up ($Z = 3.67$, Family-Wise Error corrected $p = 0.02$). In contrast to previous short-term effects, altered BOLD activations to self-referential criticism did not separate responder groups at follow-up. The structure and function of the amygdala changes immediately after effective psychological treatment of social anxiety disorder, but only reduced amygdala GM volume, and not functional activity, is associated with a clinical response 1 year after CBT.

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1. Introduction

The human brain is rapidly adaptable. As detected by non-invasive, high-resolution magnetic resonance imaging (MRI), structural change in gray matter (GM) volume in the human brain

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http://dx.doi.org/10.1016/j.bbr.2016.11.018
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may occur in less than a week by repetitive stimulation [1] and there is a growing body of studies showing short-term structural brain alterations after activities and interventions [2,3]. Longitudinal intervention studies with GM outcomes are rare although neuroimaging studies of brain plasticity over the long-term may open new avenues to understanding and treatment of mental disorders.

Cognitive behaviour therapy (CBT) is an evidence-based treatment for a range of mental illnesses. To date, there are numerous imaging studies demonstrating functional changes in neural responsivity after CBT for social anxiety disorder [4–6], panic disorder [7], and depression [8]. In addition to this, we recently showed that the amygdala GM volume declined after 9 weeks of Internet-delivered CBT for social anxiety disorder, and that this structural change correlated with symptom improvement at the behavioural level [9]. Moreover, the amygdala GM volume reduction after treatment correlated with decreased amygdala blood-oxygen level-dependent (BOLD-fMRI) responsivity to a disorder-relevant fMRI task, i.e., self-referential criticism [9]. This result is in line with the basic notion that changes in neural activity, at least in part, are accounted for by changes in GM volume [10,11]. While there are some multi-modal neuroimaging studies incorporating analyses of structure-function relationships, in psychotic disorders for instance [12], such studies are surprisingly rare in the psychiatric literature. Furthermore, long-lasting change of the structure-function interplay, has been an overlooked research question in psychiatric disorders. Only taking structural neuroplasticity into account, there are a few studies demonstrating long-term morphological changes after CBT, e.g., in obsessive-compulsive disorder [13] and spider-phobia [14], providing tentative evidence that effective psychological treatments can have long-lasting effects on brain GM volume. However, a crucial question is how long-term structural changes of this kind are affected by, or affects, neural activity.

The present study examined long-term effects of Internet-delivered CBT both on structural and functional neuroplasticity 1 year after treatment of social anxiety disorder. In line with the immediate effects at posttreatment [9], we expected to find similar long-term neuroplasticity, i.e., reduced amygdala GM volume along with diminished anxiety-related amygdala neural responsivity after successful treatment. Also, in accordance with our previous findings, we expected a correlation between reduced amygdala GM volume and symptom improvement at 1-year follow-up.

2. Methods

2.1. Subjects

The subjects were recruited from a previously randomized controlled trial of CBT for social anxiety disorder [9,15,16]. Twenty-one subjects were invited via e-mail to participate in a 1-year follow-up assessment. All accepted to answer self-reported questionnaires and to partake in a clinical interview via telephone. Thirteen subjects (59%, 13/22) accepted to undergo an additional MRI, and were thus included in the current study. We found no demographic or clinical pretreatment differences (all *p*ís > 0.23) between subjects who did vs. did not participate in the 1-year follow-up MRI session. Demographic and clinical characteristics of the 13 participants are shown in Table 1. Besides a trend ($p = 0.06$) for lower education level in long-term non-responders (vs. responders), there were no significant differences at pretreatment between the responder subgroups (all *p*ís > 0.37). Prior to treatment, all subjects suffered from social anxiety disorder according to DSM-IV [17]. One subject (classified as a non-responder at 1-year follow-up) had increased the sertraline dose from 50 to 100 mg from posttreatment to 1-year follow-up. Those who accepted to participate in the long-term follow-up gave written informed consent and were reimbursed with about € 70. The local ethical committee approved the study, which was pre-registered at ClinicalTrials.gov (ID: NCT01312571).

2.2. Treatment

As previously described [15,16], the subjects were sequentially offered Internet-delivered CBT and attention bias modification (ABM) in a cross-over design and the subjects were randomized to start either with Internet-delivered CBT or ABM [15]. The therapist-guided Internet-delivered CBT protocol encompassed a 9-week text-based intervention with weekly online support from a psychologist. In line with previous studies, ABM was delivered for 4 weeks. In accordance with several randomized controlled trials [RCTs; [18–21]] Internet-delivered CBT was found to be effective while ABM performed less well [15].

2.3. Assessment of clinical response

As for the posttreatment assessments, clinical response at 1-year follow-up was determined using a clinical interview and the Clinically Global Impression-Improvement (CGI-I) scale [22]. The scale was administrated by 2 independent clinicians blind to the experimental conditions and prior evaluations. Participants with CGI-I scores indicating much or very much improvement were defined as treatment responders. In addition, the subjects responded to the gold standard Liebowitz Social Anxiety Scale (Self-report version; LSAS-SR) [23].

The subjects were also instructed to perform a 2-min public speaking task after the MRI session, but, in contrast to the previous assessments [9], they did not have to carry out the task at 1-year follow-up. Prior to the expected speech task, anticipatory speech anxiety was assessed using a subjective unit of distress (SUDs) scale, i.e., the mean of fear and distress, rated separately on a min-max scale from 0 to 100. SUD ratings were completed at 4 time-points (approximately 60, 40, 30 and 1 min before the speech) while the subject was lying in the MRI scanner.

2.4. BOLD-fMRI experimental task

Stimuli were presented using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA), projected on a screen and viewed through a tilted mirror attached to the head coil. The experimental task has been described in detail elsewhere [9,16,24]. Briefly, we evaluated BOLD response to sentences expressing self-referential criticism (e.g., "You are stupid"; relative to criticism targeting a peer, e.g., "He is stupid"), presented for a maximum of 2500 ms. Subjects were instructed to read the sentences and then confirm this by pressing a button with the right hand. In addition, 96 fixation crosses ("+") were randomly interspersed between the sentences and were also presented for 2500 ms. Each sentence and fixation cross was separated by a cross or circle presented for 500 ms.

2.5. Imaging

2.5.1. Structural and functional image acquisition

All neuroimaging was performed in a 3T scanner (General Electric, Madison, WI, USA) equipped with a 32-channel head coil. The structural T1-weighted images were acquired with a voxel size of $0.5 \times 0.5 \times 1\,mm^3$, including 180 slices per subject and a field of view of 250 mm. The following parameters were used for the EPI sequence: TR: 2000 ms, TE: 30 ms, flip-angle: 80°, FOV: $250 \times 250\,mm^2$, matrix size: 96×96, in-plane resolution: 2.6×2.6 mm, and each volume contained 37 slices (3.4 mm thick).

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