



Impaired regulation of emotional distractors during working memory load in schizophrenia



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ABSTRACT

Schizophrenia (SZ) patients exhibit deficits in emotion regulation that affect their daily functioning. There is evidence that the prefrontal cortex plays an important role in emotion regulation. However, it remains unclear how this brain region is involved in emotion regulation deficits in SZ, and how such deficits impact performance on cognitively demanding tasks.

We examined how happy and fearful emotional distractors impact performance on working memory (WM) tasks of varying difficulty (0-back, 2-back), and brain activity using fMRI. Participants were 20 patients with SZ and 20 healthy controls (HC) matched on age, sex, race, and IQ.

A significant 3-way interaction showed that SZ patients had lower performance compared to HC when exposed to fearful and happy distractors, but only during the 2-back task. Second-level fMRI between-group analysis revealed that compared to SZ patients, HC showed significantly greater increase in brain activity with WM load in the left IFG (BA 45) when exposed to fearful distractors. Less brain activity in this region was also associated with reduction in SZ patients' performance during higher WM load and the presence of fearful distractors.

SZ patients had difficulty in performing a WM task when regulating emotions, and they failed to show the emotion-specific modulation of the left IFG observed in HC. These results suggest that SZ patients have difficulty with emotion regulation demands during effortful cognitive tasks. This also provides us with potential insight on how emotion regulation could be rehabilitated in SZ using cognitive training.

1. Introduction

Emotion regulation refers to the effortful control of experience in response to goal-unrelated or irrelevant emotional stimuli (Gross, 1998; Gyurak et al., 2011; Phillips et al., 2008). Emotion regulation is impaired in schizophrenia (SZ), and these deficits interfere with social life and daily functioning (Henry et al., 2008; O'Driscoll et al., 2014). Furthermore, it has been suggested that difficulties in emotion regulation could lead to psychotic symptoms, while adaptive emotion regulation could protect against symptom formation (Grezellschak et al., 2015). Thus, understanding the neural underpinnings of emotion regulation deficits in SZ is critical and may help develop more targeted

interventions.

Emotional working memory (WM) paradigms are often used to investigate emotion regulation processes and require participants to ignore emotional distractors while performing a WM task such as the N-back test (Erk et al., 2007; Phillips et al., 2008). Medial and lateral regions of the prefrontal cortex (PFC), as well as the dorsal anterior cingulate cortex (ACC, BA 32) are specifically active during effortful emotion regulation processes in healthy individuals (see Phillips et al., 2008, and Ochsner and Gross, 2005, for reviews). More specifically, when performing an emotional WM task, healthy subjects demonstrate robust activation in the inferior frontal gyrus (IFG, BA 45) and orbito-frontal gyrus (BA 47) when exposed to fearful distractors (Ladouceur

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et al., 2013). Hence, the modulation of the activity in these PFC regions seems important for normal regulation of emotional distractors.

There is some evidence that abnormal PFC function plays a role in emotion regulation deficits in SZ as advanced by fMRI studies during the performance of emotional WM tasks (Anticevic et al., 2012; Becerril and Barch, 2011; Eack et al., 2016; van der Meer et al., 2014). Yet, it remains unclear which regions of the PFC are involved and whether abnormal WM activation is dependent on emotional regulation ability. When required to memorize negative emotional faces in a WM task, SZ patients show increased activity in the dorsolateral PFC (Becerril and Barch, 2011). However, in an earlier study using an independent sample, our team observed reduced ventromedial PFC activity in SZ patients relative to healthy controls (HC) when fearful vs. happy faces are used as irrelevant distractors during a WM task (Eack et al., 2016). SZ patients have also demonstrated weaker dorsolateral PFC-amygdala connectivity when fielding irrelevant emotional distractors during WM (Anticevic et al., 2012) and none of these previous studies observed abnormal activity in the dorsal ACC in SZ.

We aimed to further explore these initial findings using a fMRI emotional WM paradigm with 2 different levels of difficulty or WM “load” (0-back, 2-back), and examine how different types of emotional distractors (happy and fearful) impact performance and brain activity in SZ. As SZ individuals have difficulty regulating emotions during emotional WM task compared to HC, we hypothesized that SZ will show abnormal decreased accuracy and an increased response time during the 2-back task with emotional distractors compared to HC. Moreover, we hypothesized that fearful distractors during the 2-back task will increase activation in the IFG (BA 45) and orbitofrontal gyrus (BA 47) in HC, but that SZ individuals will fail to show this normal modulation.

2. Methods

2.1. Participants

Twenty patients with SZ and 20 HC were recruited from the Early Course Treatment Program and the community referral networks, and selected as part of the baseline assessment of an ongoing two-site (Boston and Pittsburgh) randomized-controlled study (NCT #01561859) investigating the effect of cognitive enhancement therapy in early course SZ. We used data from the Pittsburgh site because of an inadequate number of HC available in the Boston site. All participants provided written consent to the study approved by the University of Pittsburgh IRB. Inclusion criteria for patients were (1) a diagnosis of schizophrenia or schizoaffective disorder verified using the SCID interview (First, 1998); (2) a duration of psychotic symptoms less than eight years; (3) clinically stabilized on antipsychotic medication (assessed via SCID and available medical history in consensus conferences); (4) age 18–45 years; (5) current IQ greater than 80 as assessed using the WASI-II (Hays et al., 2002); and (6) the ability to read (sixth grade level or higher) and speak fluent English. Exclusion criteria were (1) significant neurological or medical disorders that may produce cognitive impairment (e.g., seizure disorder, traumatic brain injury); (2) persistent suicidal or homicidal behavior; (3) a recent history of substance abuse or dependence (within the past 3 months); (4) any MRI contraindications such as ferromagnetic objects in the body and those people too large to fit into the scanner (shoulder width larger than 25 inches); and (5) decisional incapacity requiring a guardian. HC were also excluded if they had family history of psychosis or another major psychiatric illness.

2.2. Clinical measures

Patients' negative and positive symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b). Emotion recognition performance was assessed

using the PENN Emotion Recognition Task (Kohler et al., 2003). Medication data was collected by treating clinicians from medical records and confirmed when necessary with the treating psychiatrist.

2.3. Emotional faces N-back working memory task

Each participant performed an emotional face N-back (EFNBACK) task during functional magnetic resonance imaging (fMRI). The EFNBACK is a modified version of the N-back WM task, which consists of visually presenting a pseudo-random sequence of letters while participants respond to a pre-specified letter appearing on the computer screen. The N-back task includes two memory load conditions: a no-memory load condition (0-back; e.g. press the button when letter ‘M’ is presented) and a higher memory load condition (2-back; e.g. press the button whenever the current letter is identical to the letter present two trials back [M–X–M]). In the emotional N-back task, either fearful, happy, or neutral face distractors appeared on each side of the letter stimuli. A no-distractor condition was also included, but for the current study's purpose, this condition was excluded from further analysis.

Detailed instructions were provided during task practice prior to the MRI scanning session, and instructions were presented on the screen at the beginning of each block. The task was divided into 3 runs each lasting 7 min and 4 s. Each run was comprised of 8 blocks representing all combinations of memory load conditions and distractor conditions. The blocks were presented in a pseudo-randomized order. Each block included 12 trials of 500 ms. Inter-trial interval was a jittered fixation cross (mean duration = 3500 ms). Participants were instructed to respond as quickly as they could with their index finger to the target letter. Consequently, response time was solely computed when participants were responding correctly to the target letter.

2.4. Behavioral analysis

To analyze the response time and accuracy during the task, a $2 \times 3 \times 2$ ANOVA was performed to analyze 1) the effect of WM load across all distractor types (2-back vs. 0-back), 2) the effect of emotional distractors across all WM loads (neutral vs. happy vs. fearful), 3) the effect of group across all conditions (SZ vs. HC), and 4) the 3-way interaction (groups \times WM loads \times emotional distractor types). Post-hoc repeated-measures ANOVAs, and between-group independent *t*-tests were then performed to localize the specific interaction effect.

2.5. Neuroimaging analysis

2.5.1. MRI acquisition

The MRI study was performed on a 3.0T Siemens Trio Imaging Systems at the University of Pittsburgh. A T1-weighted 3D MPRAGE sequence was collected (voxel size of $1.0 \times 1.0 \times 1.2$ mm, TR 2300 ms, TI = 900 ms, TE = 2.89 ms, flip angle = 90° , FOV = 256 mm, 256×256 matrix, 160 slices, slice thickness = 1.2 mm). We also used a double echo-spin echo sequence to obtain T2 images in the axial plane to screen for neuroradiological abnormalities. fMRI images were acquired during the EFNBACK task using a gradient echo T2*-weighted sequence (voxel size of $3.2 \times 3.2 \times 3.2$ mm, TR 2000 ms, TE = 30 ms, bandwidth = 2298, flip angle = 79° , FOV = 205 mm (excluded part of the dorsal somatosensory-motor cortex), 64×64 matrix, 36 slices).

2.5.2. Preprocessing

First, the T1 anatomical image for each participant was segmented using the “New Segment” routine in Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Next, the fMRI time series images were realigned to the first volume to correct for interscan movement, and coregistered to the participants' own anatomical image. The deformation field map obtained from the segmentation step was then applied to the fMRI images to normalize them into the standard MNI space (voxel size $2 \times 2 \times 2$ mm). Finally,

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