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# Neural correlates of the emotional Stroop task in panic disorder patients: An event-related fMRI study

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ABSTRACT

Although being a standard tool to assess interference effects of disorder-specific words in clinical samples, the neural underpinnings of the emotional Stroop task are still not well understood and have hardly been investigated in experimental case–control studies. We therefore used functional magnetic resonance imaging (fMRI) to examine the attentional bias toward panic-related words in panic disorder (PD) patients and healthy controls. Twenty PD patients (with or without agoraphobia) and 23 healthy controls matched for age and gender performed an event-related emotional Stroop task with panic-related and neutral words while undergoing 3 Tesla fMRI. On the behavioral level, PD patients showed a significant emotional Stroop effect, i.e. color-naming of panic-related words was prolonged compared to neutral words. This effect was not observed in the control group. PD patients further differed from controls on the neural level in showing increased BOLD activity in the left inferior frontal gyrus in response to panic-related relative to neutral words. PD patients showed the expected attentional bias, i.e. an altered processing of disorder-specific stimuli. This emotional Stroop effect was paralleled by increased activation in the left prefrontal cortex which may indicate altered processing of emotional stimulus material.



## 1. Introduction

Patients with panic disorder (PD) display strong attentional biases toward panic-related stimuli which have been shown in various paradigms (Reinecke et al., 2011; Teachman et al., 2007). A well-established paradigm is the emotional Stroop task (cf. Williams et al., 1996) which requires subjects to name the font color of neutral or emotional words. In different groups of patients, this usually results in prolonged response latencies for disorder-specific emotional words (Williams et al., 1996). For example, most studies investigating PD patients reported increased reaction times for emotional (i.e., threat-related, disorder-specific) as compared to neutral words (see e.g., Dresler et al., 2012a; Ehlers et al., 1988; McNally et al., 1990, 1992, 1994; Williams et al., 1996). However, some recent studies failed to replicate such a behavioral emotional Stroop effect in PD (De Cort et al., 2008; Kampman et al., 2002; in unmasked condition: Reinecke et al., 2011).

In contrast to PD patients, emotional Stroop effects in healthy volunteers are less consistent and depend on specific subject characteristics (e.g., Dresler et al., 2009b; for a review see Bar-Haim et al., 2007). As compared to PD patients, functional imaging studies of the emotional Stroop task in healthy subjects are quite numerous (e.g., Canli et al., 2004, 2005; Compton et al., 2003; Isenberg et al., 1999; Mitterschiffthaler et al., 2008; Whalen et al., 1998). These either investigated emotional processes in healthy volunteers or used healthy volunteers as a control group for various clinical samples. Regions that have been repeatedly implicated in this task are the anterior cingulate cortex (ACC, e.g., George et al., 1993; Whalen et al., 1998), the amygdala (e.g., Compton et al., 2003; Isenberg et al., 1999) and prefrontal cortex (PFC) including the dorsolateral and the medial PFC (e.g., Compton et al., 2003; Engels et al., 2007; Mitterschiffthaler et al., 2008). However, neuroanatomical findings are rather inconsistent. For example, one

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positron emission tomography (PET) study revealed increased amygdala activity in response to threat-related vs. neutral words (Isenberg et al., 1999), whereas another study reported decreased BOLD signal in the amygdala for threat-related vs. neutral words (Compton et al., 2003).

Although the emotional Stroop task is widely used in clinical studies with PD patients (e.g., De Cort et al., 2008; Dresler et al., 2009a; Ehlers et al., 1988; Galderisi et al., 2008; McNally et al., 1990, 1992, 1994; Reinecke et al., 2011), the underlying neural mechanisms are not well understood, although PD – as other mental disorders – is considered to be a neurobiological phenomenon (Gorman et al., 2000). Only one functional imaging case–control study (published in English) investigated this task in PD patients (van den Heuvel et al., 2005). Patients displayed increased activity in the right amygdala and hippocampus in response to panic-related vs. neutral words; additional activation – especially apparent in the right hemisphere – was found in PFC areas (medial, ventrolateral, dorsolateral), the ACC, the middle temporal gyrus and the inferior parietal lobe. In the controls, however, panic-related words did not elicit substantial activation. In contrast, a recent Chinese study reported decreased PFC activation in PD patients using an emotional counting Stroop paradigm (Zhang et al., 2011).[1] Given current theoretical neuroanatomical models of PD (e.g., Gorman et al., 2000) that assume a general dyscoordinated regulation in the cortico-limbic-brainstem circuitry, together with the proposed involvement of prefrontal structures in the manifestation and appearance of anxiety disorders (see Berkowitz et al., 2007; Etkin, 2010), the focus of research is particularly put on these prefrontal structures, which are likely involved in the (neuro) psychological processes associated with PD (e.g., attentional biases, cognitive misinterpretations/vicious circle; Clark, 1986). Additionally, these prefrontal circuits have been proposed to be directly or indirectly approachable thus offering a variety of new therapeutic options in the treatment of anxiety disorders (see Etkin, 2012). Also, the assumption of amygdala hyperactivity in PD acting as the neural fear center (Gorman et al., 2000) needs to be assessed as unequivocal support for generally increased activation is missing (see Dresler et al., 2012b; Etkin and Wager, 2007).

Here, we investigated PD patients and comparable healthy controls undergoing fMRI while performing an emotional Stroop task. Based on previous findings (van den Heuvel et al., 2005) we hypothesized that PD patients compared to controls would show stronger emotional interference on the behavioral level paralleled by increased activation in limbic (amygdala, hippocampus) and prefrontal areas. Especially prefrontal areas should be affected as the prefrontally-mediated attentional bias suggests an altered top-down processing in PD (Gorman et al., 2000).

## 2. Methods

### 2.1. Sample

We examined 20 PD patients, recruited through the in- and outpatient facilities of the Department of Psychosomatic Medicine and Psychotherapy at the University Medical Center Hamburg-Eppendorf. Patients were currently under treatment or had been in treatment in the past for panic attacks in the department. Prior to the measurement all patients were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; Wittchen et al., 1997) by a psychologist and diagnoses were based on assessment of the given answers. Ten patients were diagnosed with PD (ICD-10 code F41.0), 10 with agoraphobia with PD (F40.01). Thirteen patients (65%) had at least one comorbid condition, which included generalized anxiety disorder (F41.1, $n = 8$), depressive episode or recurrent depressive disorder (F32, F33, $n = 5$), somatoform disorder (F45.x, $n = 3$), social or specific phobia (F40.1, F40.2, $n = 4$), obsessive-compulsive disorder (F42.x, $n = 2$), and dysthymia (F34.1, $n = 1$). PD was always the primary diagnosis. Fifteen patients were prescribed medication, which included antidepressants (selective serotonin reuptake inhibitors [SSRI], $n = 6$; serotonin-norepinephrine reuptake inhibitors [SNRI], $n = 3$; tricyclic antidepressants [TCA], $n = 3$), low-potency typical antipsychotics ($n = 7$), atypical antipsychotics ($n = 1$), benzodiazepines ($n = 2$), and non-benzodiazepine hypnotic agents ($n = 1$). Low-potency typical antipsychotics (i.e., promethazine) and benzodiazepines (i.e., lorazepam) were (mostly evening) pro re nata (PRN) medication and were not taken before the experiment, so that 12 patients were on medication. Sixteen patients fulfilled all the criteria for current PD, two were partially remitted and two showed stable remission. Patients had experience with psychotherapy as they previously or currently received (in- or outpatient) treatment in the department that comprises both psycho- and pharmacotherapy. Twenty-three healthy controls were recruited through the University Medical Center Hamburg-Eppendorf. Controls were screened for past or previous existence of any manifest Axis I disorder using an interview based on the SCID screening questionnaire that was conducted by a psychologist. Sample characteristics of the PD and control group are shown in Table 1. Patients and controls did not differ with respect to age, gender, education, handedness, and smoking status ($p$ values $> 0.076$); all subjects had normal or corrected-to-normal vision and were fluent in German language. All subjects gave written informed consent. The study was approved by the ethics committees of the University of Wuerzburg and the Medical Board in Hamburg and was in compliance with the latest declaration of Helsinki.

### 2.2. Stimuli and task

The emotional Stroop task comprised two conditions, one including neutral words (e.g., oat, coil, paper) and one including panic-related words (e.g., attack, catastrophy, emergency), that were selected from previous studies (e.g., Compton et al., 2003; Dresler et al., 2009a,b; Isenberg et al., 1999; McKenna and Sharma, 1995; McNally et al., 1990, 1992, 1994; Whalen et al., 1998). Each condition consisted of 15 words, not differing between conditions according to number of letters, numbers of syllables, and frequency in spoken and written language (all $t_{28} < 0.772$, $p > 0.445$; Dresler et al., 2012a). Evaluated by 11 people at the Department of Psychiatry (University of Wuerzburg), panic-related words were rated more panic-relevant and body-related (both $t_{10} > 25.661$; $p < 0.001$), but similarly familiar ($t_{10} = 1.312$; $p = 0.219$).

Words were visually presented against a black background in one scanning session using customized software (Presentation, Neurobehavioral Systems Inc., Albany, CA, USA, http://www.neurobs.com). Participants viewed the back-projected stimuli via a tilted mirror mounted to the head coil. Words were presented in three different colors (red, blue, green), in pseudorandomized order with the restriction that no more than three subsequent trials should belong to one condition or have the same color. Additionally, words were never repeated on subsequent trials. Each participant received a different pseudorandomized order. Participants had to respond to the word color with right index, middle and ring finger using an MRI-compatible button-box; color-finger assignment was counterbalanced. Participants were instructed to concentrate on the word color without paying attention to the word content; speed and accuracy were emphasized equally. Each word was shown three

[1] As this study is only available in Chinese with only the abstract published in English and therefore methods cannot be evaluated adequately, results (inconsistent with van den Heuvel et al., 2005) should be regarded with caution.