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Cerebral blood flow modulations during proactive control in major depressive disorder

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ABSTRACT

In addition to mood disturbance, as well as motivational and somatic symptoms, patients with major depressive disorder (MDD) frequently experience impairments in attention and cognitive control. This study investigated cerebral blood flow modulations during proactive control in MDD, which refers to cognitive processes occurring during anticipation of a behaviourally relevant event. Using functional transcranial Doppler sonography, blood flow velocities in the middle cerebral arteries of both hemispheres were recorded in 40 individuals with MDD and 40 healthy participants during a pre-cued mental arithmetic task. The task required addition of one-digit numbers, which were presented 5 s after an acoustic warning signal. Response time on the task was longer in individuals with MDD than in healthy controls. Moreover, individuals with MDD exhibited smaller bilateral blood flow increases between the cuing tone and task presentation. In contrast, no group difference arose for blood flow modulations associated with arithmetic processing. The prolonged response time accords with previous reports of attentional impairments in MDD. As a measure of brain metabolism, cerebral blood flow modulations are indirectly associated with neural activity. Therefore, reduced cerebral blood flow increase during the preparatory period may reflect diminished neural processing related to proactive control in MDD. In contrast, processes associated with the actual execution of the arithmetic task seemed to be unaffected.

1. Introduction

Major depressive disorder (MDD) constitutes a substantial public health issue; its lifetime prevalence has been projected at 20%, and it greatly reduces the psychosocial functioning and quality of life of affected patients (Kessler et al., 2005, 2010; Paykel et al., 2005). In addition to mood disturbance, motivational and somatic symptoms, individuals suffering from MDD frequently experience impairments in attention, memory and executive functions (Hoffmann et al., 2017; Porter et al., 2007; Snyder, 2013; Stefanopoulou et al., 2009). The clinical relevance of these deficits is reflected in their association with functional disability, poor quality of life, poor treatment outcome, increased risk of relapse after recovery, and the severity of residual symptoms (Alexopoulos et al., 2000, 2005; Jaeger et al., 2006; Majer et al., 2004).

Various psychological and physiological abnormalities have been associated with the cognitive impairments in MDD. Loss of motivation may play a role in low performance (Porter et al., 2007); anhedonia is assumed to reduce the amount of effort expended during cognitive challenge (Silvia et al., 2014). In addition, it has been well-established that aversive affective states and dysfunctional cognitive schemes interfere with optimal performance (Porter et al., 2007; Shah et al., 1999). On a physiological level, cognitive deficits in MDD have been related to disturbed function of the HPA axis (Egeland et al., 2005), reduced activity in the prefrontal cortex (Pu et al., 2011; Uemura et al., 2014; Yüksel and Öngür, 2010) and diminished cerebral perfusion (Alosco et al., 2013). Regarding cerebral blood flow, some studies documented reductions in measures of global brain perfusion (Alosco et al., 2013; Direk et al., 2012). In addition, MRI and PET studies suggested diminished resting blood flow in specific regions, such as prefrontal areas (Duhameau et al., 2010; Lui et al., 2009; Videbech, 2000), the anterior cingulate (Duhameau et al., 2010; Vasic et al., 2015) and subcortical structures like the basal ganglia (Duhameau et al., 2010) and parahippocampal areas (Vasic et al., 2015). However, blood flow enhancements have also been described, particularly in frontoparietal and striatal regions (Lui et al., 2009; Vasic et al., 2015).

The present study explored cerebral blood flow modulations during attention and executive functions in MDD. Cerebral blood flow

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modulations refer to transient changes in brain perfusion during sensory, cognitive or emotional processes, which result from flow metabolism coupling (Duschek et al., 2008a; Schuepbach et al., 2016). Due to an augmented metabolic rate of the nerve-cells, neural activation causes dilation of cerebral arterioles and capillaries followed by increased blood flow in the active tissue (Iadecola, 2004). Cerebral blood flow modulations can be investigated through functional transcranial Doppler sonography (fTCD), an ultrasound technique allowing continuous recording of blood flow velocities in the basal cerebral arteries at a high temporal resolution (Aaslid et al., 1982; Duschek and Schandry, 2003). Alterations in cerebral blood flow modulations during sensory and cognitive processing have been reported in various clinical conditions including schizophrenia (Schuepbach et al., 2016, 2017), fibromyalgia syndrome (Montoro et al., 2015) and migraine (Bäcker et al., 2001), and may reflect blunted or exaggerated neural activity, or abnormal temporal dynamics of activation processes.

In the present study, we applied fTCD to investigate cerebral blood flow modulations in MDD in the context of proactive control. Proactive control refers to attentional and executive functions that allow efficient regulation of sensory and motor systems during anticipation of a behaviorally relevant event, thereby optimizing readiness to react (Braver, 2012). They may include attentional activation, the maintenance of goal-relevant information, response selection or motor preparation, all of which are doubtlessly crucial in everyday life (Aron, 2011; Braver, 2012; Connolly et al., 2002). Proactive control is commonly investigated using precued tasks, in which a stimulus requiring a cognitive or behavioral response is announced by a preceding warning signal (Paulus, 2015).

Our study was based on a precued mental arithmetic task (Montoro et al., 2015). The paradigm involved simple arithmetic addition and motor responses, where each trial was preceded by an acoustic cue. The use of this warning tone allowed for induction of preparatory processes including an increase of attentional arousal, maintenance of task rules and motor preparation (Dehaene, 2000; Johnson and Proctor, 2004; Posner and Petersen, 1990). On a neural level, arithmetic processing has been related to bilateral activity in the prefrontal and parietal cortex, especially the gyrus angularis (Dehaene, 2000; Menon et al., 2000); proactive control is mainly represented in the lateral prefrontal lobe (Braver, 2012; Chambers et al., 2009). Moreover, regulation of attentional arousal has been associated with inferior parietal activity (Paus et al., 1997). These regions are supplied by the middle cerebral arteries (MCA) (Haines, 2007); therefore, fTCD recordings of flow velocities in these vessels were conducted during execution of the task.

The high temporal resolution of fTCD allows differential analysis of distinct phases of cerebral blood flow modulations (Duschek and Schandry, 2003). Previous fTCD studies using precued tasks revealed biphasic courses of flow velocities, with an initial increase component associated with response preparation, and a second one with response execution (Duschek and Schandry, 2004; Duschek et al., 2010; Montoro et al., 2015). In our study, we predicted a specific reduction of the amplitude of the first component in individuals with MDD, as a result of blunted cortical activity during proactive control. The hypothesis of deficient response preparation in MDD is supported by a study using a precued emotional conflict task, during which individuals with remittent depression showed prolonged reaction times, in addition to reduced event-related potential amplitudes (Vanderhasselt et al., 2012). This accords with earlier findings of a diminished amplitude of the contingent negative variation, an event-related potential of the EEG reflecting preparatory attention (Ashton et al., 1988; Giedke and Heimann, 1987).

The following hypotheses were tested in this study: (1) Individuals with MDD exhibit smaller bilateral MCA blood flow increases during the preparation of arithmetic processing than healthy participants. (2) Blood flow modulations associated with task execution do not differ between individuals with MDD and controls. (3) Individuals with MDD show worse task performance than controls in terms of reduced arithmetic accuracy and longer response time.

2. Material and methods

2.1. Participants

The study sample included 40 individuals with a current MDD (recurrent or single episode) according to DSM-IV-TR criteria (American Psychiatric Association, 2000), and 40 healthy individuals (23 women and 17 men in each group). Diagnoses were made using the Structured Interview for DSM-IV Disorders (SCID) (Wittchen et al., 1997). The self-reported mean duration of the disorder (time since first diagnosis) was 9.33 years (SD = 6.61 years). Individuals suffering from MDD with psychotic features, and those with severe comorbid disorders (e.g. addiction, post-traumatic stress disorder or eating disorders), were excluded from participation. To rule out the presence of mental disorders in the control group, the screening questionnaire from the Diagnostic Expert System for Mental Disorders (DIA-X-SSQ) (Wittchen and Perkonigg, 1996) was applied. Individuals suffering from a relevant physical disease were excluded from both study groups. Physical health status was assessed by means of an anamnestic interview and a questionnaire covering diseases of the cardiovascular, respiratory, gastro-intestinal and urogenital systems, in addition to thyroid, liver, and metabolic diseases. Fifteen of the individuals with MDD were currently on psychotropic medication. Seven were taking an SSRI, four an SNRI or SSNRI, two a tricyclic antidepressant, and one a combination of a tetracyclic antidepressant and an SSRI. Four individuals with MDD were on a neuroleptic in addition to antidepressant medication; one was taking a neuroleptic only. None of the participants in the control group used any kind of psychotropic medication.

Table 1 provides information about the age, level of education, body mass index (BMI) and smoking status of both study groups. In addition, scores on the German version of the Beck Depression Inventory (BDI-II) (Hautzinger et al., 2006) and the laterality quotient from the Edinburgh Handedness Inventory (Oldfield, 1971) are indicated. Thirty-three participants were university students (twenty-three in the patient group, twenty in the control group); eight patients were unemployed and the remaining participants were recruited from the workforce.

Table 1
Sample characteristics; mean values (M) and standard deviations (SD) for individuals with MDD and the control group.

	Individuals with MDD	Control group			
	M (SD)/N (%)	M (SD)/N (%)	$F[1,78]/Chi^2[2]$	p	η_p^2
Age (years)	28.90 (7.31)	29.18 (7.02)	0.002	.86	< 0.001
Years of education	15.04 (3.83)	16.60 (3.24)	0.068	.052	0.047
Body mass index (kg/m^2)	23.00 (3.17)	22.64 (2.70)	0.30	.59	< 0.01
BDI-II	28.90 (8.79)	2.45 (3.04)	323.52	< .001	0.81
Laterality quotient	62.53 (36.49)	67.80 (32.93)	0.46	.50	.006
Number of smokers	8 (20)	6 (15)	1.42	.49	

Note: The laterality quotient ranges between −100 and 100; higher values denote dominance of the right hand (Oldfield, 1971).