



Cerebral blood flow responses during prosaccade and antisaccade preparation in major depression

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Abstract

While impairments in executive functions have been well established in major depressive disorder (MDD), specific deficits in proactive control have scarcely been studied so far. Proactive control refers to cognitive processes during anticipation of a behaviorally relevant event that facilitate readiness to react. In this study, cerebral blood flow responses were investigated in MDD patients during a precued antisaccade task requiring preparatory attention and proactive inhibition. Using functional transcranial Doppler sonography, blood flow velocities in the middle cerebral arteries of both hemispheres were recorded in 40 MDD patients and 40 healthy controls. In the task, a target appeared left or right of the fixation point 5 s after a cuing stimulus; subjects had to move their gaze to the target (prosaccade) or its mirror image position (antisaccade). Video-based eye-tracking was applied for ocular recording. A right dominant blood flow increase arose during prosaccade and antisaccade preparation, which was smaller in MDD patients than controls. Patients exhibited a higher error rate than controls for antisaccades but not prosaccades. The smaller blood flow response may reflect blunted anticipatory activation of the dorsolateral prefrontal and inferior parietal cortices in MDD. The patients' increased antisaccade error rate suggests deficient inhibitory control. The findings support the notion of impairments in proactive control in MDD, which are clinically relevant as they may contribute to the deficits in cognition and behavioral regulation that characterize the disorder.

Keywords Major depression · Cerebral blood flow · Executive functions · Proactive control · Antisaccades · Transcranial Doppler sonography

Introduction

Cognitive control is a crucial factor in human information processing, enabling implementation and coordination of basic mental operations during the regulation of goal-directed behaviors [1]. Cognitive control is particularly efficient if it is activated before the occurrence of an event

requiring action. This ability, which is referred to as proactive control, may involve attentional activation, motor preparation, response selection, or prevention of inappropriate responses during anticipation of a behaviorally relevant signal, thereby optimizing readiness to react [2]. Proactive control is susceptible to failure in mental disorders and may be reduced during negative affective states [3–5].

In the present study, we investigated proactive control in patients with major depressive disorder (MDD). Impairments in higher cognitive functions in MDD have been well established [6–8]; they may impede activities in daily life and their clinical relevance is reflected by their associations with poor psychosocial function and quality of life, as well as enhanced risk of relapse after recovery, and the severity of residual symptoms [9–11]. At the neural level, cognitive distortion in MDD has been mainly related to aberrant cortical function, in particular reduced prefrontal cortical activity [12–14].

Specific deficits in proactive control in MDD have been scarcely investigated so far. However, their occurrence has

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been suggested by studies using event-related potentials (ERPs). Patients with remitted MDD exhibited diminished amplitude of the P450 ERP component during preparation for an emotional conflict task [15]. Based on a cognitive interference task, a reduction in the pre-stimulus slow wave was documented in healthy individuals with elevated Beck Depression Inventory scores [16]. Moreover, MDD was associated with decreased amplitude of the contingent negative variation (CNV) [17, 18], an ERP that reflects cortical activation during anticipation of a behaviorally relevant stimulus [19].

To obtain further insight into impairments in proactive control and their neural foundations in MDD, we investigated cerebral blood flow responses during a precued antisaccade task [20]. In the antisaccade task, eye movements are recorded, while a participant is instructed to look in the opposite direction to a visual target stimulus that suddenly appears left or right of the fixation point [21]. During the task, automatic behavior, i.e., looking at the target (prosaccade), must be suppressed in favor of deliberate, goal-directed action. In the task, prosaccades trials are commonly used as a control condition. Prosaccades require highly automatic, overt attentional, and sensorimotor processes; as such, using a combination of anti- and prosaccade trials allows for the comparison of complex cognitive control processes with more basic functions [22, 23]. Antisaccades have shown excellent reliability, as well as sensitivity, to a number of psychiatric disorders [24, 25].

In the task used in our study, a cuing stimulus predictably preceded the onset of the target stimulus by 5 s, which facilitated proactive control. The preparation of prosaccades in a precued task is mainly restricted to a short-term increase of attentional arousal, referred to as phasic alertness [26, 27]. In contrast, antisaccade preparation involves more sophisticated functions, particularly proactive inhibition, defined as a top-down mechanism that prevents an inappropriate response from occurring in an upcoming situation [1, 28].

We used functional transcranial Doppler sonography (fTCD) to assess cerebral blood flow during preparation of pro- and antisaccades. This ultrasound method enables the measurement of changes in blood flow velocities in the basal cerebral arteries during neural activation processes, which result from flow metabolism coupling [29]. fTCD allows continuous measurement with high time resolution, making it particularly suitable in the investigation of neural activity related to fast ongoing cognitive processes, such as those of proactive control [30]. It has been well established that, at the neural level, proactive inhibition is associated with activation in the lateral and dorsomedial parts of the prefrontal cortex [1, 31, 32]. Phasic alertness, in turn, has been related to the dorsolateral prefrontal cortex and the inferior parietal cortex, especially in the right hemisphere [33]. As these cortical structures form part of the perfusion territory

of the middle cerebral arteries (MCA), we assessed flow velocities in the MCA bilaterally [34].

A previous study from our group documented the suitability of fTCD in the investigation of neural activity related to proactive control based on the precued antisaccade task [35]. That study revealed a right dominant anticipatory blood flow increase in the MCA, which was stronger during antisaccade than prosaccade preparation, reflecting the higher preparatory demands of antisaccades [36]. fTCD has also been applied to explore proactive control in MDD. In a recent study, MCA flow velocities were obtained during a precued mental arithmetic task (addition problems presented 5 s after a cuing stimulus) [37]. In MDD patients, impaired task performance was accompanied by reduced preparatory flow increases in both hemispheres. In a similar vein, MDD patients exhibited diminished bilateral MCA blood flow responses during a precued Stroop task (color word interference test, [38]) addressing interference control [39]. These observations support the notion of decreased cortical activity during proactive control in MDD.

However, the cognitive processes addressed in those previous studies differ greatly from those of the precued antisaccade task. While the previously used tasks required preparation of verbal arithmetic operations and anticipation and prevention of interference, stopping of an inappropriate response (i.e., proactive inhibition) is a key process during antisaccade preparation [1, 28]. Moreover, while performance in the previously applied tasks to a certain degree relies on motor speed, in the antisaccade task, there is no confound between cognitive and peripheral motor processes. This is crucial insofar as psychomotor retardation is a common symptom of MDD, and it has been well established that motor slowing may reduce performance on cognitive tasks in the affected patients [40–42].

Applications of standard, i.e., non-cuing, variants of the antisaccade task have revealed higher rates of direction errors in MDD patients than healthy individuals for antisaccade but not for prosaccade trials [6, 43]. This may indicate that the patients' impairments mainly encompass processes related to executive functions, whereas basic attentional and visuomotor deficits only play a subordinate role. On this basis, it may be hypothesized that, in MDD, blood flow responses during antisaccade preparation may be reduced to a greater degree than those related to prosaccade preparation. However, this prediction cannot be made with certainty, as numerous studies have also documented deficits in attentional functions in MDD, including phasic alertness, as involved in prosaccade preparation [17, 18, 44].

Our principal hypothesis was that smaller bilateral MCA blood flow increases during preparation of pro- and antisaccades would occur in patients with MDD than healthy individuals. Given the executive function impairments in MDD, and due to particular deficits in antisaccades relative

Table 1 Sample characteristics of the MDD patient and control groups: mean values (M) and standard deviations (SD)

	MDD patients <i>M</i> (SD)	Control group <i>M</i> (SD)	<i>F</i> [1, 78]	<i>p</i>	η_p^2
Age (years)	28.90 (7.31)	29.18 (7.02)	0.029	0.86	<0.001
Duration of education (years)	15.04 (3.83)	16.60 (3.24)	3.88	0.052	0.047
Body mass index (kg/m ²)	23.00 (3.17)	22.64 (2.70)	0.30	0.59	0.004
Laterality quotient	62.53 (36.49)	67.80 (32.93)	0.46	0.50	0.006
Beck Depression Inventory (BDI-II)	28.90 (8.79)	2.45 (3.04)	323.52	<0.001	0.81

The laterality quotient ranges between – 100 and 100; higher values denote dominance of the right hand [46]

to prosaccades in these patients, the reduction of the preparatory blood flow response was expected to be greater for antisaccade than prosaccade trials [6, 8]. Furthermore, based on the previous evidence, we hypothesized that patients would exhibit higher error rates than controls, especially in antisaccade trials [6, 43]. Considering the relevance of proactive control in optimizing readiness to react, a positive association between the blood flow response and task performance was also predicted [45, 46].

Materials and methods

Participants

The patient sample included 40 individuals (23 women and 17 men) with a current MDD (recurrent or single episode), diagnosed using the German version of the Structured Interview for DSM-IV Disorders (SCID) [47]. Mean illness duration (interval from the first diagnosis of MDD) was 9.33 years (SD = 6.61 years). Patients suffering from MDD with psychotic features, and those with severe psychiatric comorbid disorders (e.g., addiction, trauma or eating disorders), were not included in the sample. Fifteen of the patients were using psychotropic medication; 14 were using antidepressants, among whom 12 were taking an SSRI (escitalopram, fluoxetine, sertraline, and trazodone) and 2 were taking an SSNRI (duloxetine, venlafaxine). Seven of the patients were on neuroleptic medication (aripiprazole, flupentixol, olanzapine, quetiapine, and sulpiride). Among these patients, six were taking the combination of a neuroleptic and an antidepressant; one was using a neuroleptic only. None of the patients were on benzodiazepines.

The control group comprised 23 women and 17 men, who did not suffer from mental diseases of any kind according to the Diagnostic Expert System for Mental Disorders (DIA-X-SSQ) [48]. None of the controls used any kind of medication affecting the central or peripheral nervous system. The presence of relevant physical disease served as an exclusion criterion in both study groups. Physical health status was recorded through 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.

Table 1 provides information about age, duration of education, body mass index (BMI), the laterality quotient of the Edinburgh Handedness Inventory [49], and scores on the Beck Depression Inventory II (BDI-II) [50] in both study groups. Thirty-three participants were university students (23 MDD patients and 20 controls); eight of the patients were unemployed and the remainder of the sample was in employment. The patient sample was recruited via local psychotherapists, psychosocial counselling centers, and support groups; the control group was acquired via university facilities and internet platforms.

Sample size was determined based on the previous studies comparing executive function performance between MDD patients and healthy controls (c.f. 7,8), which mostly revealed effect sizes (Cohen's *d*) in the medium range. Assuming an effect size of 0.4, an alpha level of 5%, and a beta error of 20%, power analysis revealed a required sample size of 39 per group.

The study was conducted as part of the project “Executive dysfunction in chronic hypotension and depression—central nervous and autonomic causation” funded by the Anniversary Fund of the Austrian National Bank (project 16289) [6, 37, 39]. The present part was selected for this publication as it addressed a standalone research question and applied specific methods.

Experimental task

The antisaccade task was developed and pretested in a previous study [35]. It was presented using Experiment Builder software (SR Research Ltd., Ottawa, Canada) on a computer monitor (1680 × 1050 resolution, 60 Hz refresh rate) at a distance of 60 cm from the participants' eyes. A trial began with the appearance of a small white circle (diameter of 0.5°) in the center of the screen. After 40 s, an acoustic signal was presented (400-Hz tone of 500 ms duration), which served as the cuing stimulus; 4800 ms after the cuing stimulus, the

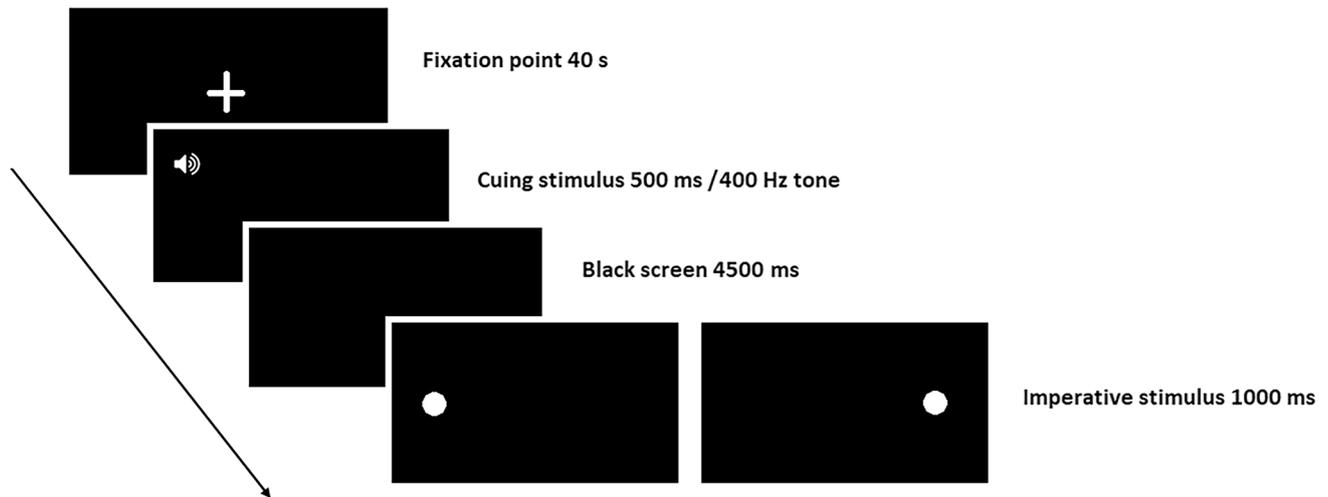


Fig. 1 Schematic of the experimental task. Sample rates: 100 Hz for fTCD; 1000 Hz for eye-tracking

circle disappeared for 200 ms and reappeared for 1000 ms at a horizontal peripheral location ($\pm 6^\circ$ with both positions used equally often). The brief disappearance of the stimulus, i.e., the gap, was introduced to increase the likelihood of errors in antisaccade trials [20, 51]. The peripheral stimulus served as the imperative stimulus, which had to be responded to either with an antisaccade or a prosaccade. The next trial began when the white circle was presented again in the center of the screen and the participant had to direct his/her gaze toward this position. Concerning antisaccades, participants were instructed to look as quickly and accurately as possible at the horizontal mirror image position of the peripheral stimulus; for prosaccades, they were asked to look as quickly and accurately as possible at the peripheral stimulus as soon as it appeared. During the 40 s inter-stimulus interval, participants had to keep their eyes open and fixate on the white circle. Two blocks of trials were presented, one of which comprised 20 antisaccades and the other 20 prosaccades. Participants were informed about the required responses (i.e., antisaccades or prosaccades) before each block. The two blocks were separated by a 1 min break. Half of the participants started with the antisaccade block and the other half with the prosaccade block. A schematic of the task is given in Fig. 1.

Recording and processing of eye movement data

The EyeLink 1000 system (SR Research Ltd.) was used for video-based eye-tracking. Movements of the right eye were recorded at a sampling rate of 1000 Hz. The device has a minimal spatial resolution of 0.01° and an average accuracy of between 0.25° and 0.5° . Centroid pupil-tracking algorithms were used to detect pupil and corneal reflection. A

five-point horizontal and vertical calibration procedure was performed before each of the 20 trial sequences of the task.

Data Viewer software (SR Research Ltd.) was applied for processing of eye movement data. The criterion for the detection of pro- and antisaccades was a minimum amplitude of 1° , minimum velocity of $30^\circ/\text{s}$, and minimum latency to onset of the imperative stimuli of 80 ms. Trials with a blink between 100 ms before and 80 ms after onset of the imperative stimulus were excluded, as were trials where the saccade contained a blink. Some trials had to be omitted, as follows: prosaccades, MDD patients, $M = 1.53$, $SD = 1.40$, controls, $M = 0.88$, $SD = 1.20$; antisaccades, MDD patients, $M = 1.75$, $SD = 2.92$, controls, $M = 0.65$, $SD = 2.01$.

The rate of direction errors was the primary measure of task performance, given by the ratio between errors and valid trials. An error in an antisaccade trial was counted when the first valid saccade was made towards the peripheral target, and in prosaccade trials when it was made in the opposite direction of the peripheral target. In addition, response latency (in ms) was computed for correctly performed trials. Only data of participants with a minimum of five correctly performed saccades and antisaccades were included in the analysis.

Recording and processing of cerebral blood flow data

For the purpose of cerebral hemodynamic recording, a commercially available Doppler sonography device (Multidop L2; DWL Elektronische Systeme, Sipplingen, Germany) was applied. Blood flow velocities were recorded simultaneously in the MCA of both hemispheres. The recordings were obtained through the temporal bone windows using two 2-MHz transducer probes. Insonation took place at a

depth between 45 and 52 mm. Following vessel identification, the ultrasonic probes were fixed to the head using a head harness.

The spectral envelope curves of the Doppler signal were stored at a rate of 100 samples per second (for the insonation technique and validation of fTCD, see ref. [30]). The envelope curves revealed by Doppler sonography were analyzed offline using the AVERAGE software [52]. Flow velocities were integrated over each cardiac cycle and averaged, time locked to the cuing stimulus. The mean flow velocity during the 10 s prior to this stimulus served as a baseline (FV_{bas}). Relative changes (percent) in flow velocity during task execution (dFV) were calculated for both MCA using the following function: $dFV = [FV(t) - FV_{\text{bas}}] \times 100 / FV_{\text{bas}}$; where $FV(t)$ represents the flow velocity over the course of time. Following this, the data were resampled at 5 Hz. Trials involving erroneous behavioral responses were excluded from the analysis.

The amplitude of the blood flow increase following the cuing stimulus, expressed by the individual maximum of dFV, was used as the dependent variable [53, 54]. The time window, in which the maximum was determined, was defined as the 3 s interval around the maximum of the blood flow response, and averaged across both arteries and both types of trials in the whole sample (3.2–6.2 s after the cuing stimulus).

Procedure

Experimental sessions were conducted in a quiet and dimly lit room. At the beginning of the session, the SCID interview was conducted and sociodemographic and clinical data were obtained. Thereafter, the ultrasonic probes were mounted and the task was presented. Participants were requested not to drink alcohol or beverages containing caffeine for 3 h prior to the experimental session.

Statistical analysis

Statistical analysis of fTCD data was based on an analysis of variance (ANOVA) model with the between-subjects factor of group (MDD patients vs. control group) and the two within-subjects factors of trial type (antisaccade vs. prosaccade trials) and hemisphere (left vs. right MCA). Blood flow amplitudes (individual maxima of dFV) served as the dependent variable. For task performance, ANOVAs with the between-subjects factor of group and the within-subjects factor of trial type were performed. Separate models were computed for error rate and response latency for correct trials. To investigate the possible effects of psychotropic drugs on cerebral blood flow amplitudes and task performance, a multivariate analysis of variance (MANOVA) was computed

for the patient group, contrasting subgroups of patients using (1) antidepressants, (2) a combination of an antidepressant and a neuroleptic, and (3) no psychotropic medication (see Supplementary Material). The relationships between blood flow amplitudes and indices of task performance were quantified using Pearson correlations in the entire sample. To control for differences in blood flow amplitude between MDD patients and controls, we subtracted the group means of the amplitudes before computing the correlations. Alpha-inflation was accounted for in the correlation analysis (eight correlation coefficients) using a Bonferroni–Holm procedure. Accordingly, the lowest p value was compared to 0.05/8, and the second lowest to 0.05/7, etc. Alpha was set at 0.05 in the ANOVAs and the MANOVA. Partial eta squared (η_p^2) is presented as an index of effect size.

Results

Figure 2 displays the flow velocity changes in the left and right MCA during prosaccade and antisaccade trials in both study groups. Steep bilateral increases were seen in both vessels and during both types of trials, beginning around 2 s after the cuing stimulus and peaking in the final phase of the preparatory interval. For prosaccade and antisaccade trials, increases in both hemispheres were smaller in MDD patients than in the control group. Increases in both hemispheres were stronger for antisaccade than prosaccade trials. Overall, blood flow increases were greater in the right than in the left MCA.¹

The ANOVA for flow velocity amplitudes revealed a main effect of group, reflecting the smaller blood flow increases in MDD patients than healthy individuals ($F [1, 78] = 4.47$, $p = 0.038$, $\eta_p^2 = 0.054$). Effects of trial type and hemisphere confirmed the larger amplitude for antisaccade than prosaccade trials and the larger amplitude in the right than left MCA (trial type: $F [1, 78] = 19.60$, $p < 0.001$, $\eta_p^2 = 0.20$; hemisphere: $F [1, 78] = 36.28$, $p < 0.001$, $\eta_p^2 = 0.32$). A significant trial type by hemisphere interaction indicated stronger lateralization for prosaccade than antisaccade trials ($F [1, 78] = 17.83$, $p < .001$, $\eta_p^2 = 0.19$). The remaining interaction effects did not reach significance (all $F [1, 78] \leq 2.47$, all $p \geq .12$, all $\eta_p^2 \leq 0.031$).

Table 2 includes the indices of prosaccade and antisaccade performance in both study groups. Error rate was higher in antisaccade than prosaccade trials (trial type: $F [1, 78] = 111.48$, $p < .001$, $\eta_p^2 = 0.59$) and higher in MDD patients than controls (group: $F [1, 78] = 7.14$, $p = 0.009$,

¹ Values at the beginning of the task period (time 0) were slightly higher in MDD patients than controls, which may be ascribed to spontaneous fluctuations of flow velocities at baseline.

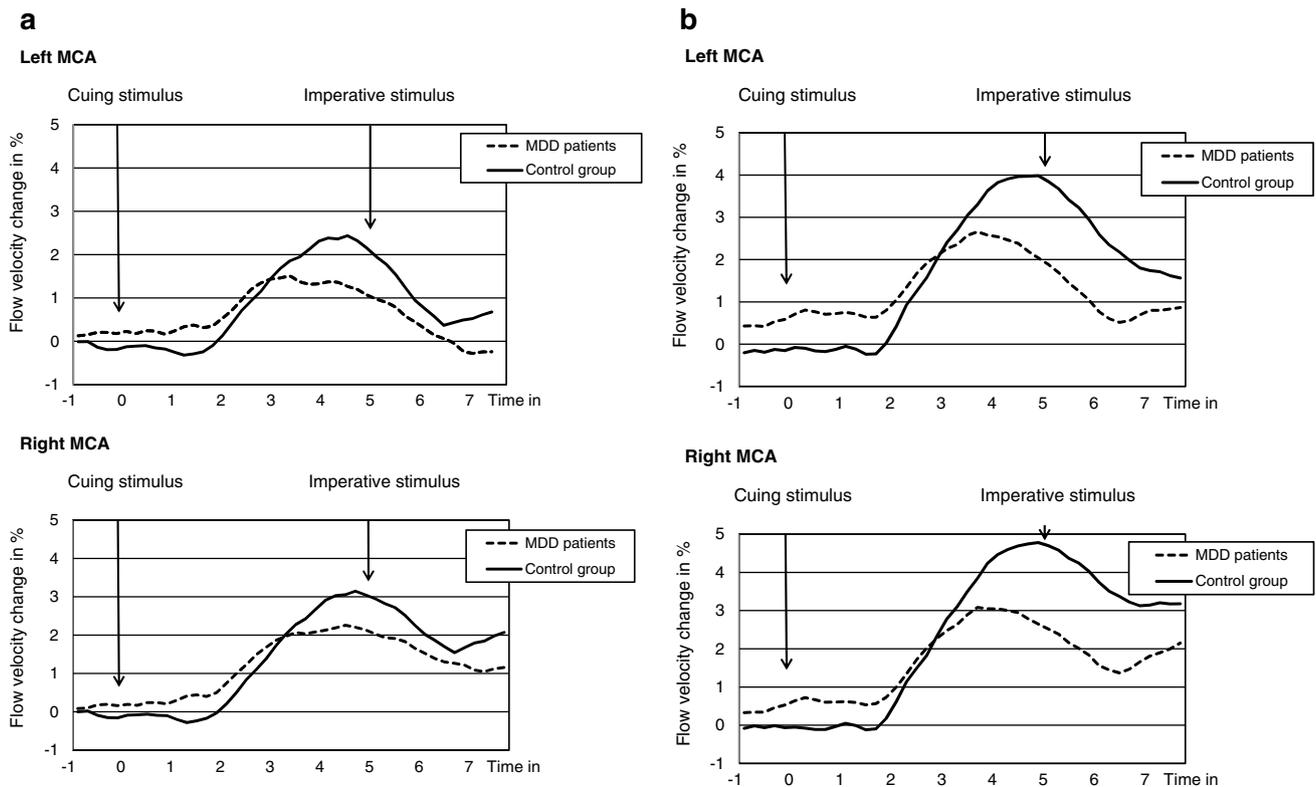


Fig. 2 **a** MCA blood flow changes during preparation of prosaccades (grand average). **b** MCA blood flow changes during preparation of antisaccades (grand average)

Table 2 Means and standard deviations (in parentheses) of performance indices

	MDD patients		Control group	
	Antisaccades	Prosaccades	Antisaccades	Prosaccades
Error rate (%)	20.88 (14.33)	1.40 (2.85)	13.44 (11.89)	0.93 (2.05)
Response latency (ms)	226.48 (45.10)	146.49 (34.73)	232.05 (61.24)	140.93 (22.92)

Table 3 Correlations between blood flow amplitudes and performance indices

Blood flow amplitudes	Prosaccades: error rate		Prosaccades: response latency		Antisaccades: error rate		Antisaccades: response latency	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
	Left MCA	0.11	0.16	0.13	0.12	-0.21	0.031	0.076
Right MCA	0.13	0.13	0.11	0.16	-0.24	0.016	0.10	0.19

$\eta_p^2 = 0.084$). Moreover, a group-by-trial type interaction arose ($F [1, 78] = 5.30, p = 0.024, \eta_p^2 = 0.064$). According to post hoc testing, the error rate of patients exceeded that of controls in antisaccade ($F [1, 78] = 6.39, p = .013, \eta_p^2 = 0.076$) trials, but not in prosaccade trials ($F [1, 78] = 0.72, p = 0.40, \eta_p^2 = 0.009$). Antisaccade trials, as compared to prosaccade trials, were associated with longer response latency ($F [1, 78] = 206.03, p < 0.001, \eta_p^2 = 0.73$); the

group and interaction effects were not significant for this parameter (group: $F [1, 78] < 0.01, p > .99, \eta_p^2 < 0.001$; interaction: $F [1, 78] = 0.87, p = 0.35, \eta_p^2 = 0.011$).

The MANOVA comparing the subgroups of patients defined according to medication use is described in the Supplementary Material. Neither a multivariate nor univariate effects arose. While no systematic subgroup differences were seen for error rates and response latencies, a trend towards lower flow velocity amplitudes was seen in

patients taking a combination of an antidepressant and a neuroleptic compared to the remaining patients. Results of the correlation analysis are presented in Table 3. According to Bonferroni–Holm-corrected testing, none of the correlations reached significance.

Discussion

Our study investigated proactive control in MDD based on cerebral hemodynamic recordings during a precued antisaccade task. The most important result was the smaller bilateral MCA blood flow which increases during preparation of pro- and antisaccades in MDD patients than healthy controls. In the total sample, blood flow amplitudes were greater during antisaccade than prosaccade preparation. While flow responses were overall stronger in the right than in the left MCA, lateralization was more pronounced for prosaccade than antisaccade trials. Regarding behavioral performance, MDD patients exhibited a higher rate of direction errors in antisaccade but not in prosaccade trials.

The results of fTCD assessments reflect diminished neural activity during proactive control in patients with a current episode of MDD. The increases in MCA blood flow velocities during preparation of pro- and antisaccades can be ascribed to the activation of neural networks related to relevant cognitive processes. Preparation of automatized behaviors, such as prosaccades, mainly involves transient enhancement of attentional tone, i.e., phasic alertness [27]. At the cortical level, this specific function of the attention system is represented in the dorsolateral frontal and inferior parietal lobes, which are supplied by the MCA [33, 34, 55]. Flow velocity increases in the basal cerebral arteries occur due to an augmentation of the metabolic rate of neurons in their perfusion territory [30, 56]. As such, a smaller increase during prosaccade preparation in MDD patients indicates reduced neural activity in these structures.

The stronger flow increase in the right than left MCA during prosaccade preparation replicated our previous study [35]. Right hemispheric blood flow lateralization has also been seen in earlier fTCD studies of preparatory attention, and reflects the well-known dominance of the right hemisphere in phasic alertness [45, 46, 57]. A right dominant noradrenergic system controlling attentional arousal has been described, which arises in the reticular formation and projects to the frontal and parietal cortices [27].

Preparation of antisaccades requires executive control in addition to phasic alertness. Here, proactive inhibition plays a key role, enabling anticipatory prevention of dominant reactions [1, 28]. Various studies using event-related fMRI have explored cortical activity during antisaccade preparation. Their results suggest a major role of the dorsolateral prefrontal cortex in proactive inhibition, in addition to the

frontal eye fields, the anterior cingulate and parietal regions [36, 51, 58]. With the exception of the anterior cingulate, these structures form part of the MCA perfusion territory; as such, it seems justified to ascribe the patients' reduced blood flow increases during antisaccade preparation to their blunted cortical activity. This is in accordance with meta-analytic data indicating decreased resting-state activity of the dorsolateral prefrontal cortex and anterior cingulate in MDD [59]; prefrontal hypoactivity in turn has been related to blunted metabolism of glutamate, the main excitatory neurotransmitter in the human brain [14].

In the entire sample, the right hemispheric lateralization of the blood flow response was less pronounced for antisaccade than prosaccade trials, which conflicts with the hypothesis of a specific role of the right hemisphere in behavioral inhibition [60]. Evidence concerning this hypothesis is still controversial: lesion studies have demonstrated stronger inhibition impairment in the stop-signal task in neurological patients with right rather than left prefrontal damage [60, 61]. However, reduced performance on a go/no-go task was also seen in patients with left inferior parietal lesions [62]. Concerning antisaccades, both right and left prefrontal cortex damage may lead to augmented error rates [63, 64]. Some fMRI studies revealed bilateral prefrontal activity during inhibition in go/no-go tasks [65, 66]. In addition, event-related fMRI studies of antisaccade preparation demonstrated relatively small right hemispheric lateralization of their underlying networks [36, 51, 58]. Therefore, our observation of a discrete hemispheric difference in the hemodynamic response during antisaccade preparation is consistent with the state of research.

In MDD patients and healthy individuals, the magnitude of the blood flow response in both hemispheres was markedly stronger during antisaccade than prosaccade trials, which also replicated our previous study [35]. This result reflects allocation of greater cortical resources during preparation of the more cognitively demanding antisaccades. In contrast to the simple sensorimotor mapping required for prosaccades, antisaccades involve the suppression of the tendency to look towards the stimulus, as well as non-standard sensorimotor transformations that require vector inversion. Accordingly, fMRI studies have consistently shown greater activity in prefrontal structures during antisaccade than prosaccade preparation [36, 51, 58]. In our behavioral data, the higher demand and need for additional processing resources of antisaccades are illustrated by the higher error rate (17.2% vs. 1.2%) and longer response latency (229.3 ms vs. 143.7 ms) in antisaccade compared to prosaccade trials.

Corroborating the previous findings, MDD patients exhibited higher error rates than controls in antisaccade but not in prosaccade trials [6, 43]. This is in accordance with earlier studies demonstrating reduced performance of MDD patients on the other measures of response inhibition

including flanker, Stroop and Hayling tasks [8, 67–69]. The specificity of the group difference to antisaccade trials that was observed here suggests specific executive function impairments in MDD [6–8]. Even though reduced attention and cognitive speed have been established in MDD, the current state of research supports the view that executive functions are particularly vulnerable to disruption in MDD, and that these impairments do not occur due to distortion of basic attentional functions [8, 70]. Response latencies in saccade and antisaccade trials did not differ between patients and controls. This is also consistent with the previous observations [6, 43] and indicates that the impairment in MDD may encompass the accuracy rather than the speed dimension of antisaccade performance. In contrast to our expectation, the extent of the reduction in the anticipatory blood flow response in MDD patients did not differ as a function of trial type. The patients' greater reduction in accuracy on antisaccade than prosaccade trials was thus not reflected in different magnitudes of the preparatory blood flow response.

Contrary to our hypothesis, the magnitude of the blood flow response during prosaccade and antisaccade preparation was unrelated to error rate and latency. This is in contrast to the previous findings of positive correlations between preparatory blood flow modulations and cognitive performance [45, 46, 53]. However, it should be noted that results concerning the association between blood flow modulations and performance are inconsistent. In addition to an independence of both variables [71], inverse associations between task-induced blood flow increases and performance have also been reported [37, 54, 72].

Our findings of blunted cerebral blood flow increase during prosaccade and antisaccade preparation are in line with the recent fTCD studies showing reduced anticipatory hemodynamic responses in MDD in precued mental calculation and cognitive interference tasks [37, 39]. Altogether, these results point towards a rather general deficit in preparatory processing in MDD patients, as shown by phasic alertness, interference anticipation, the preparation of numeric operations, and proactive inhibitory control. The findings revealed by cerebral blood flow analysis agree with ERP studies suggesting reduced cortical activity associated with response preparation in emotional conflict, Stroop and simple motor reaction tasks [15–18]. The susceptibility to failure of preparatory processes in mental disorders is also underlined by alterations in behavioral measures of proactive control in connection with reduced lateral prefrontal activity in schizophrenia and adult attention-deficit/hyperactivity disorder [3, 4].

A relevant limitation of this study pertains to the use of psychotropic medication in MDD patients, 15 of whom were taking various kinds of drugs potentially influencing attentional and executive functions and cerebral blood flow modulations. Available research indeed points towards negative

effects of antidepressant and neuroleptic treatment on cognition [7, 73, 74]. Our comparison among patients using antidepressants, those using a combination of an antidepressant and a neuroleptic, and those using no drugs revealed no significant differences in cerebral blood flow or task performance. While these groups did not differ systematically in performance speed or accuracy, a clear trend towards smaller blood flow responses in patients taking a combination of an antidepressant and a neuroleptic was seen compared with the other groups. This may suggest a reduction of preparatory neural activation due to the antidopaminergic effects of neuroleptics [75]. Considering this, it cannot be ruled out that, in these individuals, the blunted blood flow response at least partly resulted from medication rather than MDD pathology. However, due to the small size of the patient subgroups, no firm conclusion can be drawn regarding the relevance of medication to the aberrant preparatory cerebral blood flow modulations seen in MDD.

In conclusion, the present study provided relevant information regarding cognitive impairments in MDD and the physiological mechanisms involved therein. The blunted hemodynamic responses during prosaccade and antisaccade preparation support the notion of impaired neural processing in association with preparatory attention and proactive inhibition in patients. Proactive control is regarded as an important mechanism in optimizing readiness to react and prevention of inappropriate behavior [1, 28]; as such, the observed deficits may be of substantial clinical relevance.

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Compliance with ethical standards

Ethical standards The study was approved by the Board for Ethical Questions in Science of the University of Innsbruck, Austria, and, therefore, performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent.

Conflict of interest There are no conflicts of interest to disclose.

Access to research data The research data of the study are available to the public via the repository Open Science Framework (OSF: osf.io/ceba8).

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