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Short communication

Short-term cerebral blood flow variability in major depressive disorder

Stefan Duschek [a,*], Alexandra Hoffmann [a], Gustavo A. Reyes del Paso [b], Casandra I. Montoro [a]

[a] UMIT - Institute of Psychology, University for Health Sciences Medical Informatics and Technology, Eduard-Wallnöfer Zentrum 1, 6060 Hall in Tirol, Austria
[b] Department of Psychology, University of Jaén, Spain

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ABSTRACT

Background: Previous research has documented reduced heart rate and blood pressure variability in major depressive disorder (MDD), suggesting a limited capacity for cardiovascular regulation and diminished homeostatic resources in the disorder. This study aimed to complement this knowledge by investigating short-term cerebral blood flow (CBF) variability in MDD.

Methods: Using transcranial Doppler sonography, blood flow velocities in the middle cerebral arteries of both hemispheres were recorded in 35 MDD patients and 35 healthy controls, at rest and during serial subtraction task-induced mental stress. CBF variability was represented by the root mean square of successive differences (RMSSD) in the beat-to-beat mean, systolic and diastolic flow velocity.

Results: Patients, as compared to controls, exhibited smaller mean and diastolic blood flow variability in MCA both at rest and during mental stress. Mean, systolic and diastolic blood flow variability were greater during the task than at rest. CBF variability did not differ between patient subgroups composed according to medication use.

Limitations: Potential effects of blood pressure and respiration on CBF variability could not be investigated.

Conclusions: The study revealed evidence of reduced short-term CBF variability in MDD. The task-induced CBF variability increase may be ascribed to neural activity associated with arithmetic processing. Lower blood pressure variability and deficient autonomic cardiovascular control may contribute to the reduction of short-term CBF variability seen in MDD. Short-term CBF variability reflects preserved interplay of regulatory mechanisms ensuring optimal blood and energy supply to the brain. Therefore, the results suggest impaired cerebroprotective mechanisms, associated with suboptimal cerebral performance.

1. Introduction

Intrinsic variability of physiological systems reflects the activity of homeostatic regulation mechanisms, which allow such systems to flexibly respond to internal and environmental demands and perturbations (Montoro et al., 2018a). While flexible adjustment of regulatory mechanisms confers substantial health and survival benefits, abnormalities in variability may indicate reduced homeostatic capacity in association with poor function and increased risk of negative health outcomes (Parati et al., 2020).

Physiological variability in major depressive disorder (MDD) has mainly been studied in the context of cardiovascular functions; reduced short-term heart rate variability (HRV) is well-established in affected patients (e.g., Bair et al., 2020; Chang et al., 2017). In addition to indicating poor cardiovascular and general health, low HRV has been associated with deficient top-down integration of brain mechanisms that allow for flexible control of behaviour and autonomic functions (Thayer & Lane, 2009). Moreover, reduced short-term blood pressure variability was reported in MDD (Bair et al., 2020; Duschek et al., 2021). It is commonly believed that short-term blood pressure variability reflects blood pressure homeostasis, which promotes the maintenance of optimal organ perfusion (Parati et al., 2020).

In contrast, knowledge about variability in cerebral blood flow (CBF) in MDD remains scant. However, such knowledge is important because short-term CBF variability has been associated with flexible adjustment of cerebral blood supply in response to changes in metabolic requirements (Montoro et al., 2018a). CBF variability reflects preservation of the interplay of central-nervous regulatory mechanisms and is regarded as a marker of cerebrovascular health (Rickards & Tzeng, 2004). Reduced CBF variability has been observed in clinical conditions like carotid artery disease, tension-type headache and fibromyalgia (see Montoro et al., 2018a, 2018b and Rickards and Tzeng, 2014).

The present study aimed to investigate short-term CBF variability in MDD. Transcranial Doppler sonography (TCD) was applied for this

* Corresponding author.
E-mail address: stefan.duschek@umit.at (S. Duschek).

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purpose, which enables continuous assessment of flow velocities in the basal cerebral arteries with high temporal resolution (Duschek & Schandry, 2003). The analysis was based on recordings of beat-to-beat flow velocities in the middle cerebral arteries (MCA) of both hemispheres, which supply a large brain area including cortical and subcortical structures (Haines, 2007).

The main hypothesis of the study was that lower CBF variability should be observed in patients with MDD than healthy individuals. This is suggested by observations of low heart rate and blood pressure variability in MDD, and would add further credence to the notion of a reduced capacity for cardiovascular regulation and diminished homeostatic resources (Bair et al., 2020; Chang et al., 2017). To obtain a comprehensive picture of CBF variability during varying conditions, TCD recordings were made at rest and during mental stress.

2. Methods

2.1. Participants

This study was part of a larger project investigating peripheral and cerebral hemodynamic regulation in MDD (c.f. Hoffmann et al., 2018). A total of 35 outpatients with a current MDD (recurrent or single episode) diagnosed using the German version of the Structured Interview for DSM-IV Disorders (SCID) (Wittchen et al., 1997) participated. The mean illness duration (interval from first MDD diagnosis) was 9.54 years (SD=6.55 years). Patients suffering from MDD with psychotic symptoms, and those with severe psychiatric comorbidities (e.g., addiction, trauma or eating disorders), were not permitted to participate. Thirteen of the patients were using psychotropic drugs; twelve were taking antidepressants, among whom ten were taking an SSRI and two an SNRI. Six patients were on neuroleptic medication. Among these patients, five were using a neuroleptic and an antidepressant in combination; one was using a neuroleptic only. None of the patients were on benzodiazepines.

The control group included 35 participants, who did not suffer from mental disorders of any kind according to the Diagnostic Expert System for Mental Disorders (DIA-X-SSQ) (Wittchen & Perkonigg, 1996). Moreover, none of them used any kind of medication affecting the central or peripheral nervous system. The presence of relevant physical disease was an exclusion criterion in both study groups. Table 1 presents information about age, duration of education, body mass index (BMI), blood pressure and heart rate, acquired at the beginning of the experimental session (sphygmomanometrical measurement using an Omron M400 device; Omron Healthcare, Lake Forest, IL, USA), and scores on the Beck Depression Inventory II (BDI-II) (Hautzinger et al., 2006). The patient group was recruited via local psychotherapists, psychosocial counselling centers and support groups; the control group was acquired via internet platforms and snowball sampling in the community.

Participants were requested not to drink alcohol or beverages containing caffeine for 3 hours prior to the study session. The study was approved by the Board for Ethical Questions in Science of the University of Innsbruck, Austria. All participants provided written informed consent.

Table 1
Characteristics of the MDD patient and control groups: statistics of the group comparison.

	MDD patients M±SD/N(%)	Control group M±SD/N(%)	F[1,68]/ Chi^2	p	η_p^2
Age (years)	28.89±7.68	29.51±6.97	0.13	.72	<.01
Gender (N and % of women)	20 (57.14%)	19 (54.29%)	0.058	.81	
Duration of education (years)	15.13±3.79	16.71±3.29	3.31	.073	.046
Body mass index (kg/m^2)	22.82±2.96	22.69±2.53	0.039	.84	<.01
Systolic blood pressure (mmHg)	113.52±10.87	117.25±8.22	2.62	.11	.037
Diastolic blood pressure (mmHg)	72.63±6.22	74.40±5.59	1.57	.21	.023
Heart rate (beats/min)	73.61±9.17	76.05±13.06	0.82	.37	.012
Beck Depression Inventory (BDI-II)	29.63±9.12	2.49±2.97	280.38	<.01	.81

2.2. Cerebral blood flow recordings

Blood flow velocities were recorded for 3 min, at rest and during mental stress induced by a 3-min serial subtraction task. During the resting phase, participants were asked to sit still, refrain from speaking and relax with their eyes open; during the subtraction task, they had to count down from 1000, subtracting 17 each time and saying the numbers out loud.

A Multidop L2 device (DWL Elektronische Systeme, Sipplingen, Germany) was used for TCD recordings. Blood flow velocities were assessed simultaneously in the MCA of both hemispheres. The recordings were obtained through the temporal bone windows using two 2-MHz transducer probes (insonation depth of 45–52 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 sampling rate of 100 Hz. Mean flow velocity was used as the main index of CBF, because it shows the highest correlation with blood volume streaming through an artery per unit of time (Duschek & Schandry, 2003). Systolic and diastolic flow velocities were also recorded. The indices were computed from the envelope curves on a beat-to-beat basis using customized software. The root mean square of successive differences (RMSSD) was taken as a parameter of flow velocity variability.

3. Statistical analysis

For the statistical analysis, ANOVA models were computed with the between-subjects factor of group (MDD patients vs. control group), and the two within-subjects factors of experimental condition (rest vs. mental stress) and hemisphere (left vs. right MCA). The RMSSD values for the mean, systolic and diastolic flow velocity served as dependent variables. To investigate possible effects of psychotropic drugs on CBF variability, ANOVAs were computed for the patient group with the between-subjects factor of medication (antidepressants vs. antidepressant/neuroleptic combinations vs. no psychotropic medication) and the within-subjects factors of condition and hemisphere.

Potential effects of HRV on CBF variability were controlled for in the analysis. HRV was indexed by the RMSSD of intervals between systolic points of the MCA blood flow velocity recording (intersystolic intervals). In a first step of data analysis, linear regression models were computed for variability of the mean, systolic and diastolic blood flow velocity at rest and during stress, with HRV as a predictor and variability of blood flow velocity as the dependent variable. Unstandardized residuals - which are independent of HRV - resulting from the regression equations were computed (Cohen et al., 2003). All ANOVA models were conducted with the residuals as dependent variables.

4. Results

Fig. 1 displays the variability of the mean, systolic and diastolic blood flow velocity in the MCA of both hemispheres, in both study groups. Residuals in which HRV was controlled for are presented. The variability of mean and diastolic flow velocity was lower in MDD

patients than controls, both at rest and during cognitive stress (mean: F [1,68]=7.66, p<.01, η_p^2=.10; systolic: F[1,68]=1.42, p=.24, η_p^2=.020; diastolic: F[1,68]=8.08, p<.01, η_p^2=.11). All blood flow parameters showed greater variability during stress than at rest (condition effect, mean: F[1,68]=17.00, p<.01, η_p^2=.20; systolic: F[1,68]=28.95, p<.01, η_p^2=.30; diastolic: F[1,68]=13.86, p<.01, η_p^2=.17). While mean and systolic flow velocity variabilities were higher in the left than the right MCA, no hemispherical differences arose for diastolic flow velocity variability (hemisphere effect, mean: F[1,68]=7.87, p<.01, η_p^2=.10; systolic: F[1,68]=30.49, p<.01, η_p^2=.31; diastolic: F[1,68]=1,43, p=.24, η_p^2=.021). No interaction effects arose (all p>.05). ANOVAs for drug use did not reveal a main effect of medication, nor any interaction between medication and condition or hemisphere factors for the three flow velocity parameters (all p>.05).

5. Discussion

As a main result, this study revealed lower mean and diastolic blood flow variability in the MCA of both hemispheres at rest and during mental stress in MDD patients than healthy controls. This is in line with evidence of reduced heart rate and blood pressure variability in MDD (Bair et al., 2020; Chang et al., 2017); moreover, the findings complement reports of blunted CBF reactivity to cognitive challenge in MDD (e.g., Hoffmann et al., 2018). Taken together, these observations support the notion that a lack of flexibility and adaptability in cardiovascular regulation characterizes the disorder.

Various physiological mechanisms contribute to short-term CBF variability. In addition to respiration and oscillations in central nervous activity, spontaneous fluctuations in peripheral hemodynamics also play a role. Though autoregulatory mechanisms ensure virtual independence of brain perfusion from systemic blood pressure, it has been shown that short-term blood pressure variability is transmitted to CBF to some degree (Montoro et al., 2018a). Therefore, reduced blood pressure variability in MDD may at least partly explain patients' low CBF variability (Bair et al., 2020). In addition to the passive pressure-flow relationship, autonomic mechanisms, especially the baroreflex, are involved in the interaction between systemic and cerebral hemodynamics. Mediated by

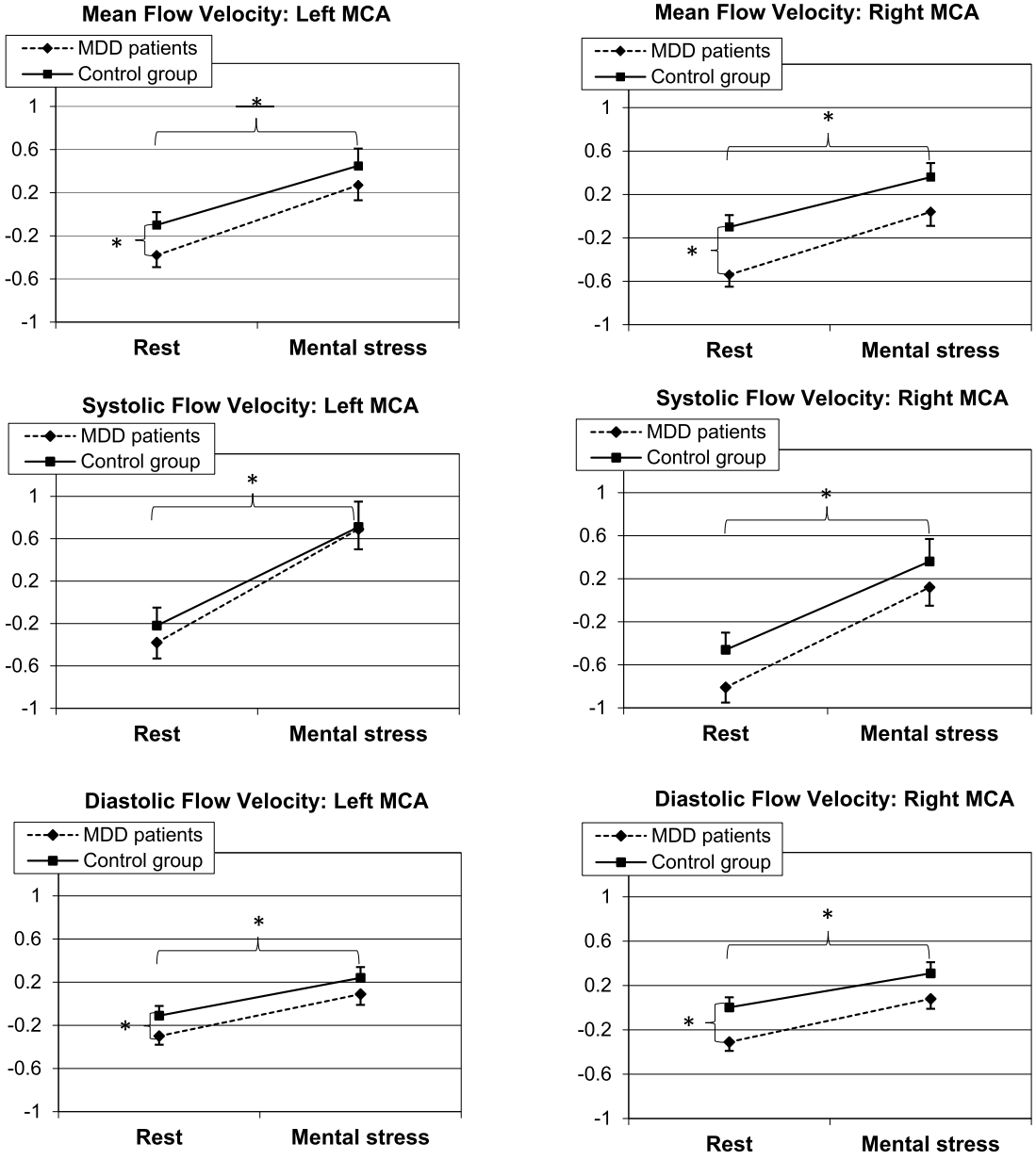

Fig. 1. Variability in mean, systolic and diastolic blood flow velocities in the MCA of both hemispheres (residuals); * indicates significant group and condition effects.

cardiovascular centers in the brain stem, the baroreflex responds to blood pressure changes by compensatory adjustment of heart rate and myocardial contractility (Duschek et al., 2013). The reflex centers, via direct or indirect neural pathways, also modulate vasomotor activity in cerebral arterioles (Hamel et al., 2002). Baroreflex function seems to be reduced in MDD (Broadley et al., 2005). Therefore, it may be that smaller cerebro-vascular baroreflex responses to blood pressure fluctuations contribute to the reduced CBF variability that characterizes the disorder.

It has been claimed that the relationship between CBF variability and health depends on the time scale considered (Rickards and Tzeng, 2014). While long-term fluctuations (hours to days) are associated with primary and secondary end organ damage, short-term (beat-to-beat) variability may be cerebroprotective and indicates intact cerebral functioning. Short-term CBF variability reflects activity of mechanisms promoting optimal cerebral perfusion and oxygenation, even at low perfusion pressures (Rickards and Tzeng, 2014). For example, high CBF variability is associated with increased endothelial nitric oxide production, leading to vasodilation and thus improved blood supply (Nakano et al., 2000). This may prevent adverse consequences of challenges like acute blood pressure decline, prolonged ischemia or blood loss. Moreover, both short-term CBF variability and reactivity correlate positively with performance on cognitive tasks, including those requiring complex mental operations, i.e. executive functions (Montoro et al., 2018a; Schuepbach et al., 2009). Considering this, deficient CBF regulation may be involved in mediating deficits in executive functions, which are prevalent in MDD and have been implicated in symptom genesis (LeMoult & Gotlib, 2019).

In our MDD patients and controls, CBF variability was greater during mental stress than at rest. This may relate to increased blood pressure variability during serial subtractions, which was observed in a recent study (Duschek et al. 2021). Moreover, increased neural activity during the task may enhance CBF variability. Structures involved in arithmetic processing, like the parietal cortex and gyrus angularis, are part of the perfusion territory of the MCA (Haines, 2007). Mean and diastolic blood flow variability were overall greater in the left than the right MCA in this study. For the task condition, this is in accordance with the dominant role of the left hemisphere in arithmetic processing (Dehaene, 2000). However, the greater blood flow variability in the left MCA at rest is difficult to explain, although left hemispheric neural activity due to anticipation of the arithmetic task or hemispherical asymmetry in resting state neural activity may play a role (Raemaekers et al., 2018).

A limitation of this study was the lack of assessment of blood pressure and respiration during TCD recordings, such that their influences on CBF variability could not be determined. Comparison of patient subgroups composed according to medication did not suggest that the medications biased the results. However, the reliability of this analysis was restricted by the relatively small group sizes. In addition, the analysis of the TCD signal was based only on the envelope curves, which represent the maximum velocity following the cardiac cycle. In future studies, it may be of interest also to consider the raw signal of the blood flow signal, which may contain additional information (Sejdlic et al., 2013). Despite these limitations, this study provided evidence of reduced CBF variability at rest and during stress in MDD. This finding is clinically relevant, as it suggests impaired CBF regulation in MDD, in association with suboptimal cerebral performance and deficits in cerebroprotective mechanisms.

Access to research data

The research data of the study is available to the public via the Open Science Framework repository (OSF: https://osf.io/37bqg/).

Author contributions

Study design: Gustavo A. Reyes del Paso, Stefan Duschek; data acquisition: Alexandra Hoffmann, Casandra I. Montoro; data analysis: Casandra I. Montoro, Gustavo A. Reyes del Paso, Stefan Duschek; manuscript preparation: Stefan Duschek; All authors have approved the final version of the manuscript.

Declaration of Competing Interest

None.

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