

## ORIGINAL ARTICLE

# From Molecular to Behavior: Higher Order Occipital Cortex in Major Depressive Disorder

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## Abstract

Medial prefrontal cortex (MPFC) and other regions like the occipital cortex (OC) exhibit abnormal neural activity in major depressive disorder (MDD). Their relationship to specific biochemical, psychophysical, and psychopathological changes remains unclear, though. For that purpose, we focus on a particular subregion in OC, namely middle temporal (MT) visual area that is known to mediate the perception of visual motion. Using high-field 7 T magnetic resonance imaging (MRI), including resting state functional MRI and proton magnetic resonance spectroscopy, the amplitude of low-frequency fluctuations (ALFF) of the blood oxygen level-dependent signal in MT, MT-seeded functional connectivity (FC), and gamma-aminobutyric acid (GABA) in MT were investigated. Applying the vision motion psychophysical task, the motion suppression index of subjects was also examined. We demonstrate significantly elevated neural variability (as measured by ALFF) in MT together with decreases in both MT GABA and motion suppression in our MDD sample. Unlike in healthy subjects, MT neural variability no longer modulates the relationship of MT GABA and motion suppression in MDD. MT also exhibits reduction in global inter-regional FC to MPFC in MDD. Finally, elevated MT ALFF relates to specifically retardation in behavior as measured by the Hamilton subscore. Together, MT provides a strong candidate for biomarker in MDD.

**Key words:** amplitude of low-frequency fluctuations, biomarker, major depressive disorder, middle temporal visual cortex, proton magnetic resonance spectroscopy

## Introduction

Major depressive disorder (MDD) is a complex psychiatric disorder where participants, besides mood symptoms, often show abnormal slowness in behavior, that is, retardation (Francesmonneris et al. 2013). Neuronally, MDD is characterized by strong changes in medial prefrontal cortex (MPFC) including the default-mode network (DMN) (Sheline et al. 2009; Andrews-Hanna et al. 2010; Kaiser et al. 2015; Yin et al. 2019; Scalabrini et al. 2020). In addition, changes in subcortical regions

like

amygdala (Tahmasian et al. 2013; Tang et al. 2013; Romanczuk-Seiferth et al. 2014; Jacobs et al. 2016) as well as others like the occipital cortex (OC) have been highlighted. Various studies show decreased activity in OC in both rest (Tao et al. 2011; Zeng et al. 2012; Kaiser et al. 2015; Scalabrini et al. 2020) and task (Furey et al. 2013; Le et al. 2017) as well as decreased inhibitory gamma-aminobutyric acid (GABA; Sanacora et al. 1999, 2004; Bhagwagar et al. 2007; Song et al. 2021) in acute MDD. Can OC serve as biomarker of MDD? Ideally, a biomarker should link

biochemical, neuronal, psychophysical, and psychopathological levels of MDD as it is, for instance, proposed in the RDoC classification (Insel et al. 2010; Cuthbert and Insel 2013). The goal of our paper is to link these levels in order to provide further support for the OC as candidate biomarker of MDD.

The OC is heterogeneous as it includes various subregions like early visual cortex (EVC) at the bottom and middle temporal (MT) visual area towards the upper end of the visual hierarchy (Born and Bradley 2005; Wengler et al. 2020). While previous studies in MDD targeted EVC (Zomet et al. 2008; Bubl et al. 2009; Salmela et al. 2021), a recent study focused mainly on MT (Song et al. 2021). MT is a higher order occipital region that is strongly involved in processing visual motion (Tadin et al. 2003; Born and Bradley 2005; Schallmo et al. 2018). Interestingly, psychophysical studies demonstrate that MDD patients show decreased ability in discriminating moving stimuli, a capacity that is well known to be related specifically to MT (Tadin et al. 2003; Golomb et al. 2009; Norton et al. 2016; Schallmo et al. 2018). Correspondingly, a recent study demonstrates that MT exhibits biochemical deficits in GABA leading to alteration in excitation–inhibition balance (EIB) (Song et al. 2021). This leaves open whether the changes in visual motion and GABA are related to abnormal neural activity in MT of MDD and how that, in turn, impacts its relationship to MPFC/DMN.

Resting-state activity in MDD is characterized by both inter-regional and intra-regional changes. Intra-regional activity can, for instance, be measured by neural variability that, describing the changes in the amplitude across time, is operationalized by the amplitude of low-frequency fluctuations (ALFF) (Zang et al. 2007; Zuo et al. 2010). Interestingly, MDD shows widespread abnormalities in ALFF in various regions like MPFC/DMN and OC including both increases and decreases (Womer et al. 2014; Zhang et al. 2014; Cui et al. 2016; Song et al. 2020). However, whether MT and EVC exhibit local-regional neural variability (ALFF) changes in MDD and how these are related to the more global inter-regional functional connectivity (FC) to MPFC/DMN remains yet unclear.

Inter-regional relationships are measured by FC, which is known to be abnormally high in especially MPFC/DMN of MDD (Sheline et al. 2009; Zeng et al. 2012; Kaiser et al. 2015). Recently, Scalabrini et al. (2020) demonstrated that inter-regional FC changes in DMN of MDD can be traced to the brain's global activity, its overall topographic organization, rather than local-regional changes. This raises the question whether changes in OC and specifically MT including its FC to MPFC/DMN are local-regional or, alternatively, may be related to a more global source as related to the whole brain's topography. We therefore aim distinguishing local-regional and more global changes in our neuronal analyses of MT and its FC to MPFC/DMN by conducting these analyses with and without global signal regression (GSR) (Huang et al. 2018; Scalabrini et al. 2020).

The goal of our multilevel study is to investigate intra-regional neural activity changes in OC, that is, MT (and EVC) of acute MDD as well as how especially MT is related to (i) psychophysical measures of visual motion; (ii) biochemical indices like GABA; (iii) inter-regional connectivity to MPFC/DMN; and (iv) specific depressive symptoms like retardation. For that purpose, we use high-field 7 T functional magnetic resonance imaging (fMRI) in both healthy and MDD. Beyond linking intra- and inter-regional changes of OC and MPFC/DMN, the focus on MT offers the opportunity to investigate biochemical (GABA), neuronal (ALFF), and psychophysical (visual motion) levels including their relationship and how that is disrupted in MDD.

Furthermore, we hypothesize that MT ALFF may mediate between MT GABA and motion suppression in HC subjects, but, due to its supposed changes, no longer modulates the relationship of MT GABA and motion suppression in MDD. Such multilevel approach can contribute to establish OC and specifically MT as candidate biomarker of MDD. In addition to diagnostic purposes, investigation of MT and its relation to MPFC/DMN also offers novel therapeutic options as MT. Being located at the outer surface of the brain (Tadin et al. 2011), MT and, more generally, OC, provide an easily accessible target for noninvasive brain stimulation (Zhang et al. 2020).

We demonstrate abnormally elevated intra-regional ALFF in MT of acute MDD that disrupts its modulatory role (mediation) of the relation between MT GABA and visual motion suppression. Moreover, MT exhibits decreased inter-regional FC with MPFC/DMN in MDD, which can be traced to a more global (rather than local-regional) source (as it disappears when applying GSR). Finally, changes in local intra-regional ALFF of MT, a region mediating specifically visual motion (Tadin et al. 2003; Born and Bradley 2005; Schallmo et al. 2018), are related to abnormally slow motion and speed in depressive behavior, that is, retardation. Together, our findings demonstrate the importance of higher order OC, that is, MT for local-regional function, global topography, and specific depressive symptoms in acute MDD. That singles out MT as a strong candidate biomarker and potential treatment target in MDD.

## Materials and Methods

### Ethics

This study was approved by the ethical committee of Hangzhou Seventh People's Hospital. All participants signed the informed consent and all testing was conducted in line with the [declaration of Helsinki](#).

### Participants

Given the special scanning in 7 T, we recruited a cohort of 18 adult MDD subjects who were suffering from an acute depressive episode. An independent group of age- and gender-matched healthy subjects ( $n=32$ ) was recruited as HC group (Table 1). All subjects had normal or corrected to normal vision, and had the education background above the college degree. Inclusion criteria of the MDD subjects were: (i) presence of an acute depressive episode and the diagnosis MDD in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) as (a) established by the assessing psychiatrist, and (b) confirmed with Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al. 1998); (ii) clinical symptoms of depression as measured by a Hamilton Depression Rating Scale (HAM-D-17)  $\geq 18$ ; (iii) MDD subjects treated with the agent of selective serotonin reuptake inhibitors (SSRI). Exclusion criteria were: (i) any other psychiatric disorder, or a mental disorder caused by a physical illness or substance abuse or a personality disorder; (ii) history of traumatic brain injury, epilepsy, or other known organic lesion of the central nervous system; (iii) presence of psychotic symptoms during the depressive episodes; (iv) subjects who were taking benzodiazepines during experiment time as they may affect occipital GABA concentration; and (v) history of endocrine disease or blood, heart, liver, kidney dysfunction, another medical disorder such as diabetes, or pregnancy.

**Table 1** Demographics and participant psychophysics data and patient clinical data

Variables	MDD patients (n = 18)	Healthy controls (n = 32)	P value
Gender (M/F)	8/10	12/20	0.639
Age, years (SD)	23.6 (6.1)	24.5 (3.0)	0.524
Suppression index (SD)	0.03 (0.08) <sup>a</sup>	0.09 (0.07) <sup>a</sup>	<b>0.024</b>
HAMD-17 scores (SD)	23.6 (3.6)	—	—
Treatment, n (%)			
Antidepressants	16 (88.9)	—	—
SSRI	15 (83.3)	—	—
Combination	1 (5.6)	—	—
No antidepressants	1 (5.6)	—	—
Antipsychotics	13 (72.2)	—	—
Benzodiazepines	9 (50)	—	—
Mood stabilizers	5 (27.8)	—	—

<sup>a</sup>One patient with MDD and one healthy subject were unable to complete the psychophysics task, so MDD: n = 17; HC: n = 31. Bold font indicates P < 0.05.

All subjects participated in the motion spatial suppression psychophysical, resting-state fMRI and MRS experiments, but only part of the MRS data (16/18 MDD and 22/32 healthy subjects) survived quality control (see the part of MRS data processing), and only some of participants (17/18 MDD and 31/32 healthy subjects) successfully completed the psychophysical experiment.

### Measurement of Visual Motion Suppression

All stimuli were produced using Psychophysics Toolbox (Brainard 1997) based on MATLAB (MathWorks, Natick, MA, USA) and were shown on a linearized monitor (1920 × 1080 resolution, 100-Hz refresh rate, Cambridge Research System, UK). The viewing distance was 72 cm from the screen, with the head stabilized by a chinrest. Stimuli were drawn against a gray (56 cd/m<sup>2</sup>) background.

The details of the procedure for measurement are available in our recent study (Song et al. 2021). Briefly, large (diameter of 10°) and small (diameter of 2°) stimuli were vertically drifting sinusoidal gratings with high contrast (contrast: 50%; spatial frequency, 1 cycle/°; speed, 4°/s) (see Supplementary Fig. S1 in Song et al. (2021)). The edge of the grating was blurred with a raised cosine function (width, 0.3°). The grating was ramped on and off with a Gaussian temporal envelope, and the grating duration was defined as 1 SD of the Gaussian function. The duration was adaptively adjusted in each trial, and duration thresholds were estimated by a staircase procedure. Thresholds for large and small gratings were obtained from a 160-trial block that contained four interleaved three-down/one-up staircases. For each participant, we computed the correct rate for different stimulus durations separately for each stimulus size. These values were then fitted to a cumulative Gaussian function, and the duration threshold corresponding to the 75% correct point on the psychometric function was estimated for each stimulus size. Stimulus demonstration and practice trials were presented before the first run. Auditory feedback was provided for each wrong response. To quantify the spatial suppression strength, we calculated the spatial suppression index (SI), defined as the difference of log<sub>10</sub> thresholds for large versus small stimuli (Tadin et al. 2003; Schallmo et al. 2018).

$$SI = \log_{10}(\text{large threshold}) - \log_{10}(\text{small threshold}) \quad (1)$$

### MR Experimental Procedure

We performed MR experiments in a 7 T whole body MR system (Siemens Healthcare, Erlangen, Germany) with a Nova Medical 32 channel array head coil. Session included resting-state fMRI (rsfMRI), structural image scanning, fMRI localizer scan (part of the subjects), and MRS scan within human MT complex (hMT+) for each subject. Resting-state scans were acquired with 1.5-mm isotropic resolution (transverse orientation, TR/TE = 2000/20.6 ms, 160 volumes, slice number = 90, flip angle = 70°, eyes closed). Structural images were acquired using a MP2RAGE sequence (TR/TI1/TI2 = 5000/901/3200 ms) with 0.7-mm isotropic resolution. Spectroscopy data were acquired using a <sup>1</sup>H-MRS single-voxel short-TE STEAM (Stimulated Echo Acquisition Mode) sequence (Frahm et al. 1989) (TE/TM/TR = 6/32/7100 ms) with 4096 sampling points, 4-kHz bandwidth, 16 averages, eight repetitions, 20 × 20 × 20 mm<sup>3</sup> volume of interest (VOI) size, and variable power and optimized relaxation delays (VAPOR) water suppression (Tká et al. 1999). Prior to acquisition, first- and second-order shims were adjusted using fast, automatic shimming technique by mapping (FASTMAP) along projections (Gruetter 1993). Two nonsuppressed water spectra were also acquired: one for phase and eddy current correction (only RF pulse, four averages) and another for metabolite quantification (VAPOR none, four averages). Voxels were positioned based on anatomical landmarks using a structural image scan collected in the same session, while avoiding contamination by CSF, bone, and fat. The hMT+ VOIs were placed in the ventrolateral occipital lobe, which was based on anatomical landmarks (Dumoulin et al. 2000; Schallmo et al. 2018). In these hMT+ VOIs, we did not distinguish between the middle temporal (MT) and medial superior temporal (MST) areas (Schallmo et al. 2018), both of which are motion selective (Huk et al. 2002). For 10 subjects, we, using fMRI, also functionally identified hMT+ as a check on the placement of the VOI. For these 10 healthy subjects, a protocol was used with a drifting grating (15% contrast) alternated with a static grating across blocks (10 s block duration, 160 TRs total). Using fMRI blood oxygen level-dependent (BOLD) signals, these localizer data were processed online to identify the hMT+ voxels in the lateral OC, which responded more strongly to moving versus static gratings (as in the method of Schallmo et al. (2018)). We did not scan the functional localizer for all MDD patients in order to reduce experimental load and time for the acute depressed subjects. In addition, we only used the left hMT+ as the target

region to scan, which was motivated by studies showing that left hMT+ is more related to visual perceptual effects (Tadin et al. 2011).

### MRS Data Processing

Spectroscopy data were preprocessed and quantified using magnetic resonance signal processing and analysis (<https://www.cmrr.umn.edu/downloads/mrspa/>), which runs under MATLAB and invokes the interface of the LCMoDel (Version 6.3-1 L) (Chen et al. 2019). First, we used the nonsuppressed water spectra to perform eddy current correction and frequency/phase correction. Second, we checked the quality of each FID (16 averages) visually and removed those with obviously poor quality. Third, the absolute concentrations of each metabolite were quantitatively estimated via the Water-Scaling method. For partial-volume correction, the tissue water content was computed as follows (Ernst et al. 1993):

$$\text{Tissue water content} = f_{\text{gm}} * 0.78 + f_{\text{wm}} * 0.65 + f_{\text{csf}} * 0.97 \quad (2)$$

where  $f_{\text{gm}}$ ,  $f_{\text{wm}}$ , and  $f_{\text{csf}}$  were the GM/WM/CSF volume fraction in MRS VOI and we used FAST (fMRI's automated segmentation tool, part of the FSL toolbox) (Zhang et al. 2001) to segment the three tissue compartments from the T1-weighted structural brain images. For water T2 correction, we set water T2 as 47 ms (Marjanska et al. 2012). Our concentrations were mM per kg wet weight. Furthermore, LCMoDel analysis was performed on all spectra within the chemical shift range of 0.2–4.0 ppm.

Poor spectral quality was established by a Cramer-Rao Lower Bound (CRLB) of more than 20% (Provencher 1993, 2001; Cavassila et al. 2001), and some data were excluded from further analysis. The signal-to-noise ratio (SNR) and full-width at half maximum (FWHM, the estimate of linewidth) were also used to control the spectral quality. All spectra with SNR < 15 or FWHM > 18 Hz were discarded. Spectral quality measures, that is, SNR, CRLBs, and the FWHM, were presented for difference between MDD and HC groups (see Supplementary Table S1). Overall quality of the obtained spectra can be regarded as good.

### MRI Data Processing and Analysis

Resting-state functional images were preprocessed using the DPABI toolbox (Yan et al. 2016) based on SPM 12 (<http://www.fil.ion.ucl.ac.uk/spm/>) including: removal of the first five volumes, slice timing, realignment, coregistration of anatomical and functional images for each subject, segmentation of the anatomical images using DARTEL, linear detrend, nuisance covariates regression (with realignment Friston 24-parameter, white matter and CSF signal, both with and without global signal) (Friston et al. 1996), normalization to the standard MNI space with a resolution of  $1.5 \times 1.5 \times 1.5 \text{ mm}^3$  using DARTEL, spatial smoothing with a 3 mm FWHM Gaussian filter, and band-pass filtering with Standard frequency band (SFB, 0.01–0.1 Hz) as well as Slow3 (0.073–0.198 Hz), Slow4 (0.027–0.073 Hz), and Slow5 (0.01–0.027 Hz) (Buzsaki and Draguhn 2004; Zuo et al. 2010).

Before ALFF and FC analysis, we defined the region of interest (ROI). Left MT was described by a sphere with a radius of 10 mm (centered with  $-43, -73, 10$  in MNI space) (Malikovic et al. 2007),

left EVC was represented by Occipital\_Sup\_L mask, which was taken from AAL template, and bilateral MPFC was defined by the bilateral BA10 mask, which was obtained from Brodmann template.

After preprocessing, the Fast Fourier transformation was used to transform the time series for each voxel into the frequency domain, and the power spectrum was obtained. Within the SFB (0.01 to 0.1 Hz) as well as Slow3 (0.073 to 0.198 Hz), Slow4 (0.027 to 0.073 Hz), and Slow5 (0.01 to 0.027 Hz) frequency band, the averaged square root (i.e., ALFF value) of power spectrum activity was respectively calculated<sup>28</sup> and then transformed to Z score for further comparison between groups. For both conditions, with and without GSR, we extracted the mean ALFF value within left MT and left EVC of each subject.

In addition to neural variability (ALFF) of MT, we also calculated FC in SFB in two distinct ways comparing HC and MDD, respectively. First, we took left MT as seed region and calculated its FC to the rest of the brain in a voxel-based way. Since the MPFC is a key region in MDD (Kaiser et al. 2015; Scalabrini et al. 2020), we also calculated FC of MT with a predefined region of MPFC (Brodmann 10) in both HC and MDD. Both sets of FC analyses were conducted with and without GSR as to identify their local or global source (Scalabrini et al. 2020). All the FC values were Fisher-Z-transformed. Data Processing and Analysis for Brain Imaging (DPABI) was used to investigate whether there were statistical differences in FC maps of MDD patients compared with healthy group. Using Gaussian random-field (GRF) theory, the significance threshold is voxel-wised  $P < 0.005$ , cluster-wised  $P < 0.05$ .

### Statistical Analysis

PROCESS version 3.4, a toolbox in SPSS, was used to examine the mediation model. There are some prerequisites for mediation analysis: the independent variable should be a significant predictor of the mediator, and the mediator should be a significant predictor of the dependent variable. We examined whether the association between MT GABA and SI was mediated by ALFF in MT. Bias-corrected bootstrap methodology was used to evaluate the significance of the direct and indirect effect, in which 95% confidence interval (CI) was calculated with 5000 independent samples. If the bootstrap 95% CI of indirect effect did not contain zero, it indicated a significant mediating effect in the model.

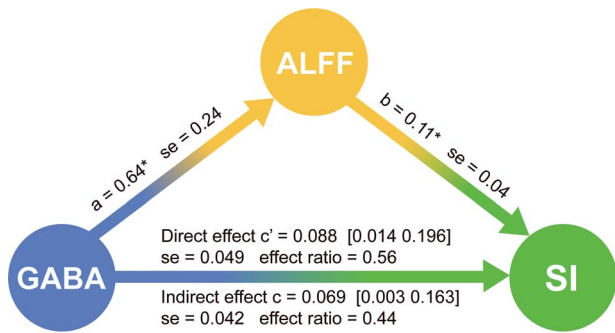
SPSS 20 (IBM, USA) was used to conduct all the remaining statistical analysis in the study. We evaluated the correlation of variables (GABA, SI, ALFF, FC and depressive symptoms) using Pearson's correlation analysis. Student's *t* test was used to examine the differences between MDD and healthy groups. Differences or correlations were considered statistically significant if  $P < 0.05$ . Significances with multiple comparisons were tested with false discovery rate (FDR) correction. All analyses were controlled for medication effects (see Limitations for more details).

## Results

### Relationship of MT Neural Variability, MT GABA, and Motion Suppression in Healthy Subjects

Firstly, we used Pearson's correlation analysis to investigate how the three variables (neuronal: ALFF, biochemical: GABA and psychophysical: SI) are related to each other in the HC group ( $n = 22$ ). The correlations between GABA and SI ( $r = 0.59, P < 0.05$ ),





\* $P < 0.05$ , \*\* $P < 0.01$  FDR correction

**Figure 1.** Mediation analysis in HC. ALFF serves as mediator between GABA (predictor) and SI (outcome).

GABA and ALFF in SFB ( $r=0.52$ ,  $P < 0.05$ ), ALFF in SFB and SI ( $r=0.67$ ,  $P < 0.01$ ) were all significant in healthy subjects, which allowed us to apply mediation analyses.

We then tested the mediation model in the healthy subject group (Fig. 1). There were both significant direct and indirect effect in our mediation model with ALFF in MT as a mediator (Direct effect:  $c' = 0.088$ , [0.014 0.196];  $se = 0.049$ ; effect ratio = 0.56; Indirect effect:  $c = 0.069$ , [0.003 0.163];  $se = 0.042$ ; effect ratio = 0.44). This suggests that neuronal activity (ALFF) in MT partially mediates the relationship of MT GABA and motion suppression.

### Increased Neural Variability in MT of MDD

Compared with HC, the MDD group showed significantly increased ALFF in MT in SFB ( $T=2.57$ ,  $P < 0.05$ ) as well as in all three sub-bands including Slow3 ( $T=3.54$ ,  $P < 0.01$ ), Slow4 ( $T=2.71$ ,  $P < 0.05$ ) and Slow5 ( $T=1.87$ ,  $P < 0.05$ ) frequency band (Fig. 2A). We also found significantly elevated ALFF within EVC in SFB ( $T=2.50$ ,  $P < 0.05$ ) as well as in Slow3 ( $T=2.59$ ,  $P < 0.05$ ), Slow4 ( $T=2.48$ ,  $P < 0.05$ ) and Slow5 ( $T=2.32$ ,  $P < 0.05$ ) in MDD (Fig. 2B). In addition to the standard pre-processing that includes GSR in the analysis of ALFF, we also conducted the same analyses without GSR; this yielded similar results that suggests a truly local-regional (rather than global) source of ALFF changes in MT (see Supplementary Fig. S1).

### No Coupling of MT GABA, ALFF, and Motion SI in MDD Group

The time threshold of small moving grating in MDD ( $5.11 \pm 1.28$  ms,  $n=17$ ) is longer than HC ( $4.51 \pm 0.73$  ms,  $n=31$ ) which is almost significant ( $P=0.06$ ). Similar to the previous results (Song et al. 2021), there is significant longer time threshold in small stimuli of MDD than HC subjects. Consistent with a previous study (Song et al. 2021), we found that both MT GABA ( $T=-2.10$ ,  $P < 0.05$ ) and motion SI ( $T=-2.43$ ,  $P < 0.05$ ) were decreased in MDD compared with the healthy group (Fig. 3A). We conducted Pearson's correlation analysis in MDD group ( $n=16$ ). Unlike in healthy subjects (Fig. 3B left), the three variables (ALFF, GABA, and SI) did not correlate with each other. Together, these results demonstrate that, unlike in healthy subjects (shown in Fig. 1), the elevated MT ALFF no longer modulates the relationship between MT GABA and motion SI in MDD (diagram shown in Fig. 3B right).

### Decreased Functional Connectivity Between MT and MPFC in MDD

In order to probe relationship of MT to MPFC, we took MT as seed to investigate its FC changes with the rest of the brain. The results of voxel-wised FC are shown in Table 2 and Figure 4A. With the seed region placed in the left MT, MDD patients exhibited significantly decreased FC of MT with MPFC when compared with the HC group. This holds only when we did not apply GSR, whereas this effect disappeared when including GSR; that suggests a more global rather than local-regional (as either within MT or MPFC themselves) source (see also Scalabrini et al. 2020).

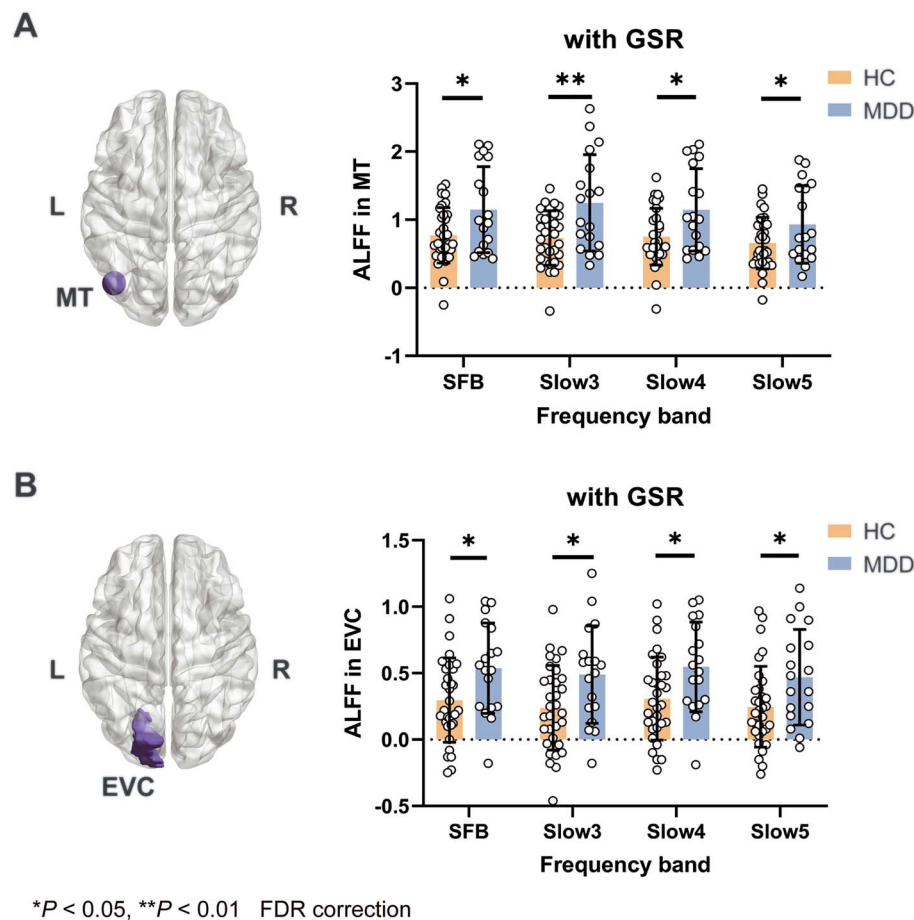
In order to further confirm these results, we took both left MT as well as bilateral BA10 (MPFC) as regions and correlated their time series with each other (i.e., FC). We again obtained significant MT-MPFC FC (in SFB including 0.01–0.1 Hz) decrease in MDD ( $T=-2.34$ ,  $P < 0.05$ ) which only hold when not applying GSR (while the significant difference disappeared when applying GSR:  $T=-1.68$ ,  $P > 0.05$ ); this speaks for a more global source of MT-MPFC FC changes in MDD (Fig. 4B). The rsFC comparison in all sub-bands including slow 3, 4, and 5 is displayed in Supplementary Figure S2.

### Neural Variability in MT Relates to Retardation in Depressive Behavior

In the box plots (Fig. 5A), it could be seen that there are no outliers for ALFF of slow 3 in MT with GSR and retardation score in MDD group, which increased the confidence of the subsequent correlation analyses. In MDD patients, ALFF of slow 3 within MT was positively correlated with retardation score (of HAMD) ( $r=0.48$ ,  $P < 0.05$ , Fig. 5B). In contrast, there was no significant correlation slow 3 ALFF in EVC and retardation ( $r=0.42$ ,  $P > 0.05$ ). The inclusion or exclusion of GSR in preprocessing did not affect these correlation results (see Supplementary Fig. S3); this suggests a local-regional impact of neural variability in MT on retardation in behavior. Unlike local intra-regional ALFF, we did not observe significant correlation of the more global inter-regional FC of MT-MPFC with the retardation score, for both with ( $r=-0.054$ ,  $P > 0.05$ ) and without GSR ( $r=0.14$ ,  $P > 0.05$ ) (shown in Supplementary Fig. S4). The difference between local intra-regional (ALFF in MT) and global inter-regional (MT-MPFC) signals is further supported by the fact that we neither obtained correlations of MT-MPFC rsFC and MT ALFF for the whole sample nor for MDD and HC alone (shown in Supplementary Tables S1 and S2).

### Discussion

We investigated neuronal activity in a higher order occipital region, namely MT and how it relates to biochemical, psychophysical, and psychopathological changes in MDD. Our main findings are: (i) significantly higher neural variability (ALFF) in MT; (ii) neural variability (ALFF in MT) mediates the impact of molecular (GABA) on psychophysical performance (motion SI) in HC subjects (shown in Fig. 1), but no longer modulates their relationship in MDD (diagram shown in Fig. 3B right); (iii) decrease in MT's global inter-regional FC to MPFC as "typical MDD region"; (iv) elevated neural variability in MT (ALFF) relates to specifically retardation in depressive behavior. In sum, we demonstrate multilevel changes in MT of MDD that provides further support for its eventual role as candidate biomarker.



**Figure 2.** Group difference in ALFF between MDD and HC with GSR analyses. (A) MDD exhibited significantly elevated ALFF in MT compared with HC. (B) MDD showed significantly elevated ALFF in EVC compared with HC.

**Table 2** Significantly altered brain region in voxel-wise FC without GSR between MDD and HC group

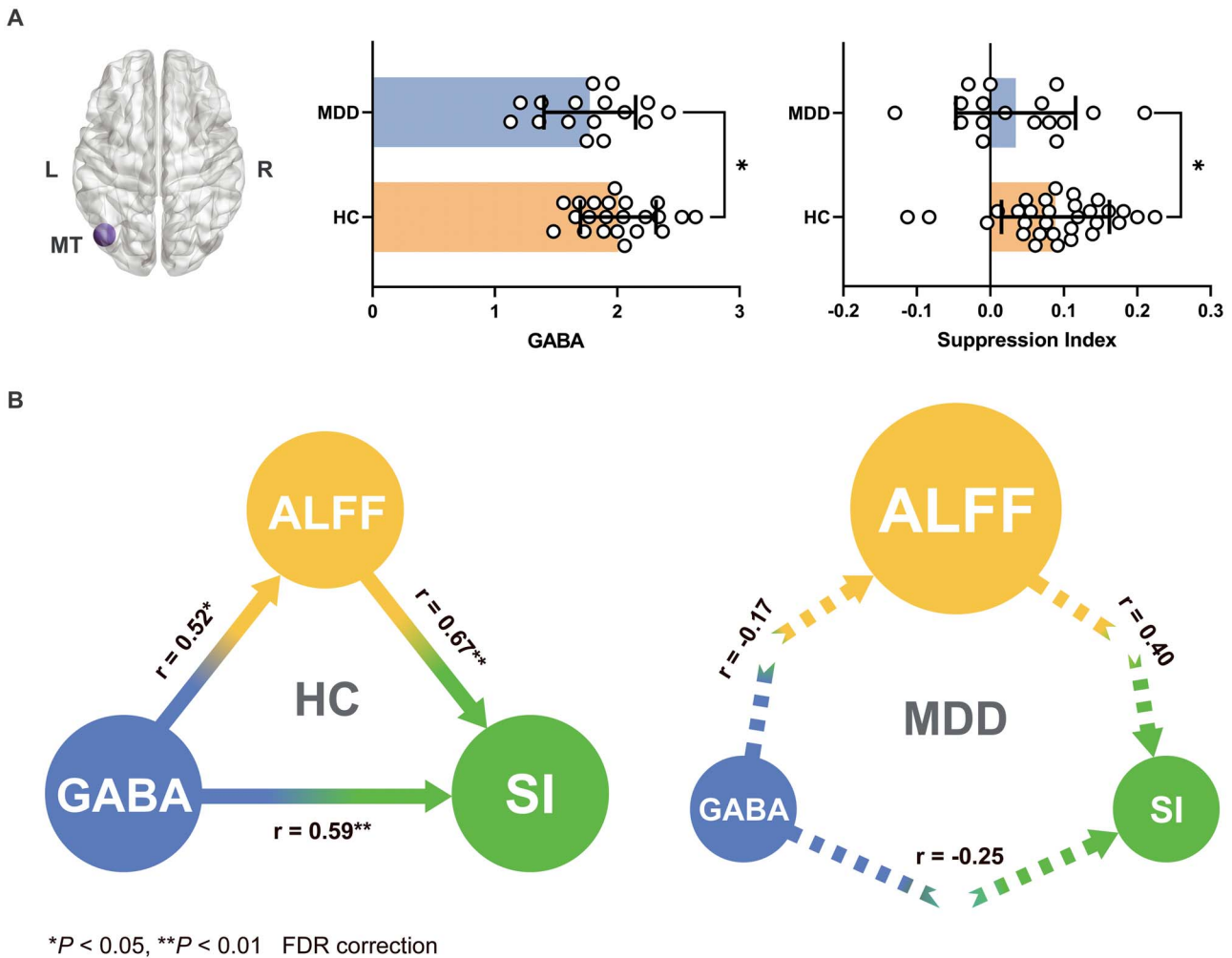
Seed	Cluster size	Effect regions	BA	Peak t-value	MNI coordinates			
					X	Y	Z	
MT	MDD < HC	253	MPFC	BA10	-2.68	3	49.5	-6

Corrected by GRF correction (voxel-wise  $P < 0.005$ , cluster-wise  $P < 0.05$ ). The peak coordinates were showed in the standard MNI space.

In a first step, we, in healthy subjects, established relationship of MT neural variability to MT GABA and visual motion suppression (which is known to be mediated by MT (Tadin et al. 2003; Born and Bradley 2005; Schallmo et al. 2018)). This yielded significant correlation of all three measures that allowed us to conduct a mediation model. Probing different models, we show that higher levels of GABA in MT lead to higher degrees of motion suppression, which is partially mediated by the level of neural variability in MT. This confirms our hypothesis, and provides direct connection of biochemical, neural, and psychophysical levels in healthy subjects. That is in line with recent findings (Schallmo et al. 2018), which also show relationship of GABA to vision motion performance (Schallmo et al. 2018; Song et al. 2021). At the same time, our findings extend these results by showing the key role of MT neural variability in mediating the effects of inhibitory GABA on motion suppression.

MDD subjects exhibit significantly elevated neural variability in MT. This is in accordance with recent findings showing altered neural activity in OC in general during both rest and task states (Zhang et al. 2014; Cui et al. 2016; Le et al. 2017; Northoff et al. 2018; Zhang et al. 2020). At the same time, our findings extend these observations by showing that specifically local-intra-regional neural variability is altered in MDD. This suggests that MT (and also EVC) exhibit intra-regional changes that are present already during the rest state. The local truly intra-regional nature of these changes is further supported by the fact that they remained unaffected by the presence or absence of GSR.

Is the elevated ALFF of MT in MDD a primary impairment or, alternatively, a compensatory mechanism of a yet unclear deficit? In case of compensation, one would expect to observe enhanced cognitive performance (Cabeza et al. 2018; Wang et al.



**Figure 3.** Relationship between MT ALFF, MT GABA, and SI in MDD. (A) Reduction of GABA and SI in MDD. (B) The three variables (ALFF, GABA, and SI) correlated with each other in healthy subjects (left). Mediation model schematic in MDD (right): the abnormally elevated ALFF in MT (larger circle) disrupts its mediation of the relationship between lower MT GABA (smaller circle) and decreased SI (smaller circle) in MDD.

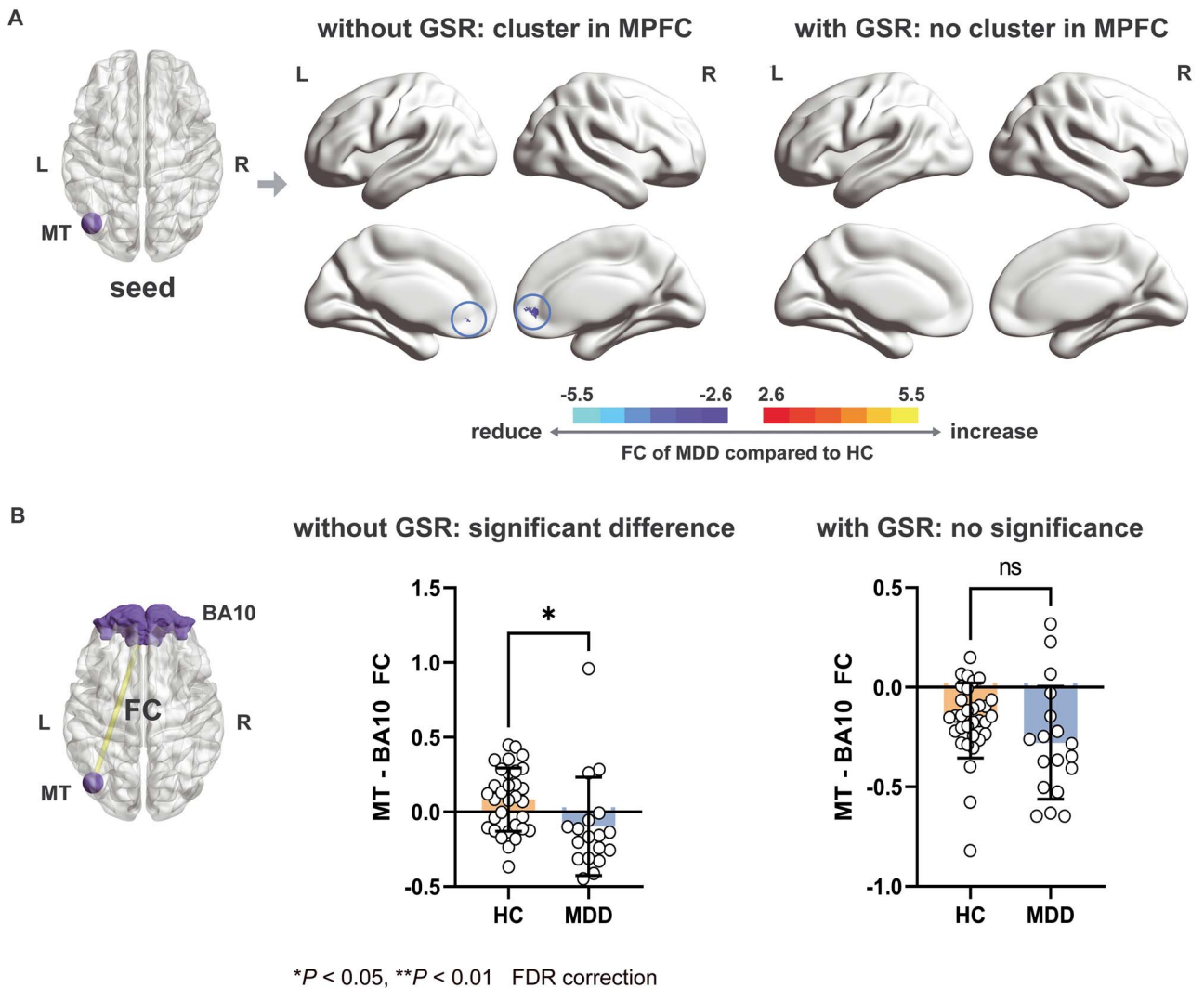
2019). This stands in contrast to our psychophysical results where the threshold of small stimuli of MDD ( $5.11 \pm 1.28$  ms,  $n = 17$ ) is longer (rather than shorter) and thus impaired (rather than enhanced) than in HC ( $4.51 \pm 0.73$  ms,  $n = 31$ ; almost significant ( $P = 0.06$ )). Albeit indirectly, this suggests that the abnormal intra-regional ALFF increase in MDD may be indicative of a primary impairment in MT rather than a consequence of a compensatory mechanism.

Our results tentatively suggest that abnormal increase of ALFF in MT may be driven by reduced GABA in the same region (Fig. 3A). This hints upon a deficit in neural inhibition in the neural activity of MT which, as we suppose, is manifest in abnormal increase of its neural variability (ALFF). The importance of deficient GABA in MT is further supported by the fact that its modulatory impact on psychophysical performance (motion SI) is decoupled from elevated ALFF in MT. Reduced gaba-ergic inhibition may lead to decreased suppression of redundant information in visual perception as manifest in the here observed longer duration time of small stimuli and decreased motion suppression (SI) in MDD. Whether this could also be the neural and psychophysical mechanism of abnormal perception in MDD in

terms of wearing “gray colored glasses” (Fitzgerald 2013) remains to be investigated in the future.

The effects of altered MT extend beyond the OC. Taking MT as seed regions, MDD subjects show significantly lower FC of MT with MPFC. This was observed only when conducting no GSR whereas it disappeared when including GSR. That suggests a more global source of MT-MPFC FC changes rather than a primarily local-regional source (in either MPFC or MT alone independent of each other); if, in contrast, there were a primarily local-regional source, one would have expected no difference in MT-MPFC FC with and without GSR. Together, we may want to distinguish local-regional and global-inter-regional changes of MT, that is, neural variability and FC, with both being altered in MDD. This lends further support to the importance of global activity changes impacting the relationship of sensory input regions like MT with DMN regions like MPFC in MDD (Scalabrini et al. 2020).

Finally, the importance of MT for MDD is further supported by our psychopathological findings. The degree of neural variability in MT is related to specifically retardation in behavior: the more neural variability in MT, the more retardation in behavior. This



**Figure 4.** Group difference in MT – MPC FC between MDD and HC, for both conditions with and without GSR. (A) Voxel-wise seed-based FC map of MDD versus HC, when MT was the seed region. Left: Without GSR in preprocessing, we found a significant cluster in MPFC, which indicated that the FC between left MT and MPFC was decreased; right: with GSR in preprocessing, there was no cluster in whole brain, which reflected the influence of global signal on MT-MPFC FC. (B) ROI-based MT-BA10 (MPC) FC of MDD versus HC. Left: Without GSR in preprocessing, MT-BA10 FC showed significant reduction in MDD compared with HC; right: with GSR in preprocessing, there was no significant difference in MT-BA10 (MPFC) FC between the two groups, which reflected that the abnormality in this FC in MDD was likely be related to the global signal.

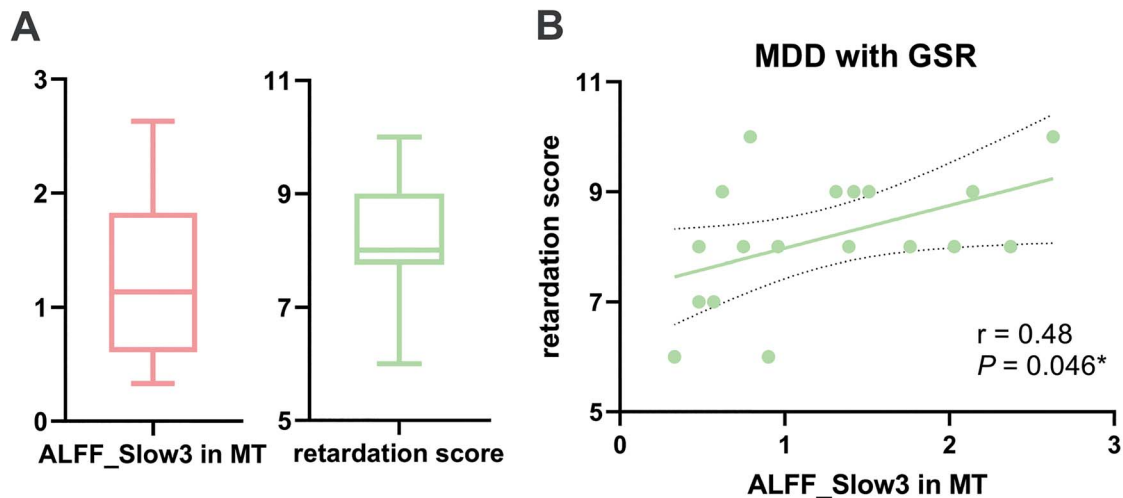
suggests that the speed of behavior, i.e., retardation, is related to the degree of change on the neural level, that is, neuronal speed (see also in the reference Northoff et al. (2018)). However, whether it is really the speed of neural activity in MT that mediates its relationship with speed on the behavioral level, that is, retardation, remains to be explored in the future. If so, motion including speed would be shared by neural (ALFF), psychophysical-perceptual (motion suppression) and psychopathological (psychomotor retardation) levels thus serving as its “common currency” (Kolvoort et al. 2020; Northoff et al. 2020) as basis of “spatiotemporal psychopathology” (Northoff 2016, 2018; Northoff and Stanghellini 2016).

### Limitations

We admit that the main limitation of the present study is the possible confounding effects of medication. Indeed, almost all of

the acute MDD patients in our sample were taking medications, including mood stabilizers, antipsychotics, antidepressants, and benzodiazepines, which may possibly influence results. Following recent suggestions and standards, we examined the potential impact of the psychotropic medication load—the number and dosage of different medications, we then used the codes 0, 1, 2, and 3 to indicate no medication, and dose-equivalents below, equal, or above the mean effective daily dose, respectively (Davis and Chen 2004). We generated a composite measure of the medication load by summing all individual medication codes for each category and each individual MDD patient. We investigated the potential impact of medications on MRS and imaging data by correlating the resulting pharmacological load with GABA concentration, ALFF in SFB and slow 3 in MT, and FC between left MT and bilateral BA10. The medication load did not correlate with this measure in antidepressants, antipsychotics, mood stabilizers, and benzodiazepines ( $P > 0.05$ ).





**Figure 5.** Relationships of neural variability (ALFF) in MT with retardation score. (A) Box plots of ALFF in slow 3 in MT with GSR (left) and retardation score (right), which can be seen that none of them have outliers. (B) ALFF of slow 3 in MT is significantly correlated with HAMD retardation score.

Then, to further control for an eventual effect of pharmacotherapy on the GABA concentration, ALFF in SFB and slow 3 in MT, and FC between left MT and bilateral BA10, we compared these variables by using a *t* test for each medication class (mood stabilizers, antidepressants, benzodiazepines, and antipsychotics), between those patients who were in treatment with the respective drug and those who were not. We found no differences between patients who were in treatment with mood stabilizers ( $n=5$ ) and patients who were not ( $n=13$ ) ( $P > 0.05$ ), between patients who were in treatment with antidepressants ( $n=16$ ) and patients who were not ( $n=2$ ) ( $P > 0.05$ ), between patients who were in treatment with benzodiazepines ( $n=9$ ) and patients who were not ( $n=9$ ) ( $P > 0.05$ ), as well as between patients who were in treatment with antipsychotics ( $n=13$ ) and patients who were not ( $n=5$ ) ( $P > 0.05$ ).

Yet another limiting factor is the rather low subject number. However, all subjects underwent the multilevel investigation: from molecular to behavior. We combined 7 T MRS with psychophysical testing, which allowed us to link occipital (especially the MT) GABA to visual perception and psychopathological symptoms in all subjects both healthy and MDD. Nevertheless, future larger scale MDD studies with non-MDD psychiatric comparison groups are necessary to support the utility of higher-order OC, that is, MT as potential biomarker target of acute MDD.

## Conclusion

Candidates for biomarkers of MDD should span across different levels by establishing, for instance, relation of neuronal to biochemical, psychophysical, and psychopathological measures as proposed in the RDoC classification (Insel et al. 2010; Cuthbert and Insel 2013). The present study takes a first step in this direction by conducting multilevel investigation of a particular subregion in OC, namely MT. MDD shows elevation of neural variability in MT, which disrupts its modulation of the relationship between biochemical (GABA) and psychophysical (motion suppression) levels. Moreover, MT is abnormally connected to

MPFC, which can be traced to a more global rather than local-regional source. Finally, we show that elevated neural variability in MT is related to specifically retardation in behavior. Together, our findings link biochemical, neuronal, psychophysical, and psychopathological levels in MDD with respect to MT. This provides further support for MT being a strong candidate biomarker of MDD, which also opens novel therapeutic options as MT is an easily accessible target for stimulation (Zhang et al. 2020).

## Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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