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Extending the "resting state hypothesis of depression" – dynamics and topography of abnormal rest-task modulation

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A R T I C L E I N F O

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A B S T R A C T

Major depressive disorder (MDD) is characterized by changes in both rest and task states as manifested in temporal dynamics (EEG) and spatial patterns (fMRI). Are rest and task changes related to each other? Extending the "Resting state hypothesis of depression" (RSHD) (Northoff et al., 2011), we, using multimodal imaging, take a tripartite approach: (i) we conduct a review of EEG studies in MDD combining both rest and task states; (ii) we present our own EEG data in MDD on brain dynamics, i.e., intrinsic neural timescales as measured by the autocorrelation window (ACW); and (iii) we review fMRI studies in MDD to probe whether different regions exhibit different rest-task modulation. Review of EEG data shows reduced rest-task change in MDD in different measures of temporal dynamics like peak frequency (and others). Notably, our own EEG data show decreased rest-task change as measured by ACW in frontal electrodes of MDD. The fMRI data reveal that different regions exhibit different rest-task relationships (normal rest-abnormal task, abnormal rest-normal task, abnormal rest-abnormal task) in MDD. Together, we demonstrate altered spatiotemporal dynamics of rest-task modulation in MDD; this further supports and extends the key role of the spontaneous activity in MDD as proposed by the RSHD.

1. Introduction

Major depressive disorder (MDD) is a multifaceted complex systemic disorder of the brain. Based on various resting state changes, the brain's spontaneous activity is considered to play a key role in shaping task states including their associated symptoms (Kaiser et al., 2015; Scalabrini et al., 2020). This has led to the development of the "resting state hypothesis of depression" (RSHD) (Northoff et al., 2011) which provides an overarching pathophysiological-psychopathological framework for MDD integrating translational, subcortical-cortical, biochemical, and symptom dimensions (Northoff et al., 2016a and b; Scalabrini et al., 2020). One key feature of the RSHD is that it conceives the brain's spontaneous activity in a wider sense, namely as basis for any subsequent task states (Huang et al., 2017; Northoff et al., 2010a and bb; Wainio-Theberge et al., 2021; Wolff et al., 2021). Changes in the spontaneous activity should subsequently lead to abnormal task states including altered rest-task modulation. While such abnormal rest-task modulation has been demonstrated in other psychiatric disorders like autism (Lian and Northoff, 2021), anxiety disorders (Angeletti et al., 2021; Tumati et al., 2021), and schizophrenia (Gomez-Pilar et al., 2018; Northoff and Gomez-Pilar, 2021), it remains an open issue in MDD. The goal of our paper is to fill that gap by probing rest-task modulation in both EEG and fMRI of MDD.

Resting state changes concern network abnormalities like the default-mode network (DMN), salience network, and even occipital network (Kaiser et al., 2015). The DMN especially seems to exhibit hyperactivity in the resting state (Hamilton et al., 2015; Kaiser et al., 2015; Scalabrini et al., 2020). Moreover, resting state changes have also been observed on the more global level of the whole brain as measured with the global signal concerning the relationship of DMN to non-DMN (Han et al., 2019; Scalabrini et al., 2020). However, how these resting state changes are related to, and eventually modulate, task-related activity in MDD remains unclear. Filling this gap in our knowledge is the goal of our paper.

Abnormalities of task states in MDD have been reported in various regions including the DMN. Specifically, task-related changes are

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elicited by various tasks ranging from perceptual to affective and cognitive tasks (Grimm et al., 2009; Mayberg et al., 2014; Hamilton et al., 2015; Davey et al., 2018). Interestingly, regions showing task-related abnormalities also exhibit resting state changes like DMN regions (Kaiser et al., 2015; Northoff et al., 2011; Scalabrini et al., 2020). In addition to such regional rest-task overlap in fMRI, EEG studies reveal changes in similar dynamic measures in rest and task states including scale-free activity (Duncan et al., 2020), peak frequency (Wolff et al., 2020), and others (see below). Is there a relationship between rest and task states in MDD? Do changes in resting state modulate task-related activity in an abnormal way, i.e., rest-task modulation? These are the key questions guiding our paper.

Findings in healthy participants demonstrate a close relationship of rest and task states (Ito et al., 2020; Mennes et al., 2010; Northoff et al., 2010a and b for overview). Both fMRI and EEG studies show that the neural effects of external stimuli or tasks are not simply added onto the ongoing level of resting state, i.e., additive rest-stimulus interaction (He., 2013; Huang et al., 2017; Wainio-Theberge et al., 2021; Wolff et al., 2021). Instead, the degree of changes induced by the external stimuli or tasks strongly depends upon the level of the resting state or, specifically, the prestimulus activity: if the prestimulus activity level in its variability and amplitude are high, the external stimulus or task can induce high levels of task-related activity while the converse holds in the case of low prestimulus activity (He., 2013; Huang et al., 2017; Wainio-Theberge et al., 2021; Wolff et al., 2020). Together, these findings in healthy participants suggest strong modulation of task states by the resting state, i.e., rest-task modulation, also described as “state dependence” (Northoff and Gomez-Pilar, 2021).

Given that MDD shows changes in both rest and task states, we hypothesize abnormal rest-task modulation in depression. For that purpose, we recruit evidence from multimodal imaging, including EEG and fMRI. Considering both of these modalities together helps to provide an explanation of the spatial (fMRI) and temporal (EEG) abnormalities exhibited by MDD subjects. Moreover, considering both fMRI and EEG allows us to cover the whole frequency range from infraslow (fMRI) to faster (EEG) frequencies thereby linking the different timescales of the brain in their impact on rest-task modulation. To broaden the scope of our investigation, we combine our own EEG data on rest-task dynamics with a narrative review and illustration of combined rest-task EEG and fMRI studies in the literature. Specifically, we (i) review recent EEG literature on combined rest and task studies in MDD; (ii) present our own EEG data on brain dynamics in MDD by their intrinsic neural timescales as measured by the autocorrelation window (ACW) (see Fig. 1 lower right) (Murray et al., 2014; Northoff and Gomez-Pilar, 2021; Wolff et al., 2019; Zilio et al., 2021) and (iii) review recent combined rest-task fMRI studies in MDD to probe whether different regions exhibit different rest-task relationships (see Fig. 1 lower left) (see Fig. 1 for overview).

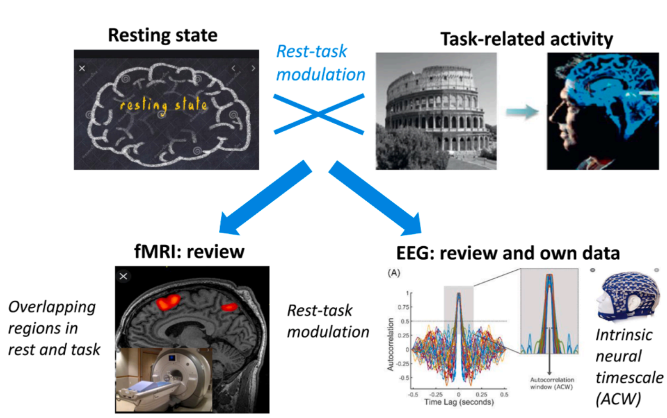

Fig. 1. Overview of investigation.

2. Methods

2.1. Review of EEG and fMRI studies combining rest and task states

Various studies measuring resting state or task-related activity separately have been conducted in MDD. However, there are only a few studies combining both, investigating rest/prestimulus-task modulation. Without assuming to account for all data in a complete way, we here start with a short review of those studies (fMRI and EEG) that showed up in a PubMed search when the words ‘rest AND task AND major depressive disorder AND fMRI’ and ‘rest AND task AND major depressive disorder AND EEG’ were used. The same was done for prestimulus, replacing rest in our search entries (August 2020). All included studies are shown in Table 1; results for fMRI and EEG rest-task studies are demonstrated in Tables 2 and 3 respectively.

2.2. 2 Intrinsic neural timescales in EEG during rest and task – our own data

2.2.1. Participants

For the resting state, 3 min of continuous eyes-closed data was gathered from 25 healthy controls (14 female) and 28 patients (19 female) with MDD. The mean age of all participants was 45.9 years and the standard deviation was 15.8 years. Of these, the 25 controls and 26 of the MDD patients completed an auditory oddball task, with four blocks of 600 auditory stimuli per block. Through headphones, the standard auditory stimulus (1000 Hz, 100 ms length, $p = 0.85$) was randomly interspersed with two rare ($p = 0.15$) deviant stimuli (small pitch 1050 Hz and 100 ms; large pitch 1200 Hz, 100 ms). The study was approved by the Research Ethics Board of the Royal Ottawa Mental Health center, and all participants provided written informed consent before the EEG or questionnaires were administered.

An MDD participant was defined by a Beck Depression Inventory (BDI) score > 13 (Beck et al., 1961,1988). BDI values ≤ 13 are considered healthy or minimal symptoms.

2.2.2. EEG data acquisition and analysis

This EEG data was collected using a 32-channel BrainVision EasyCap, BrainVision Recorder software and a BrainVision V-8 amplifier (Brain Products, GmbH). The 3-minute continuous eyes-closed EEG data in the resting state was recorded at a sampling rate of 500 Hz. Recordings were preprocessed in MATLAB (v2018b) using the EEGLAB toolbox (v14). The data from the electrodes was bandpass FIR filtered with anti-aliasing from 1 to 40 Hz. The channels with less than 85% similarity with their neighboring channels were spherically interpolated. Data was re-referenced to the average of all electrodes (Majkowski et al., 2016; Stam et al., 2003). Infomax Independent Component Analysis (ICA) was then performed, followed by the multiple artifact rejection algorithms (MARA) (Winkler et al., 2011, 2015) to remove artifacts such as blinks and saccades.

2.2.3. Calculation of the autocorrelation window as index of intrinsic neural timescale

The autocorrelation window (ACW) was calculated in MATLAB (v2018b) using a custom MATLAB script and according to the methods of Honey et al. (2012). The ACW is an estimation, defined as the full-width-at-half-maximum of the autocorrelation function, which gives a temporal measure of the power time course. Windows of 20 s with 50% overlap and a lag of 1 s were used to calculate the ACW. The mean values for each channel were taken for each participant over the time series. In the frontal grouping we took the average of electrodes Fp1, Fpz, and Fp2.

2.2.3.1. Statistical analysis. The statistical analysis was performed in Statistical Package for the Social Sciences (SPSS) (IBM). One-way

Table 1
Summary of all rest-task studies in MDD.

Study	Modality	Disorder	# of subjects, HC, etc.	TaskHow long was resting stateEyes closed or open for resting stateType of task
Stewart et al., 2014	EEG 64 channels	MDD	143 HC 163 MDD (aged 17–34)	4 min EC 4 min EO →two resting-state EEG sessions done (16 min altogether Directed Facial Action Task
Wolff et al., 2019	EEG 32 electrodes	MDD	28 acute depressed MDD 25 HC	3 min EC Three-stimulus auditory oddball paradigm
Duncan et al., 2020	EEG 30 electrodes	MDD	26 MDD 37 HC	3 min EC 3 min EO
Satterthwaite et al., 2015	fMRI	MDD and Bipolar I & II	23 BD (27 for rest) 22 MDD (23 for rest) 32 HC (22 for rest)	6 min, 12 s resting state (eyes open or closed not mentioned) Monetary reward task
Sambataro et al., 2017	fMRI	MDD	19 unmedicated MDD 19 HC	10 min EO Motion prediction task
Young et al., 2018	fMRI	MDD	36 unmedicated MDD	6 min 24 s EO → done twice Real time fMRI neurofeedback training
Shi et al., 2015	fMRI	MDD	32 MDD 36 HC	75 s EO Serial presentation of a gray square forward mask, an emotional face image target stimulus, and a central fixation cross. Participants were asked to determine the gender of the people in the photographs
Erdman et al., 2020	fMRI	MDD	56 HC 24 medicated MDD (aged 18–65)	5 min EO Gambling task
Yang et al., 2016	fMRI	MDD	19 MDD 19 HC	5 min EO Three types of pictures, corresponding to each task condition, were applied, with positive (e.g., joyful, exciting), neutral, and negative (e.g., aversive) valences, respectively.
Loeffler et al., 2018	fMRI	MDD	10 MDD 16 remitted MDD 26 HC	7 min EO Emotion regulation task
Davey et al., 2012	fMRI	MDD	18 MDD 19 HC (aged 15–24)	12.3 min EC Modified block-design version of the MSIT

ANOVAs were used for comparisons between MDD and control groups. They had a significance level of 0.05 and the false discovery rate (FDR) (Benjamini and Hochberg, 1995) applied to correct for multiple comparisons. Because the BDI scores were not normally distributed, non-parametric one-tailed Spearman correlations were used to correlate BDI scores with each measure. Again, the FDR correction was applied and the significance level was 0.05.

3. Results

3.1. Review of EEG combined rest and task studies in MDD – reduced rest-task differences

Table 3 and Fig. 3 provide an overview of all rest-task EEG studies in MDD. Stewart et al. (2014) conducted an EEG study with 64 channels in 143 participants with major depressive disorder and 163 healthy controls. Participants performed a direct facial action task as well as resting states (eyes open and eyes closed). The task required participants to make approach and withdrawal facial expressions, followed by a rating of what emotion they felt while making the respective facial expression. Depressed individuals showed higher alpha power activity for average, Cz, and linked mastoid reference electrodes of the left frontal area when compared to healthy controls in resting state, along with less alpha power activity in the average reference during the direct facial action task. Finally, current-source-density transformed right-left hemispheric asymmetry was present in both resting state and the emotional task in MDD subjects. Together, these findings suggest a carry-over of resting state changes to task states (Fig. 2).

Wolff et al. (2019) analyzed data from a three-stimulus auditory oddball paradigm. The study comprised 28 acute depressed MDD patients and 25 healthy controls measuring 32-electrode EEG. When comparing rest and task activity, they found subjects with higher peak frequency (PF) in the theta band resting state showed lower prestimulus complexity when presented with standard stimuli relative to deviant stimuli. In the theta band for deviant stimuli, the coefficient of variation (CV) showed a positive correlation with both trial-to-trial variability (TTV) area under the curve (AUC) as well as power sliding (PS), the time-resolved change in frequency band power. These correlations demonstrate that the greater the dispersion around the mean in the theta band, the greater the variability increase along with the power increase for deviant stimuli. Additional analyses found that participants with higher resting state theta power showed lower complexity before and after both deviant and standard stimuli. This suggests that the resting state in MDD can no longer process complex stimuli.

Resting state analyses found MDD participants to show reciprocal modulation of the PF and CV in the theta band relative to the alpha band: PF was higher and CV lower in MDD than in controls in the theta band while the reverse was observed in the alpha band. This indicates an unstable resting activity pattern with opposite modulation of alpha and theta peak frequency in MDD. Cognitively, this may be related to abnormal cognitive loads in internally–(theta PF) and externally–(alpha PF) oriented cognition in MDD.

Moreover, Wolff et al. demonstrate reduced change in TTV after stimulus onset for deviant stimuli as well as decreased change in Lempel-Ziv Complexity (LZC) compared to HC. In addition, MDD subjects showed larger AUC of frequency sliding (FS) in the alpha band for deviant stimuli; furthermore, AUC of power sliding (PS) for both deviant and standard stimuli was greater in the MDD group than the controls. When analyzing TTV and both FS and PS, they found: 1) positive correlations between TTV variability changes and theta power in both standard and deviant stimuli; 2) positive correlations between TTV variability and PF in the theta band for deviant stimuli only; 3) a negative correlation between TTV variability and PS in the alpha band for standard stimuli only. Together, these findings demonstrate that the abnormal dynamics of resting state in MDD is carried over to subsequent task-related activity with the latter showing decreased dynamics (like

Table 2
fMRI Rest-Task Results.

Study	Neuronal findings in prestimulus	Neuronal findings in task-related activity	Relation of prestimulus and task-related activity	Psychological findings w/ relation to neuronal findings
Satterthwaite et al., 2015	Left ventral striatum, anterior insula, VTA, and thalamus, patients with unipolar MDD showed reduced nodal connectivity strength relative to both BD and HC, who did not differ from one another	Diminished activation of bilateral ventral striatum, posterior cingulate, anterior insula, and anterior cingulate in MDD and BD compared to HC	- No relation calculated	- Higher levels of depression were correlated with diminished activation of key hubs (task) of the reward system, including bilateral ventral striatum and posterior cingulate, as well as reward salience regions such as the anterior insula and anterior cingulate - Dimensional depression severity correlated with diminished resting-state functional connectivity across both unipolar and bipolar depression (nodal connectivity strength of the left ventral striatum exhibited a robust negative relationship with depression severity; connectivity at individual network edges also revealed diminished connectivity with greater depression severity, including connectivity between the ventral striatum and the thalamus, as well between as the ventral tegmental area and the ventromedial prefrontal cortex)
Sambataro et al., 2017 Spatial abnormalities mentioned in rest and task neuronal findings present in both rest and task for MDD relative to HC	Reduced connectivity in PCC, bilateral superior parietal cortex, anterior hippocampus, left dorsolateral PFC within the executive network (EN) Reduced connectivity in left parahippocampus in ventral DMN Reduced connectivity in left temporo-parietal cortex in dorsal DMN along with increased connectivity in the left precuneus	Reduced connectivity in PCC, bilateral superior parietal cortex, anterior hippocampus, left dorsolateral PFC within the executive network (EN) Reduced connectivity in left parahippocampus in ventral DMN Reduced connectivity in left temporo-parietal cortex in dorsal DMN along with increased connectivity in the left precuneus	Greater LFO (low frequency oscillations, spontaneous neuronal signal fluctuations with frequency < 0.08 Hz) amplitude ($0.04 < f < 0.08$ Hz in salience network (SN) during task relative to rest in MDD compared to HC	
Yang et al., 2016	Left subgenual part of the anterior cingulate cortex (sgACC), left DLPFC, left precuneus, right angular gyri AG, bilateral middle temporal gyri (MTG), and bilateral AI showed significantly increased zALFF (standardized amplitude of low frequency fluctuations) values Compared with HC, regions with significantly decreased zALFF values in the MDD group were found at the left postcentral gyrus, left lingual gyrus (LG), right cuneus, bilateral precentral gyri, and bilateral parahippocampal gyri / amygdalae rsFC: (increased correlation to seed) left AI & left sgACC, left mPFC, left LG, right calcarine, and left precuneus (decreased correlation to seed) left AI & right insule, right caudate nucleus, NAcc, right dACC, left middle cingulate gyrus, right superior parietal lobule, bilateral DLPFC, supplementary motor area (SMA) (increased correlation to seed) right AI & right insule, left middle occipital gyrus, bilateral LG, bilateral superior temporal gyrus (decreased correlation to seed) right AI & right caudate nucleus, left	In the positive condition, MDD patients showed only decreased brain activation amplitude in the left anterior insula (AI), right orbital part of the inferior frontal gyrus around the AI, dorsal part of the anterior cingulate cortex (dACC), left precuneus, bilateral (AG), bilateral dorsolateral prefrontal cortices (DLPFC), and bilateral thalamus extending to the putamen, caudate nuclei, pallidum, and other subcortical areas In the neutral and negative conditions, decreased brain activation was observed in the right precuneus and left DLPFC in MDD	When rest and task were overlapped, the common regions were the bilateral AI, left precuneus, and right AG	

(continued on next page)

Table 2 (*continued*)

Study	Neuronal findings in prestimulus	Neuronal findings in task-related activity	Relation of prestimulus and task-related activity	Psychological findings w/ relation to neuronal findings
	putamen, left mPFC, left dACC, right MCG, right SMA, bilateral PCC, AG, DLPFC			
Loeffler et al., 2018 - More internal attributions of negative events and less internal attributions of positive events in MDD compared to HC - MDD showed more internal attributions of negative events compared to positive events, while HC showed the opposite	No difference between groups in resting state connectivity of precuneus	HC compared to MDD showed increased activation in the right lingual gyrus during internal attributions and increased activation in the left lingual gyrus during internal positive > external positive MDD engaged the right fusiform gyrus more strongly than HC during external attributions MDD showed stronger engagement of left precuneus, extending to left PCC in external attribution (compared to view) Increased activation in MDD in the right superior frontal gyrus during external compared to internal attributions of negative events	- No relation calculated	
Davey et al., 2012	- Not reported	When comparing the two groups directly, no significant differences in task-related activation or deactivation were observed	MDD demonstrated less connectivity of the sgACC with the right ventral caudate/NAcc during rest when compared to task MDD showed greater connectivity between the sgACC and adjacent ventromedial frontal cortex regions at rest compared to task performance	Positive correlation between VS/ NAcc activation during reward processing and RRS scores in HC
Young et al., 2018	During rest, bilateral amygdala-precuneus and amygdala-right thalamus connectivity significantly explained variance in the treatment response after controlling for amygdala change and baseline **MADRS** (Montgomery-Åsberg Depression Rating Scale) scores During positive memory recall, amygdala-left precuneus and amygdala-right inferior frontal gyrus connectivity were significantly correlated with improvement in depressive symptoms after controlling for baseline severity and amygdala activity change	Increased connectivity with the amygdala in the amygdala rtfMRI-nf (real-time fMRI neurofeedback training) group compared to parietal rtfMRI-nf group was observed in the right middle frontal gyrus, hippocampus, parahippocampal gyrus, thalamus, left dorsal ACC, and bilateral precuneus Decreased connectivity in bilateral temporal pole Increased connectivity with amygdala and multiple prefrontal cortical (right inferior frontal gyrus/lateral orbital cortex, dorsal ACC and ventrolateral PFC, left medial frontopolar cortex, bilateral medial PFC), striatal regions (bilateral putamen, right caudate), as well as the right insula, cerebellum, and bilateral thalamus and precuneus in amygdala group vs parietal group Decreased connectivity with amygdala and right temporal pole following training	- No relation calculated	
Shi et al., 2015 - Prestimulus	- Not reported - All analyses were done with comparison of the task to resting state	- Not reported	Increased activation of left middle frontal gyrus in MDD compared to HC; decreased functional connectivity in bilateral PFC, mPFC	FC of the right inferior frontal gyrus and middle frontal gyrus correlated negatively with CERQ-maladaptive scale (Cognitive Emotion Regulation Questionnaire) scores in MDD
Erdman et al., 2020 - RRS and BDI scores were highly correlated	Left OFC connectivity with the right NAcc is positively correlated with ruminative tendency in both groups	Decreased VS/NAcc activation in MDD compared to HC	- No relation calculated	

TTV) in response to external stimuli or tasks.

Duncan et al. (2020) completed an EEG study consisting of 26 patients with MDD and 27 healthy controls undergoing 3 min of both eyes open and eyes closed scans. The study acquired EEG data from 30 electrodes and conducted detrended fluctuation analysis (DFA) of alpha and beta bands at each electrode. They found that the switch to eyes open from eyes closed resulted in reduced DFA in both the alpha and beta bands. Alpha band changes were seen in frontal and occipital

Table 3
EEG Rest-Task Results.

Study	Neuronal findings in resting state and/or prestimulus	Neuronal findings in task-related activity	Relation of prestimulus and task-related activity	Psychological Findings
Stewart et al., 2014	MDD showed higher left frontal alpha power activity relative to HC	MDD group displayed less left frontal alpha power activity than HC during approach and withdrawal conditions	No relation calculated	
Wolff et al., 2019	In the theta band for MDD participants, the peak frequency (PF) was higher, and coefficient of variation (CV) and power lower than the healthy controls.In the alpha band, PF and power were lower and CV higher in MDD relative to HC. è Reciprocal modulation of PF and CV in theta and alpha bands in MDD subjects Indicates unstable resting activity pattern in these bands for MDD	MDD showed smaller area under curve (AUC) of the trial-to-trial variability (TTV) curve between stim onset and 500 ms when compared to HC Change in TTV after stim onset reduced in task-relevant deviant tones for MDD HC showed larger change in LZC than MDD for deviant stimuli In alpha band for deviant stimuli, AUC of frequency sliding (FS) was larger for MDD relative to HC; for both deviant and standard stimuli, AUC of power sliding (PS) was larger for MDD than HC In theta band, there was no difference between groups in FS for both stimuli; PS for MDD was higher for deviant stimuli and lower for standard stimuli For AUC: no difference in FS in alpha band Increase in AUC TTV after deviant stim onset resulted in decreased theta PF and increased theta power	Subjects with higher PF of theta band in resting state showed lower prestimulus complexity when shown standard stimulusIn theta band for deviant stimuli, CV and TTV AUC showed a positive correlation; CV and PS also showed a positive correlation - Greater the dispersion around the mean in theta band, greater the variability increase as well as theta power increase for dev. stim Participants with higher resting state theta power showed lower complexity before and after both deviant and standard stim è Instability of MDD resting state is shown through pre and post stim activity Decreased changes in LZC and TTV	
Duncan et al., 2020	DFA values in the EC condition were greater for the low than the high BDI groups	No difference in DFA values in EO between low and high BDI groups	Switch to EO from EC resulted in decreased DFA in alpha and beta bands - Alpha band changes were primarily found in frontal and occipital areas, extending through the midline - Reductions in beta band DFA were seen across all electrodes (largest at frontal and posterior electrodes and the smallest at electrodes associated with sensorimotor cortex)	Beta DFA changes had a negative relationship with BDI scores at posterior and midline electrodes Beta band EC DFA values correlate with brooding rumination

regions, extending through the midline structures. Beta band DFA changes were primarily found at the frontal and posterior electrodes. DFA changes between eyes open and closed were inversely correlated with depressive symptom severity, measured by the BDI. Together, these findings demonstrate that the MDD subjects show decreased dynamic change in the fluctuations of alpha and beta band power, as measured by DFA, during the transition from rest to task. Importantly, such decreased rest-task difference in DFA is related to depression symptom severity underscoring its importance for psychological symptoms.

3.2. Our own EEG rest-task data – intrinsic neural timescales in mdd

We also recorded EEG in our own MDD sample during both rest and task conditions. The ACW computed the intrinsic neural timescales, specifically in the frontal electrodes. There were no significant differences in ACW of the frontal electrodes between MDD and controls in either rest or task. However, ACWs tend to be longer in task in MDD (Fig. 3). Subtracting ACW task from ACW rest revealed a highly significant reduction in rest-task difference of ACW in MDD (Fig. 3). Together, these findings demonstrate decreased rest-task dynamics in MDD with less modulation of ACW during the transition from rest to task.

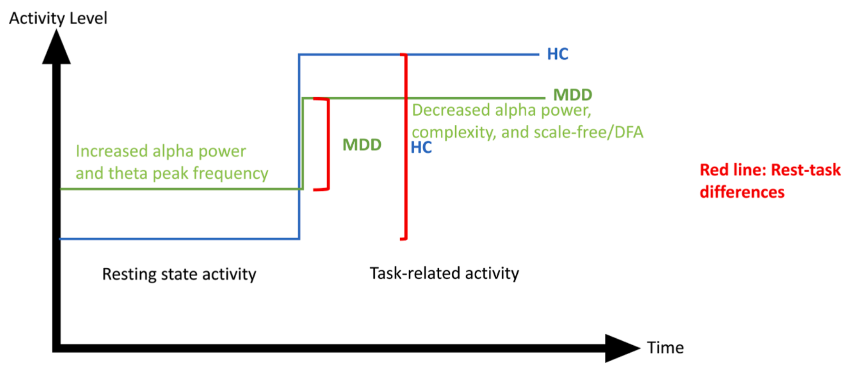

Fig. 2. EEG rest and task studies in MDD.

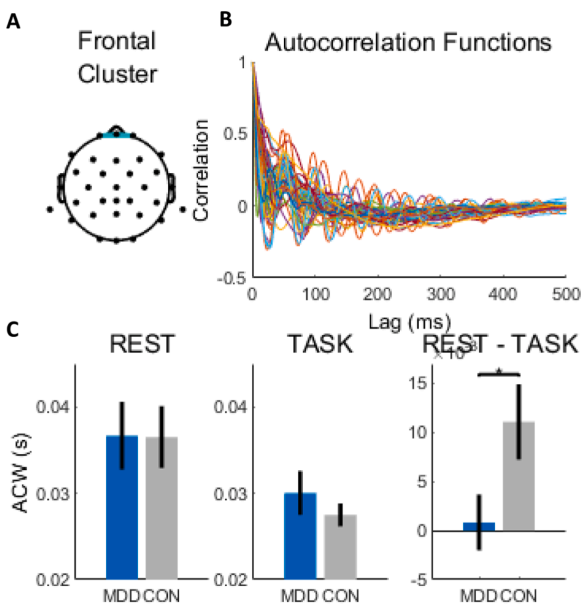

Fig. 3. The autocorrelation window (ACW) in frontal cluster of electrodes in both rest and task. A: The frontal cluster of electrodes was the mean of all three prefrontal electrodes. B: The autocorrelation function (ACF) for each participant. From this function, the full-width-at-half-maximum (FWHM) was measured as the ACW. C: (left plot) The ACW widths during rest for each group found no difference. (center plot) Likewise, the ACW widths during task for each group found no difference. (right plot) A significant difference between groups was found when the difference between rest and task was measured. The MDD group had a significantly lower rest-task difference than the healthy controls.

3.3. Review of combined rest and task fMRI studies in MDD – different rest-task relationships in different regions

Table 1 (and also Table 4 for all regions implicated) and Fig. 4a-c provide an overview of all combined rest-task fMRI studies in MDD. Satterthwaite et al. (2015) demonstrate that MDD participants show overlap in diminished activation during rest and task state, particularly in the left ventral striatum (VS) and anterior insula (AI). In resting state, MDD subjects show reduced activity in the ventral tegmental area (VTA) and thalamus compared to controls. While performing the task, MDD participants exhibited diminished activation of the right VS, posterior cingulate cortex (PCC), and anterior cingulate cortex (ACC) relative to controls (see Fig. 1a). With regards to psychological findings, they concluded that higher levels of depression, measured by total BDI, were correlated with diminished activation in the bilateral VS, AI, PCC, and ACC, all of which are related to the reward system and salience regions (Figs. 4a-c and Supplementary Figure 1). The results demonstrate that MDD participants have abnormal spatial dynamics in both resting and task states.

Another study conducted by Yang and colleagues (2016) measured amplitude of low-frequency fluctuations (ALFF) in both rest and task states, with the MDD group showing increased activation in resting state and decreased activation during the task in the bilateral AI, left precuneus and right angular gyrus. Regions which displayed decreased standardized ALFF (zALFF) in resting state included the left subgenual part of the anterior cingulate cortex (sgACC), left dorsolateral prefrontal cortex (DLPFC), and bilateral middle temporal gyri (MTG). Conversely, regions which displayed decreased zALFF values in resting state comprised of the left postcentral gyrus, left lingual gyrus (LG), right cuneus, bilateral precentral gyri, and bilateral parahippocampal gyri and amygdalae. In the positive task state analyses, MDD patients had decreased brain activation in the AI, the dorsal part of the anterior cingulate cortex, the bilateral DLPFC, and bilateral thalamus extending to the putamen, caudate nuclei, and pallidum. Furthermore, in both the neutral and negative conditions, the right precuneus and left DLPFC showed decreased activation (Fig. 4a-c and Supplementary Figure 2). Their findings regarding amplitude of low-frequency fluctuations point towards decreased rest-task modulation in individuals with MDD.

Sambataro et al. (2017) recruited 19 unmedicated subjects with MDD and 19 controls in a motion prediction task. In addition to 10 min of eyes open resting state, they measured functional connectivity (FC) with fMRI. The MDD group demonstrated reduced FC in the PCC, the bilateral superior parietal cortex, the anterior hippocampus, and the left DLPFC across both the rest and task states. Additionally, participants with MDD showed reduced FC in the left parahippocampus in the ventral DMN in both rest and task states. Furthermore, with task relative to rest, MDD showed greater low frequency oscillation (LFO, frequencies < 0.08 Hz) amplitude than controls (Fig. 4a and b and Supplementary Figure 1). Analyzing the rest-task differences, Sambataro et al. demonstrate that participants with MDD exhibit abnormal FC in both rest and task, illustrating a different pattern of modulation between the two states.

Rest-task modulation abnormality in MDD is also demonstrated by Loeffler et al. (2018). They focused on the precuneus and neural correlates of emotional control using fMRI in 10 patients with current MDD, 16 patients with remitted MDD (both MDD groups medicated) and 26 controls. The task regarded emotional regulation, where participants rated facial emotions in an internal attribution condition (facial emotion due to the participant) or an external attribution condition (facial emotion unrelated to the participant) for positive and negative events. Using a seed-based resting-state fMRI approach, the group examined whole-brain connectivity with the precuneus, due to its involvement in emotion regulation and self-referential processing. No group differences were found in the resting-state whole-brain connectivity.

However, task state analyses showed decreased activation for MDD in the right lingual gyrus during internal attributions and increased activation of the left lingual gyrus during the internal positive events.

Table 4
Regions showing abnormalities in rest and/or task.

	Abnormal rest-Normal task	Normal rest-Abnormal task	Abnormal rest-Abnormal task
Left postcentral gyrus	↓		
Ventral tegmental area	↓		
Precentral gyrus	↓		
Amygdala	↓		
Right parahippocampus	↓		
Cuneus	↓		
Middle temporal gyrus	↑		
Left caudate nucleus		↓	
Right ventral striatum		↓	
Putamen		↓	
Left angular gyrus		↓	
Right precuneus		↓	
Pallidum		↓	
Right dorsolateral prefrontal cortex		↓	
Right lingual gyrus		↑	
Right fusiform gyrus		↑	
Right superior frontal gyrus		↑	
Superior parietal cortex			↓
Right caudate nucleus			↓
Anterior hippocampus			↓
Left parahippocampus			↓
Left ventral striatum			↓
Thalamus			↓
Left precuneus			↑

During external attributions compared to the neutral condition, MDD subjects engaged the right fusiform gyrus, and the left precuneus extending to the left PCC more strongly than healthy controls. MDD participants showed increased activation in the right superior frontal gyrus during external attributions of negative events relative to that of internal attribution. In relation to psychological scales, FC of the right inferior frontal gyrus and middle frontal gyrus correlated negatively with CERQ-(Cognitive Emotion Regulation Questionnaire) maladaptive scale scores in MDD (Fig. 4a-c and Supplementary Figure 3). Considering rest and task together, the abnormal task-related spatial dynamics of MDD participants suggests a fundamental difference in rest-task modulation compared to controls.

Turning now to a study by Davey et al. (2012), who conducted an fMRI study with 18 MDD participants (half on antidepressants) and 19 controls participating in a blocked multi-source interference task and 12 min of resting state interleaved within the task in 15 sec intervals. When comparing resting state to task activity, the MDD group demonstrated reduced connectivity of the subgenual ACC with the right ventral caudate and nucleus accumbens. Conversely, MDD showed greater connectivity between the subgenual ACC and adjacent ventromedial frontal cortex regions at rest compared to task performance (Fig. 4a-c and Supplementary Fig 4). These findings indicate abnormal modulation from rest to task states in participants with MDD in comparison to controls

Investigating the effect of real time fMRI neurofeedback (rtfMRI-nf) training on the amygdala, Young et al. (2018) recruited 36 unmedicated MDD participants. Using an autobiographical memory recall test, 18 patients received amygdala rtfMRI-nf and 16 received control rtfMRI-nf. In resting state, the amygdala group showed increased connectivity between the amygdala and the right middle frontal gyrus, hippocampus, parahippocampal gyrus, thalamus, left dorsal anterior cingulate cortex, and bilateral precuneus compared controls. Neuronal findings for the task state displayed increased connectivity relative to controls in the following regions: the amygdala, multiple prefrontal cortical regions, striatal regions, the right insula, the cerebellum, the bilateral thalamus, and the precuneus. In both rest and task states, decreased connectivity of the amygdala-temporal pole was observed in the amygdala group. From this study, one can infer atypical spatial connectivity patterns in both rest and task states for MDD individuals.

Exploring rest-task modulation and its relation to the DMN, Shi et al. (2015) investigated 32 patients with MDD and 36 healthy controls who performed a gender judgment task interleaved with rest periods. MDD participants exhibited increased activation of the left middle frontal gyrus relative to healthy controls. Additionally, MDD individuals showed decreased functional connectivity in the bilateral prefrontal cortex and the medial prefrontal cortex. Their findings contribute to the conclusion that individuals with MDD display altered spatial dynamics in both rest and task.

Finally, Erdman and colleagues (2020) examined task-related neuronal activity and found the MDD group to exhibit decreased ventral striatum and nucleus accumbens activation relative to healthy controls. These results demonstrate anomalous task-related spatial dynamics. In sum, the combined rest-task fMRI studies show that different regions exhibit different rest-task relationships including normal rest-

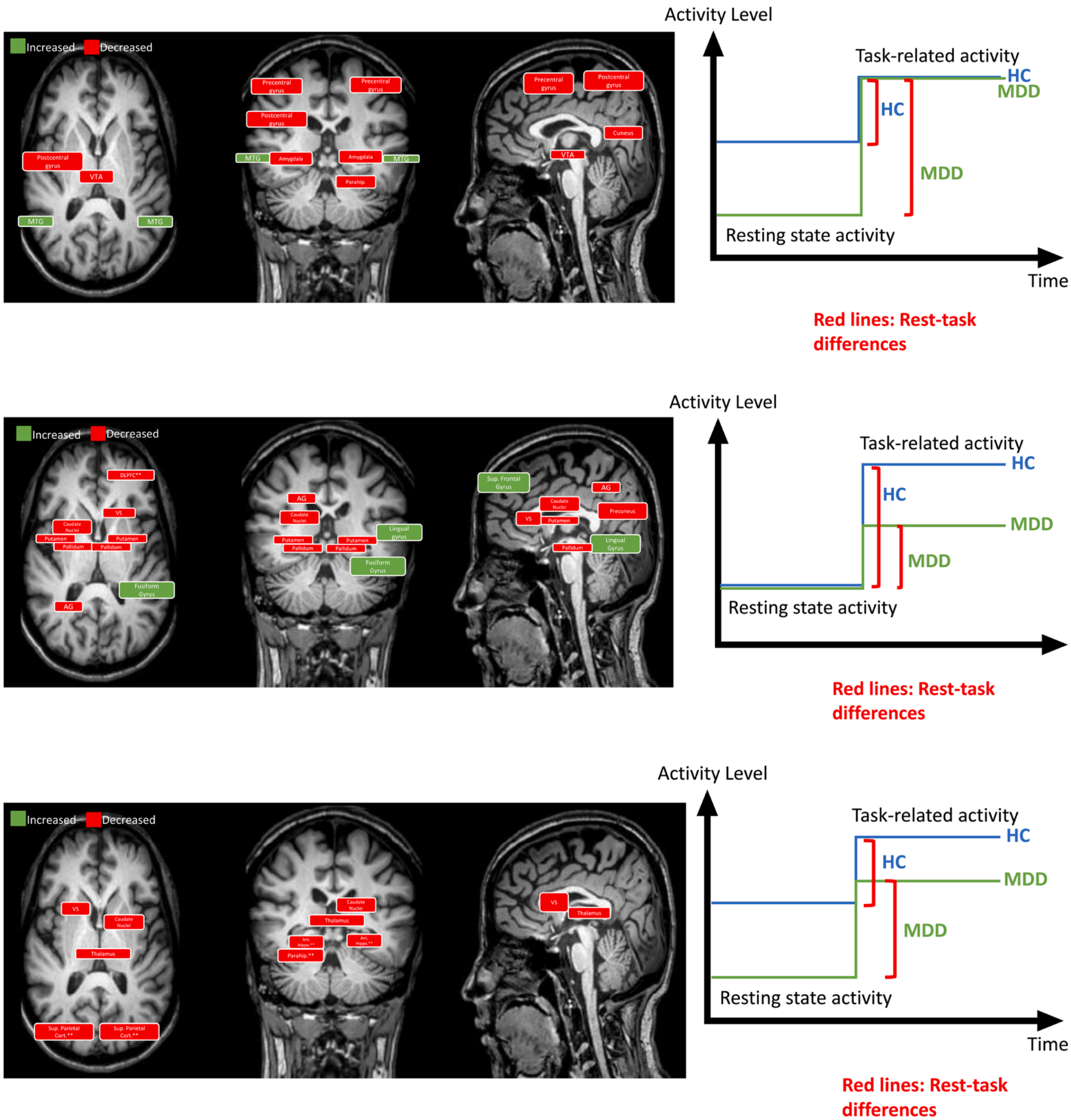

Fig. 4. a) Abnormal rest-Normal task (Satterthwaite et al., 2015; Yang et al., 2016) b) Normal rest-Abnormal task (Satterthwaite et al., 2015; Yang et al., 2016; Loeffler et al., 2018). c) Abnormal rest-Abnormal task (Satterthwaite et al., 2015; Yang et al., 2016; Sambataro et al., 2017; Loeffler et al., 2018). Abbreviations: Ventral tegmental area, VTA; Middle temporal gyri, MTG; Ventral striatum, VS; Angular gyri, AG; Nucleus Accumbens, Nacc; Dorsolateral prefrontal cortex, DLPFC; Sup., superior; Ant., anterior; Cort., cortex; Parahippocampus., parahip. [Red: decreased activity; Green: increased activity].

abnormal task, abnormal rest-normal task, and abnormal rest-abnormal task (see Fig. 2a-c).

4. Discussion

We here investigate the relationship of rest and task states in MDD, i.e., rest-task modulation. Combining multimodal imaging (EEG, fMRI) review and our own data, our main findings are as follows. First, we show decreased rest-task dynamics in MDD during EEG in both the reviewed studies and our own data. These results show that MDD subjects remain unable to sufficiently change their resting state activity level during task states. Importantly, this holds for different tasks as well as for different dynamic measures (like ACW, DFA, peak frequency, etc.)–this points towards a most basic and fundamental yet unclear change in the temporal dynamics of the brain's spontaneous activity in MDD that remains independent of specific forms of cognition. Secondly, reviewing combined rest-task fMRI studies, we observe that, in MDD, different regions display various rest-task relationships including normal rest-abnormal task, abnormal rest-normal task, and abnormal rest-abnormal task when compared to healthy controls. This suggests a complex and heterogeneous rest-task spatial pattern in MDD.

Together, we demonstrate abnormal spatiotemporal dynamics of rest-task modulation in MDD. This, as we suppose, carries major implications for perception and cognition as postulated in the "resting state hypothesis of depression" (RSHD) (Northoff et al., 2011; Northoff, 2016c). The RSHD postulates a most fundamental and basic role for the brain's spontaneous activity, i.e., the resting state, by mediating abnormalities in task states and associated symptoms. The current findings support and extend this assumption by showing abnormal temporal dynamics, i.e., EEG, and varied spatial topography, i.e., fMRI, of rest-task modulation in MDD. This further point out the need to consider both rest and task states in conjunction (rather than in isolation) including their interaction, i.e., rest-task modulation to grasp the complex findings in brain imaging of MDD.

4.1. Abnormal dynamics of rest-task modulation

Our first main finding concerns decreased temporal dynamics of rest-task modulation in the EEG studies of MDD. Despite applying different measures of temporal dynamics like alpha power (Stewart et al., 2014; Wolff et al., 2020), scale-free activity (DFA) (Duncan et al., 2020), theta/alpha peak frequency (Wolff et al., 2020, and intrinsic neural timescales (ACW) (own data)), all studies show decreased rest-task modulation in MDD. Moreover, this holds across different paradigms in the task states. Albeit tentatively, these results suggest that the abnormal temporo-spatial dynamics of the resting state in MDD strongly impacts task-related activity–the former may be carried over to the latter albeit in yet unclear ways. The exact mechanisms driving such abnormal temporal dynamics like the decreased change in the intrinsic neural timescales, i.e., ACW in our EEG data, remain yet unclear, though.

The second main finding concerns the spatial pattern of rest-task modulation in MDD. Our review of combined fMRI rest-task studies in MDD reveals a heterogeneous picture of different rest-task combinations in different regions. Various subcortical regions like the VTA, amygdala and others (as well as pre- and postcentral gyrus) show decreased resting state activity (see also Conio et al., 2020; Kaiser et al., 2015) while exhibiting normal task-related activity. That contrasts with other subcortical regions like the hippocampus, ventral striatum, and thalamus (and superior parietal cortex and precuneus) that exhibit decreases in both rest and task (see Fig. 2a-c and Table 4). We also found decreased rest-task modulation for regions within the DMN (PCC, precuneus, medial prefrontal cortex) which exhibited mostly increased resting state and decreased task states. Together, our findings show different constellations: some regions exhibit rest changes but no task changes, normal rest and abnormal task, and changes in both rest and task. Limited by the low number of fMRI studies combining both rest and task, we tentatively assume heterogeneous rest-task relationships of different regions in MDD.

4.2. From abnormal rest-task modulation to psychopathological symptoms

How do the abnormalities in rest and task, including rest-task modulation, impact cognition and symptoms in MDD? We currently do not know. Resting state activity is related to internally-oriented cognition like mind wandering (Christoff et al., 2016; Northoff, 2018), mental time travel (Schacter et al., 2012), and self-referential processing (Davey et al., 2016; Northoff et al., 2006; Northoff, 2016c) while task-related activity is obviously more related to externally-oriented cognition (Dixon et al., 2014). Moreover, evidence from healthy subjects show that rest/prestimulus-task modulation impacts visual perception and cognition (see Huang et al., 2017; Northoff et al., 2010a and b; Wainio-Theberge et al., 2021; Wolff et al. 2021). Together, these findings in healthy subjects suggest a key role for rest-task modulation in perception and cognition. Abnormal rest-task modulation as observed in MDD may distort the balance or relation of internally- and externally oriented cognition. If there is low modulation of task by rest, i.e., decreased rest-task difference, one would assume predominance of internally- over externally oriented cognition. This is indeed the case in MDD showing abnormally heightened attention to the own self, i.e., increased self-focus as a typical hallmark of an increased internally-oriented cognition (Hamilton et al., 2015; Northoff, 2007, 2016; Northoff et al., 2011; Scalabrini et al., 2020). Increased focus on the self in depressed individuals is compatible with the rest-task abnormalities observed in especially the DMN, a network of the brain highly associated with resting state and self-referential processing (Murray et al., 2012,2015; Northoff et al., 2006, 2015; Qin et al., 2020; Scalabrini et al., 2017,2019). With an increased focus on the self, difficulty switching from the resting state's internally-oriented cognition to the more externally-oriented cognition of task-related states is to be expected in depressed individuals. The reduced rest-task modulation of the DMN may then be manifested in abnormal elevation of internally-oriented cognition including increased self-focus during external tasks–this has been described as the co-occurrence of 'increased self-focus' and 'decreased environment-focus' in MDD (Northoff et al., 2016a and b; Northoff et al., 2011). Moreover, it may shift the usually balanced hierarchy between interoceptive, exteroceptive, and mental layers of self (Qin et al., 2020) towards the mental self as that is mainly mediated by the DMN (Qin et al., 2020). This may psychopathologically be manifested in the abnormal predominance of cognitive features of self like rumination (Hamilton et al., 2015) with the co-occurrent decrease of the exteroceptive-social (social withdrawal) and interoceptive (abnormal feeling of own body) aspects of the self (Northoff et al., 2016a and b; Northoff et al., 2011).

One key finding of our study is the alteration in the intrinsic neural timescales in MDD as measured by ACW. Extrapolating from the smaller difference in ACW from rest to task for MDD suggests a less reactive resting state in depressed individuals: the timescales of the resting state can no longer adapt to the timescales required for processing the ones of the task states. The resting state's timescales in MDD are thus too sluggish and may be ultimately too slow to react to the usually fast timescales required to process the information of the external stimuli or tasks. This is well compatible with the close relationship of ACW with the neuronal speed (as measured by median frequency; Honey et al., 2012; see also Fig. 5). Decreased neuronal speed may be related to the well-known observation that MDD patients experience their own inner time as too slow while, at the same time, they perceive the outer time of the external environment as too fast (Fuchs, 2013; Northoff et al., 2018). Future studies are warranted to link such decreased temporal dynamics in the neuronal slow-fast shift of rest-task modulation to the subjects' experience/perception of their inner and outer time speed and ultimately with psychopathological symptom like social withdrawal, i.e., 'decreased environment-focus' (Northoff, 2016a; Scalabrini et al., 2020).

4.3. Methodological considerations

Predictive coding models of depression use a computational basis and suggest depressive responses manifest as adaptations to attract social support, where psychopathology emerges as a result of chronic prediction errors (Smith et al., 2021). Models of predictive coding are congruent with the rest-task approach, where predicted input or so-called prior, as generated by the spontaneous activity in the prestimulus period, can shape task activity, culminating in predictive errors. These mechanisms modulate both internal and external thought processes and support the hypothesis of viewing rest and task states as a dynamic, interdependent pair. Future studies are warranted that link predictive coding to the mechanisms of specifically temporal dynamics as for instance the here observed changes in ACW may drive an abnormal prediction error.

We tentatively suggest our findings demonstrate a disbalance of internally- to externally-oriented cognition as measured by spatiotemporal dynamics, as a result of low modulation of task by rest in MDD (Fig. 5). Overall, we emphasize that analyzing the brain's extrinsic activity alone does not demonstrate a well-rounded view of depression and still leaves diagnostic markers of MDD elusive. Using research from healthy subjects and other disorders in addition to MDD, we illustrate the importance of considering both intrinsic and extrinsic activity of the brain, i.e., rest and task states, as interdependent components that permeate amongst one another.

The importance of abnormal rest-task modulation for MDD and psychiatric disorders in general is supported by a recent studies showing abnormal rest-task modulation in autism (Lian and Northoff, 2021), anxiety disorders (Tumati et al., 2021), and schizophrenia (Gomez-Pilar et al., 2018; Northoff and Gomez-Pilar, 2021). There is similarity in that all disorders share abnormal spatiotemporal dynamics as a core mediator of modulation between rest and task states. At the same time, key

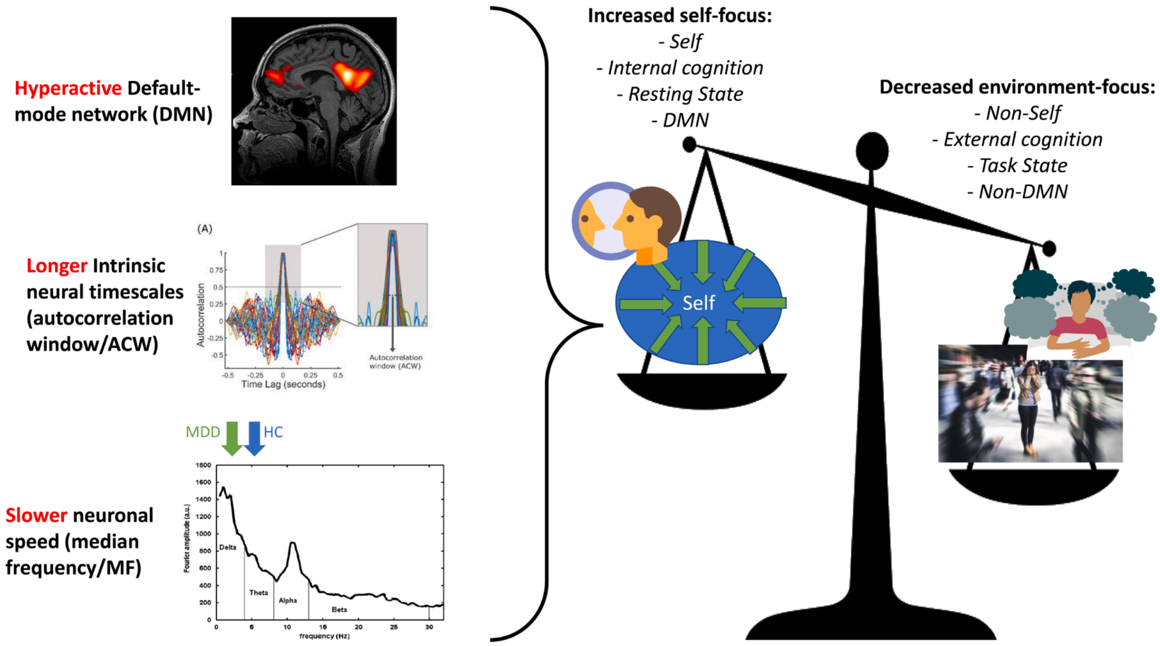

Fig. 5. From neuronal (left) to psychopathological (right) changes. Our findings of decreased rest-task modulation in MDD suggest a fundamental disbalance between intrinsic and extrinsic processes, as supported by the temporal and spatial abnormalities observed across the studies. Slower frequency fluctuations overpower depressed individuals and subsequently, they experience abnormal slowness of inner-time while outer-time is perceived as accelerated. Low rest-task modulation of the DMN supports the increased focus on the self and internal cognition we see in MDD, along with difficulty differentiating internally- and externally-oriented cognition. Taken together, these findings, albeit tentative, suggest a less reactive resting state in MDD, which results in the cognitive and psychological features that characterize depression.

distinctions must be made amongst each disorder with respect to the specific dynamics in rest, task, and rest-task modulation; this suggests that rest-task modulation may be a strong candidate for possible differential diagnosis serving as biomarker.

Finally, our study must be considered exploratory. This is due to the low number of reviewed fMRI and EEG studies including both rest and task states. Moreover, the case number in our own EEG study was rather low so that results must be considered preliminary. However, notwithstanding the exploratory character of our investigation, it carries important methodological implications to include both rest and task states in brain imaging of MDD including the calculation of their relationship as by rest-task correlation and rest-task difference.

5. Conclusion

In conclusion, we demonstrate evidence for abnormal spatiotemporal dynamics of rest-task relationship in both fMRI and EEG of MDD. The reviewed studies and our own data reveal changes in both rest and task states with the brain dynamics no longer properly changing during the transition from rest to task. This suggests a most basic and fundamental change in the spatiotemporal dynamics of the brain's spontaneous activity which, through the resting state, affects its task states, i.e., abnormal rest-task modulation. Future studies are warranted to link the abnormal rest-task dynamics to perception and cognition and ultimately specific psychopathological symptoms including abnormally slow time speed perception, increased self-focus, rumination, and social withdrawal ('decreased environment-focus').

Together, our findings strongly support and extend the 'Resting state hypothesis of depression' (RSHD) (Northoff, 2016c; Northoff et al., 2011; Scalabrini et al., 2020) by showing how changes in the spontaneous activity mediate the dynamic and topography of abnormal rest-task modulation in MDD. This provides a broader more comprehensive view of the changes in rest and task states in MDD including the methodological need to consider both rest and task states in brain imaging. At the same time, it also opens new ways of linking neuronal changes to psychopathological symptoms. The altered spatiotemporal dynamics and topography of rest-task modulation may translate into corresponding spatial and temporal changes in perception and cognition of MDD as basis for the psychopathological symptoms–the RSHD thus aligns with what has been described as 'Spatiotemporal Psychopathology' (Northoff, 2016a and b, 2017, 2018).

6. Disclosures

Dr. Northoff, Dr. Wolff, and Anvita Gupta report no potential conflicts of interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2021.111367.

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