Intrinsic activity temporal structure reactivity to behavioural state change is correlated with depressive rumination

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Abstract

Patients with major depressive disorder (MDD) tend to focus their thoughts on their personal problems and negative self-reflection. This negative self-focus has a major impact on patient quality of life and is associated with a range of cognitive deficits. Self-related thoughts, such as those seen in rumination, have been associated with intrinsic activity within cortical midline structures. In normal conditions this intrinsic activity is responsive to behavioural state, changing as an individual switches from an internally to externally oriented context. It was hypothesised that this responsiveness would be blunted in patients with MDD (n = 26; control n = 37) and that the degree to which an individual was fixed in a particular intrinsic state would be correlated with reported ruminatory behaviours. This was tested by measuring intrinsic EEG activity temporal structure, quantified with detrended fluctuation analysis (DFA), in eyes-closed and eyes-open task-free states and contrasting between the conditions. The difference between the internally oriented eyes-closed and externally oriented eyes-open states was then correlated with ruminatory behaviour, measured with the Rumination Response Scale. Healthy controls showed a robust beta band DFA change between states, moving from a critical to sub-critical activity state with the opening of the eyes. This change was not seen in MDD patients, with the eyes-closed DFA remaining similar to that in eyes-open. A negative correlation was seen between the DFA difference and rumination scores over the midline electrodes. These results identify a reduced reactivity of intrinsic activity properties in MDD that is related to greater ruminative symptoms.

Key words

Negative thought; self-focus; long-range temporal correlations; criticality

Introduction

Rumination is a mental process involving repetitive thoughts about one's feelings and problems (Smith and Alloy, 2009). In those with depression this process is predominantly maladaptive, impacting other thought processes and interfering with daily functioning (Lane and Northoff, 2017). For example, rumination has been associated with deficits in problem-solving (Donaldson and Lam, 2004), attentional control (Lyubomirsky et al., 2003), and impacts upon memory (Liu et al., 2017). Negative rumination is associated with worse outcomes in those suffering or recovering from depression (Huffziger et al., 2009; Spinhoven et al., 2018; Surrence et al., 2009) and represents a risk factor for developing depression in healthy individuals (Spasojević and Alloy, 2001).

The self-related thoughts that are a feature of rumination have been associated with ongoing, spontaneous activity within the brain (Huang et al., 2016; Nejad et al., 2013; Qin et al., 2016). Such intrinsic activity has also been found to be altered in depression, both in terms of connections between brain regions and in local activity properties (Brakowski et al., 2017; Zhong et al., 2016). Interestingly, activity within intrinsic networks correlates with reported rumination and is modulated by rumination induced in a task (Berman et al., 2011; Zamoscik et al., 2014; Zhu et al., 2012). Together, these findings appear to point to a functional overlap between the properties of ongoing spontaneous activity and ruminative self-oriented thoughts related to depression (Li et al., 2018).

Ongoing brain activity appears to function close to an unstable equilibrium point (Deco and Jirsa, 2012). This critical state, where the system is on the boundary between order and disorder (Beggs and Timme, 2012), has been linked to efficient information processing and optimal behavioural performance (Irrmischer et al., 2018b; Palva et al., 2013; Palva and Palva, 2018). A system in a critical state is characterised by scale-free activity distributions and long-range temporal correlations (LRTC; Plenz and Thiagarajan, 2007), which can be measured with techniques such as detrended fluctuation analysis (Peng et al., 1995). Such approaches have been used to study brain activity in a variety of species and experimental conditions (Bellay et al., 2015; Priesemann et al., 2009; Ribeiro et al., 2010; Shriki et al., 2013).

This prior work suggests that the brain displays variability around a critical state depending upon the current behavioural condition (Bellay et al., 2015; Hahn et al., 2017). One such behavioural

change is the switch from having closed eyes to having them open (Yan et al., 2009), resulting in a change from an internally oriented state to one that is oriented towards the external environment (Marx et al., 2004). This eyes-open (EO) effect is known to influence the activity in multiple brain networks, impacting upon neural oscillations within different frequency bands (Barry et al., 2007; Barry and De Blasio, 2017). Activity in the eyes-closed (EC) condition appears to be closer to criticality, moving towards sub-critical dynamics in the eyes-open condition (Hahn et al., 2017; Jao et al., 2012).

The ability to effectively shift between dynamic cortical states depending on behavioural state has been linked to cognitive performance (Irrmischer et al., 2018b). This may reflect an ability to move easily from a critical state, where there is the maximum potential to respond flexibly to changing demands, to a sub-critical one where processing can be focussed on a single task (Beggs and Plenz, 2003; Irrmischer et al., 2018b). Extending this principle to rumination, we could hypothesis that such continuous thoughts would constitute a task state that individuals remain in. That in turn would be reflected in a reduced reactivity of the dynamic cortical state, meaning that it would not shift between critical and sub-critical states as normal when the participant changes their overall behavioural condition.

A group of participants with a range of ruminative behaviours was recruited to test this hypothesis. Following a dimensional approach (Insel et al., 2010), data from healthy participants (HC) were combined with data from people diagnosed with major depressive disorder (MDD). All participants had EEG recordings made during eyes-open and eyes-closed rest. DFA exponents were then calculated and compared between the two behavioural states. This DFA change, taken as a proxy for the shift in criticality, was related to reported rumination. A smaller difference in eyes-closed versus eyes-open DFA, taken to reflect a reduced flexibility in the cortical state, was expected to be correlated with greater reported rumination.

Methods

Participants

Thirty-seven healthy participants and twenty-six patients with MDD took part in the experiment. Three patients did not have usable data and were excluded (MDD n = 23), leaving a total study group of 60 participants. Age and sex did not differ between groups (Table 1A). Patients were recruited from the Department of Psychiatry at Shuang-Ho Hospital, New Taipei City. Controls

were recruited from the local community. All patients were diagnosed according to DSM-5 criteria for current episode MDD (American Psychiatric Association, 2013). The majority of patients were medicated at the time of the study (22/23) and had a mean time since current episode onset of 5.8 months (± 6.1 SD). Patients with comorbid Axis I disorders were excluded, as diagnosed by a senior psychiatrist and confirmed by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). All participants were informed about the purpose of the study and procedures before giving written informed consent. This study was approved by the Joint Institutional Review Board, Taipei Medical University, Taipei City, Taiwan (N201603080).

	Control (n = 37)	MDD (n = 23)	Difference
A			
Age	38.8 ± 12.9	38.7 ± 13.5	$t = 0.2$
Sex	31F, 6M	18F, 5M	$X^2 = 0.1$
B			
BDI	7.0 ± 6.1	28.0 ± 12.8	$t = 8.4$**
RRS	39.5 ± 9.4	63.2 ± 13.5	$t = 7.9$**
RRS Brooding	9.2 ± 2.4	15.0 ± 13.5	$t = 7.5$**
RRS Reflective	9.3 ± 3.3	12.7 ± 3.1	$t = 3.9$**

Table 1: Demographics and questionnaires.

Demographic details and questionnaire scores for the controls and MDD groups. Values given are group means ± standard deviation. Differences between the groups were compared with independent sample t-tests or chi-squared tests, as appropriate. ** denotes $p < 0.001$.

Psychological scales

All participants completed the Rumination Response Scale (RRS; Treynor et al., 2003) and the Beck Depression Inventory II (BDI; Beck et al., 1996). Total scores for the RRS were calculated, along with Depression-related, Brooding, and Reflective rumination subscores (Treynor et al., 2003). The focus here was on the Brooding and Reflective subscores as these target ruminative behaviours that have less overlap with general depressive symptomatology (Treynor et al.,

2003). Brooding rumination is generally taken to be maladaptive while Reflective rumination is a more positive behaviour (Smith and Alloy, 2009). MDD patients had higher scores than controls in all the scales measured (Table 1B).

EEG acquisition and preprocessing

EEG was recorded with Ag/AgCl electrodes mounted in an elastic cap (Easycap, Brain Products GmbH) using a 28-electrode arrangement following the International 10-20 System, including mono-polar electrodes (FP1/2, F7/8, F3/Z/4, FC3/Z/4/5/6, C3/Z/4, T7/8, CP1/Z/2/5/6, P3/Z/4/7/8, O1/Z/2) and four channels to record vertical and horizontal eye movements. Electrodes to record vertical movements were placed on the supraorbital and infraorbital ridges of the left eye, while those to record horizontal movements were placed on the outer canthi of the right and left eyes. A1 and A2 mastoid electrodes were used as an online reference (averaged across both). Online EEG was recorded with a BrainAmp amplifier (Brain Products GmbH). The data were sampled at 1000 Hz with a bandwidth of DC to 1000 Hz. Data were recorded with BrainVision Recorder 1.2 software.

Participants sat in front of a computer screen with their chins on a chin-rest. During the eye-open session participants fixated a black fixation cross on a gray background. The instructions given to participants were to keep their eyes on the fixation cross, relax, and try to not fall asleep. The procedure during the eyes-closed session was the same but participants were instructed to keep their eyes closed. Eyes-open and eyes-closed data were both recorded for three minutes. The order was counterbalanced across participants. EEG recordings were made at approximately the same time of day for all participants (10-11am).

Data were preprocessed using EEGLAB (sccn.ucsd.edu/eeglab/index.php) and custom scripts running on MATLAB (MathWorks, version 2016b). EEG signals were FIR-filtered (1-45Hz band-pass, Blackman window with 1 Hz transition band) and then ICA was used to exclude eye movement induced artifacts. All signals were visually inspected to exclude any transient artifacts caused by head movements which were manually excluded and omitted from the subsequent analysis. All signals were then re-referenced to the common average.

Detrended fluctuation analysis

DFA analysis was performed with the Neurophysiological Biomarker Toolbox (NBT, nbtwiki.net; Hardstone et al., 2012) toolbox for MATLAB. Preprocessed data were firstly band-pass filtered (FIR-filter) into the theta (4-7 Hz), alpha (8-13 Hz), and beta bands (13-30 Hz). The Hilbert transform was then used to extract the amplitude envelopes in these bands for each electrode. Root-mean-square fluctuations of the integrated and linearly detrended envelope time series were calculated as a function of window size. Time windows corresponded to equally spaced points on a logarithmic scale of data lengths corresponding to 5-14 s for the theta band, 2-14 s for the alpha band, and 1-14 s for beta (50% window overlap). These window sizes were selected to exclude temporal autocorrelations introduced by the band-pass filters (Irrmischer et al., 2018b). The DFA exponent is the slope of the line fitted through the fluctuation amplitudes against window lengths plotted on a logarithmic scale (Hardstone et al., 2012).

Statistical analysis

DFA values during the EC condition were related to RRS scores at each electrode. This was done for the theta, alpha, and beta bands using robust regression, as implemented in the statsmodels python toolbox (statsmodels.org), to reduce the potential impact of outlying values on results. *P*-values were adjusted with Benjamini-Hochberg FDR correction, implemented in statsmodels, to control for multiple comparisons (Benjamini and Hochberg, 1995). A significance level of $p < 0.05$ was used. Electrodes where there was a significant correlation between EC DFA and RRS scores were identified and the mean DFA value across these for each frequency band calculated. These mean values were then submitted to additional analyses.

Firstly, the mean DFA values for each frequency band were entered into a robust regression analysis with the Brooding and Reflective subscales of the RRS. The purpose of this regression analysis was to establish if DFA values correspond with one of these rumination styles specifically. Standardised model beta coefficients and their bootstrapped 95% confidence intervals are reported, along with coefficient *t*-statistics and *p*-values.

DFA values at the significant electrodes were then compared between the EC and EO conditions using robust permutation tests of the difference in medians (5000 samples). Outlying values were excluded with reference to the median absolute deviation to the median, with a cut-off of 2.24 (Wilcox and Rousselet, 2018). This analysis aimed to test the reactivity of the

intrinsic activity properties to the change in state. Following this, the EC and EO DFA values were compared between the control and MDD groups, as were EC-EO difference values. The latter tests aimed to quantify differences in intrinsic activity reactivity between controls and patients. Group medians are reported, along with their difference and its 95% confidence interval.

Finally, EC-EO differences were correlated through robust regression with the Brooding subscale of the RRS (controlling for the Reflective subscale scores) to establish any link between the intrinsic activity reactivity and maladaptive ruminatory behaviours. A correlation was also made with BDI scores to test for a relationship with more general depressive symptoms.

Results

Eyes-closed DFA and rumination

The correlation between DFA during the EC condition and RRS scores was tested across all participants at each electrode. As shown in Figure 1, a negative relationship was found in both the alpha and beta bands. Theta band DFA values were not correlated with RRS scores at any electrode. The correlation in the alpha band was located at a single electrode in the right central region. Correlations with beta band activity were seen at 12 electrodes located along the midline and in occipital regions.

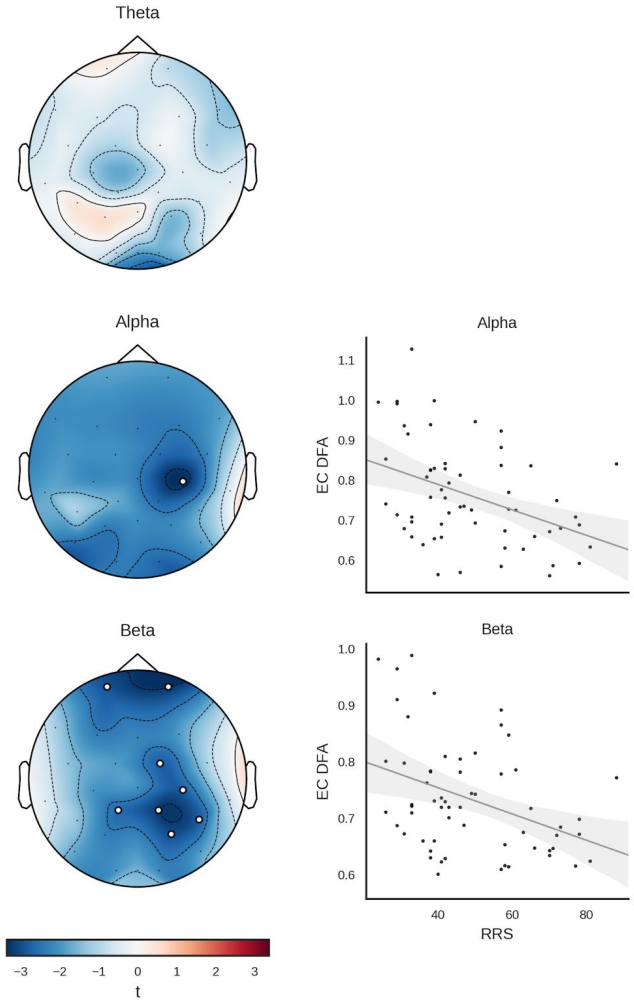

Figure 1: Topographical maps of RRS score correlations.

DFA values in the theta band (top) were not correlated with RRS scores. Negative correlations were found with alpha (middle) and beta (bottom) DFA. Corresponding scatter plots illustrate this correlation for alpha and beta. Mean DFA values across all significant electrodes were calculated and plotted against RRS scores. Significant electrodes after correction for multiple comparisons are indicated in white ($p_{FDR} < 0.05$). Topographic plots were made with the MNE toolbox (Gramfort et al., 2013).

Regression analyses were used to further specify the aspects of rumination that were related to the EC DFA values. DFA values in the alpha band were related to the brooding RRS subscale (β = -0.46, 95% CI = [-0.79 -0.14], t = -2.54, p_{FDR} = 0.022; Figure 2A) but not the reflection subscale (β = -0.09, 95% CI = [-0.27 0.45], t = 0.50, p_{FDR} = 0.62; Figure 2B). The same effect

was seen in the beta band, with a negative relationship between brooding and DFA (β = -0.45, 95% CI = [-0.81 -0.13], t = -2.62, p_{FDR} = 0.018; Figure 2C) but none with reflection (β = 0.14, 95% CI = [-0.22 0.50], t = 0.80, p_{FDR} = 0.42; Figure 2D).

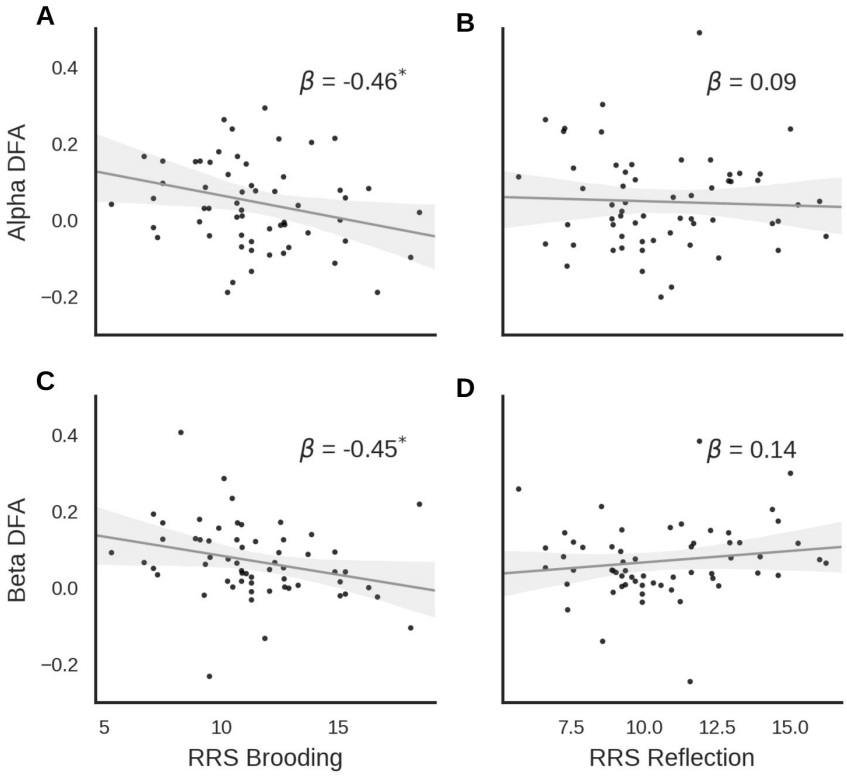

Figure 2: RRS subscales and DFA value correlation.

A negative correlation between mean DFA values and the Brooding subscale of the RRS was seen for both (A) alpha and (B) beta band activity. No relationship was found with the Reflective subscale. Note that values in each plot are adjusted for the effect of the other variable and so the position of specific data points on the different axes may differ. * denotes p < 0.05.

Differences in DFA between conditions and groups

The DFA values in the EC and EO conditions were then compared. Values in both conditions were between 0.5 and 1, indicating that LRTC were present. Across all participants, opening the eyes caused a reduction in DFA at the electrodes associated with RRS scores in the beta band (EC M = 0.72, EO M = 0.65, ΔM = 0.071, 95% CI = [0.03 0.1], p < 0.001) but not in alpha (EC M = 0.74, EO M = 0.68, ΔM = 0.047, 95% CI = [-0.01 0.1], p = 0.054).

Separating out the patient and control groups, DFA values in the alpha band were not found to differ in either the EC (HC M = 0.78, MDD M = 0.69, ΔM = 0.083, 95% CI = [-0.008 0.16], p_{FDR} = 0.054) or the EO (HC M = 0.69, MDD M = 0.67, ΔM = 0.023, 95% CI = [-0.055 0.098], p_{FDR} = 0.28) conditions (Figure 3A). The change in DFA between EC and EO also did not differ between the two groups (HC M = 0.07, MDD M = 0.02, ΔM = 0.05, 95% CI = [0.009 0.11], p_{FDR} = 0.054; Figure 3B).

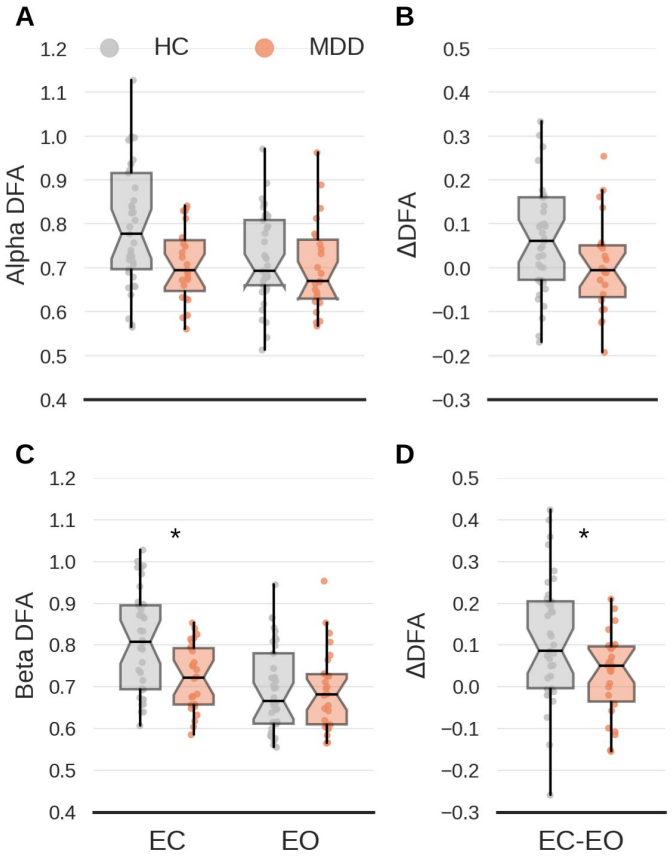

Figure 3: DFA changes between EC and EO.

DFA values were compared between groups for the EC and EO condition in (A) the alpha and (C) the beta bands. A significant difference was seen in the beta band for the EC condition only. DFA differences for each band were also compared (B&D). Beta band EC-EO differences were significantly higher in controls than in MDD. * denotes $p_{FDR} < 0.05$.

Within the beta band, controls showed higher DFA values than MDD in the EC (HC M = 0.74, MDD M = 0.68, ΔM = 0.061, 95% CI = [0.004 0.13], p_{FDR} = 0.024) but not EO conditions (HC M = 0.67, MDD M = 0.63, ΔM = 0.036, 95% CI = [-0.029 0.052], p_{FDR} = 0.112; Figure 3C). Controls

showed a larger change in DFA between EC and EO than did MDD (HC M = 0.07, MDD M = 0.02, ΔM = 0.05, 95% CI = [0.009 0.11], p_{FDR} = 0.024; Figure 3D). The EC-EO difference was significantly different from zero for the controls (p_{FDR} < 0.001) but not for MDD (p_{FDR} = 0.062).

EC-EO differences and depressive symptoms

Changes in DFA between EC and EO were related to reported rumination and depressive symptoms. The difference in DFA between EC and EO in the alpha band was not related to either the Brooding (β = -0.31, 95% CI = [-0.62 -0.03], t = -1.84, p_{FDR} = 0.13; Figure 4A) or the Reflective (β = -0.05, 95% CI = [-0.38 0.27], t = -0.29, p_{FDR} = 0.77) RRS subscales. The EC-EO difference was, however, negatively related to BDI scores (β = -0.39, 95% CI = [-0.57 -0.22], t = -3.72, p < 0.001; Figure 4B).

A negative relationship was found in the beta band between the EC-EO DFA difference and the Brooding RRS subscale (β = -0.45, 95% CI = [-0.73 -0.07], t = -3.16, p_{FDR} = 0.004; Figure 4C), with no effect found for the Reflective subscale (β = 0.21, 95% CI = [-0.08 0.53], t = 1.45, p_{FDR} = 0.15). A negative relationship was also seen between the EC-EO difference and BDI scores (β = -0.35, 95% CI = [-0.56 -0.12], t = -3.43, p = 0.001; Figure 4D).

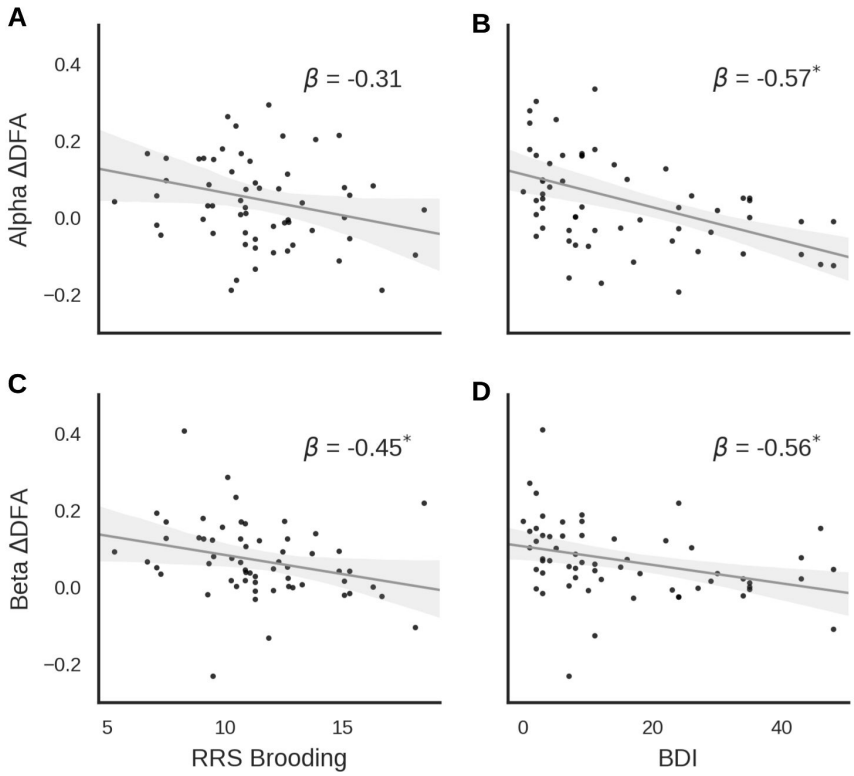

Figure 4: EC-EO differences and questionnaire scores.

A negative correlation between EC-EO DFA changes and the Brooding subscale of the RRS was seen for (B) the beta but not (A) the alpha bands. EC-EO changes in both frequency bands were negatively correlated with BDI scores (B&D). Note that values in the RRS Brooding plots are adjusted for RRS Reflective scores and so the position of specific data points on the different axes may differ. * denotes $p < 0.05$.

Discussion

Detrended fluctuation analysis was used to quantify long-range temporal correlations within EEG activity recorded at rest with the eyes open and closed. These DFA values were then related to reported ruminative and depressive behaviours in a group of healthy controls and patients with MDD. It was found that DFA values for alpha and beta band activity during eyes closed were correlated with brooding, and not reflective, rumination at a subset of electrodes. DFA values at these electrodes were then found to reduce when the eyes were opened. This DFA change between eyes closed and open was smaller for MDD patients, with the size of the

LRTC change also correlated with brooding rumination and with depressive symptoms more generally.

The negative correlation between EC alpha DFA exponents and rumination seen here is consistent with previous work reporting similar correlations with alpha DFA at frontal and central electrodes (Bornas et al., 2015, 2013; Putnam and McSweeney, 2008). A correlation with beta DFA at midline electrodes was also seen in the current work. The relationship between beta LRTC and rumination has not been tested previously but oscillatory power in this band has been found to be related in a similar manner (Ferdek et al., 2016). Importantly, the observed correlations were specific to Brooding rumination scores and not Reflective. Reductions in LRTC within alpha and beta bands thus appear to be related to maladaptive ruminative responses and not to an increase in self-reflective thought in general.

Beta DFA values were found to be higher in controls than in patients during the EC condition. Changes in beta band EEG activity in general have been seen consistently in MDD studies (Newson and Thiagarajan, 2019). A number of studies have also reported changes in EC LRTC specifically. These have described reductions in beta band DFA exponents, along with changes in theta and broadband activity (Lee et al., 2007; Linkenkaer-Hansen et al., 2005). The reduction in beta LRTC seen in MDD is also seen in other disorders, including Alzheimer's (Montez et al., 2009) and schizophrenia (Nikulin et al., 2012), although with different spatial distributions. Altered activity dynamics are also seen in Parkinson's disease (Hohlefeld et al., 2012), epilepsy (Monto et al., 2007), and autism (Lai et al., 2010). This suggests that a disruption to the temporal structure of brain activity may be a common feature of pathological conditions (Hardstone et al., 2012), with symptomatic variation arising from the specific brain networks and frequency ranges within which such changes occur (Northoff and Duncan, 2016).

Opening the eyes produced a reduction in beta DFA values in healthy participants. The higher DFA values in the EC state are likely to reflect brain activity operating near criticality, where information handling and capacity to respond to varied inputs are optimised (Gautam et al., 2015; Hahn et al., 2017; Shew et al., 2011). In contrast, the lower DFA values in the EO state may reflect a system operating closer to sub-critical levels, meaning that activity has less temporal complexity and can dwell more consistently close to a particular configuration (Irrmischer et al., 2018b). Unlike the control group, MDD patients did not show a change in beta

band DFA values between EC and EO. Instead, values were constant at EO levels in both conditions. The degree of change in DFA between EC and EO was correlated with rumination, such that those with more fixed DFA values reported more ruminative behaviours. This was specific to Brooding, and not Reflective, rumination. Reduced changes in alpha DFA were not correlated with rumination but were related to general depressive symptoms.

Similar to opening the eyes, a reduction in LRTC can also seen when people engage in a particular task, as compared to a task-free state (He, 2011; Irrmischer et al., 2018b, 2018a). This might suggest that those with more rumination remain attentive to specific thoughts consistently, meaning that the switch from a sub-critical state in the EO condition to a one closer to criticality in EC does not happen. An analogous inability to switch between attentional targets has been reported previously, providing some support for this position (Apazoglou et al., 2019; Lo et al., 2012). On the other hand, increased so-called task-negative network activity, compared to task-positive, appears to be a consistent finding in depression studies (Hamilton et al., 2011; Knyazev et al., 2016) that has been related to ruminative symptoms (Hamilton et al., 2011). The potential inconsistency between these explanations may point to a need for additional research into the neural impact of the EO/EC switch in order to understand how it interacts with additional cognitive loads and with the directing of internal or external attention, as well as on the task positive/negative network construct (Murphy et al., 2019).

The lack of flexibility in neural temporal structure demonstrated by the lack of EC-EO difference in MDD is likely to be related to an overall cognitive inflexibility that influences performance in other domains. Rumination has been associated with poor performance in a number of contexts, including problem-solving (Donaldson and Lam, 2004), attentional control (Lyubomirsky et al., 2003), and memory tasks (Liu et al., 2017). This cognitive inflexibility has important clinical implications as it acts as a risk factor for developing depression and is related to suicide (Miranda et al., 2012) in a manner that is mediated by brooding (Miranda et al., 2013). Interventions that improve capacity in this area, such as exercise (Wu et al., 2019), may therefore be key tools for both prevention and treatment of depression.

Evidence suggests that a critical state emerges from a balance of neuronal inhibition and excitation (Beggs and Plenz, 2003; Gireesh and Plenz, 2008; Poil et al., 2012). The GABA and glutamate systems, the primary inhibitory and excitatory transmitters in the brain, have been

shown to be altered in MDD (Godfrey et al., 2018; Voineskos et al., 2019). As well as this, neuromodulators such as serotonin and dopamine, which influence neural excitability, are known to be affected in MDD (Belujon and Grace, 2017; Morrissette and Stahl, 2014) and to play a role in cortical activity changes between EC and EO conditions (Wan et al., 2019). It thus seems possible that the reported changes in cortical dynamic reactivity are related to changes in these systems (Hu et al., 2019; Ramirez-Mahaluf et al., 2017; Wiebking et al., 2014). This could further imply a mechanistic explanation for maladaptive rumination in some people, whereby altered neural tone makes transitions between attractor states more difficult (Ramirez-Mahaluf et al., 2017). Further research into the link between cortical dynamics and specific neurotransmitters is merited to investigate this possibility further.

A number of limitations of this work must be noted. Firstly, although the sample size used was relatively large (n = 60), it will be important to replicate the results in an independent sample in the future. Secondly, the majority of the MDD patients who took part were medicated with drugs targeting a variety of neurotransmitter systems. Given the variability in systems targeted, it is unlikely that the relationship found between behaviour and EEG properties across the full patient plus control dataset are driven by medication effects but this cannot be ruled out and so studies on unmedicated patients would be justified. This would be particularly important when testing particular models of neurotransmitter changes that may be driving ruminative behaviours. Finally, it would be of interest in future to record longer periods of rest than used here to analyse potential dynamic shifts in LRTCs over time.

To conclude, DFA was used to quantify LRTC in neural activity during rest with the eyes open and closed in a group of healthy participants and patients with MDD. Rumination and depressive symptoms were related to an inability to shift between a critical and sub-critical state between the EC and EO state, with those with more symptoms remaining in a state with lower DFA values. This may reflect a general cognitive inflexibility resulting from a lack in neural activity reactivity.

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