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Inflexibly sustained negative affect and rumination independently link default mode network efficiency to subclinical depressive symptoms

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ABSTRACT

Aberrant DMN connectivity and activity have been robustly linked to Major Depressive Disorder (MDD) and risk for depression. This link has mostly been explained in terms of rumination, a form of negative, repetitive cognitive processing. Yet, accumulating findings are indicating altered DMN dynamics during emotional processing in MDD, pointing at a potential emotion-related DMN pathology in depression linked to inflexibly sustained emotional responses. Such a link might be especially important in understanding risk of depression. However, whether inflexible emotional processing (i.e. emotional inertia) is connecting aberrant DMN organization to risk of depression as well as how this might relate to rumination remains unclear. Addressing this gap, 34 participants underwent a resting-state fMRI and a 7-day Experience Sampling phase. Using regression and multiple mediation analysis we investigated the relations between negative emotional inertia, rumination, DMN organization and risk of depression as indicated by high subclinical depressive symptoms. The findings indicated that DMN efficiency at rest was positively associated with depressive symptoms and risk of depression. Both negative emotional inertia in daily life and rumination were independently mediating this relationship. While negative emotional inertia was connected to a broad increase in the coupling of DMN regions, rumination was only related to an increase in node strength of the dorsomedial Prefrontal Cortex. These findings are pointing towards an emotional-related DMN pathology contributing to risk of depression. Furthermore the findings are indicating that this relationship is independent from the rumination-related link between the DMN and depression - representing different aspects of DMN organization.

1. Introduction

Major Depressive Disorder (MDD) is a high prevalence affective disorder characterized by persistent negative mood and/or anhedonia *complemented with* additional emotional, somatic and cognitive symptoms (APA, 2013; Gotlib and Joorman, 2010). The World Health Organization estimates that over 350 million people are affected by depression and that it is one of the leading causes for disability worldwide (WHO, 2012). Understanding the biological basis of vulnerability to and pathogenesis of depression is of key importance to develop more effective treatment and lower the burden of this disorder.

In this line of research, alterations of the organization of the Default Mode Network (DMN) have received considerable attention as a possible central factor in the pathogenesis of MDD. Indeed, there is accumulating evidence of such alterations being robustly associated with depressive symptoms (Kaiser et al.,2015) as well as risk for depression (Posner et al., 2016). These results are especially interesting given the role of the DMN in task-independent self-referential processes with an internal focus of attention (Raichel et al., 2001), like mind-wandering and self-generated thought (Andrew-Hanna et al., 2014), offering a window into understanding the alteration of spontaneous and intrinsic processes in MDD. Accordingly, in particular rumination, usually defined as passive, self-referential, repetitive patterns of negative thought (Nolen--Hoeksema et al., 2008) and considered a stable marker for MDD and depression risk (McLaughlin and Nolen-Hoeksema, 2011; Spasojevic and Alloy, 2001), has been consistently linked to aberrant DMN activity (Hamilton et al., 2011) as well as connectivity (Berman et al., 2011; Zhu et al., 2017; Nejad et al., 2013) and is considered to provide a key

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pathway connecting DMN-related dysfunction to MDD.

Yet, besides the internal, negative self-referential cognitive processing involved in rumination, there are indications that changes of DMN organization observed in depression might also be involved in how people process external emotional information, pointing to a potential emotional pathway of how DMN alterations may contribute to depression. In particular, reduced suppression of DMN activity and connectivity - especially including the midline DMN hub regions - during emotional processing have robustly been described in MDD (Ho et al., 2015; Grimm et al., 2009; Sheline et al., 2009; Grimm et al., 2011) as well as associated to depression severity (Grimm et al., 2009). Given the important role of DMN deactivation in goal-directed cognition as well as processing the external world (Anticevic et al., 2012), these findings could reflect inflexibly increased allocation of resources to internal processing, coming at the cost of flexibly processing, and thus responding to the external environment (Greicus and Menon, 2004; Smallwood et al., 2008; Anticevic et al., 2010). In other words, inflexibly elevated activity and connectivity of the DMN might go hand in hand with inflexible emotional responding to outside events, contributing to the altered emotional processing connected to depression.

Such inflexible emotional responding in MDD has also been observed in daily life emotion dynamics - in particular in the form of an increased autocorrelation of negative emotional experience, labeled emotional inertia. This increased autocorrelation captures the extent to which one's emotional state can be predicted by one's previous emotional state (Houben et al., 2015), and reflects the extent to which emotional states are self-predictive versus flexibly responding to outside events. Besides depressive severity (Koval et al., 2012), inertia of negative emotions has been associated to genetic risk markers of depression (Van Roekel et al., 2018) as well as shown to be predictive of the onset of depressive episodes (Kuppens et al., 2012), pointing to an important role in risk of depression. Most interestingly, emotional inertia has been found to contribute to depression independently from rumination (Brose et al., 2015; Koval et al., 2012).

Alterations in both emotional inertia as well as rumination might therefore be representing two independent pathways of how alterations of the DMN could contribute to depressive symptoms and risk of depression. However, while most research so far has focused on the role of rumination linking DMN alterations to depression, as far as we know, no research has examined how organizational changes of the DMN at rest might contribute to depressive symptoms by altering emotional processing.

Accordingly the current study has three main goals. The first goal is to replicate previous research, showing a relation between DMN organization at rest and depressive risk indicated by a high level of subclinical depressive symptoms. The second goal is to test if rumination and emotional inertia are capable of independently explaining (e.g. mediating) the observed link between DMN-organization and depressive symptoms using multiple mediation analysis. Importantly, when examining these relations, we will in addition control for participant's average levels and variability in negative affect, to verify whether relations with inertia go beyond relations with simpler measures of emotion (cfr, Dejonckheere, et al, 2019). Finally the third goal is to identify the specific DMN regions involved by investigating similarities and differences in the regional pattern of DMN changes related to rumination and emotional inertia as well as their relationship to depression.

To address these goals, 34 participants underwent a resting-state fMRI session, were assessed with questionnaires measuring subclinical depressive symptoms and rumination, and participated in an experience sampling (ESM) phase, in which they indicated their emotional states several times a day over seven days during normal daily life and from which we derived their level of emotional inertia. We focused on subclinical symptoms in a normal sample, since understanding the targeted relationships may be especially important for the development and risk of MDD (see also Koval et al., 2012; Dejonckheere et al., 2018 for a similar approach). Furthermore choosing a non-clinical sample might reduce the risk of illness-related confounds on measuring emotion dynamics in daily life due to strong differences in environmental factors.

Regarding predictions we expect that increased DMN integration, as indicated by network efficiency, is positively related to subclinical depressive symptoms as well as increased in a subgroup with high levels of depressive symptoms pointing to high risk of developing MDD (aim 1). Furthermore we expect emotional inertia and rumination to represent two independent mediators of this relationship (aim 2). Investigating the association of emotional inertia and rumination to differences in the node strengths (Fornito et al., 2016) (i.e. the sum of all connection weights) of single DMN regions (aim 3), we expect to find differences in the pattern of associations across DMN regions. More specifically, we expect emotional inertia to be connected to a more global increase in node strength over all DMN-regions especially involving the major DMN hub regions (i.e. Anticevic et al., 2012; Greicus and Menon, 2004; Smallwood et al., 2008), indicating a general increase in the allocation of resources to internal and environment-independent processes. In contrast we expect rumination, in line with previous results, to be associated to alterations of the node-strength of specific regions, specifically involving the subgenual Anterior Cingulate Cortex (sgACC; Hamilton et al., 2015) and dorsomedial Prefrontal Cortex (dmPFC; Zhu et al., 2017), potentially indicating specific changes of DMN-related processes such as the abnormal self-focus (as proposed for the dmPFC; Zhu et al., 2017; Sheline et al., 2010) or stronger involvement of negative affect (as proposed for the sgACC; Hamilton et al., 2015).

2. Methods and materials

2.1. Participants

Using online advertisements and flyers, a participant pool of 287 subjects was recruited and asked to fill out an online screening questionnaire. Based on this screening questionnaire, 38 participants were selected based on suitability to undergo an fMRI-scan and additional study specific exclusion criteria including no color blindness, no history of psychiatric or neurological disorders, and right handedness (for a complete list of exclusion criteria see Supplementary Material 4). Since the specific recruitment led to a primary participant pool heavily skewed to younger ages with only very few potential participants beyond the age of 35 we introduced an age limit of 35 in order to prevent outliers in our analysis. The selection process was further guided to achieve an approximately uniform distribution of scores on the BFI-2 neuroticism scale (Soto and John, 2017). This procedure ensured that the sample of participants represented a sufficiently wide range of trait differences of emotional experience in the population (see also Koval et al., 2013; Dejonckheere et al., 2018 for a similar approach). To achieve this, the original participant pool was divided into five groups, representing five distinct sections of neuroticism scores (very low [< 2], low [2-2.5], middle [2.5-3], high [3-3.5], very high [>3.5]). An approximately equal number of participants from every section were invited to participate in the study. Thirty-eight participants participated in the fMRI part of the study but only 36 completed the subsequent ESM part. Additionally one participant had to be excluded from the analysis because of a critical life event between the fMRI part and the ESM part of the study and another participant had to be excluded because of registration problems during MRI preprocessing.

The final sample consisted of 34 (20 female) participants between 18 and 33 years of age (M = 24.06). All subjects gave written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee Research UZ / KU Leuven (S59871).

2.2. Measures

2.2.1. Brain Imaging

In the first part of the study, participants underwent a 10 min resting

state session inside the fMRI-scanner. For this period they were presented with a black screen and a white fixation cross and instructed to relax but to try not to fall asleep and keep their eyes open.

Scanning Protocol. All scans were acquired with a 3 T MRI-Scanner (Philips Medical Systems). For all functional scans T2*-weighted multiband sequences containing 40 slices (TR/TE=1200/30ms, voxel-size =2.7 × 2.7 × 3mm,FOV = 216 × 120 × 216) were acquired. High-resolution T1-weighted structural images were acquired containing 184 slices (TR/TE = 9.75/4.6 ms, voxel-size 1 × 1 × 1mm,FOV = 256 × 256 × 184).

Preprocessing. Preprocessing of the structural MRI data including intensity normalization, removal of non-brain tissue as well as calculating ventricle and white matter tissue masks was performed with Freesurfer (http://surfer.nmr.mgh.harvard.edu) (Fischl, 2012; Fischl et al., 2002). Preprocessing of the resting state sessions was performed using AFNI (http://afni.nimh.nih.gov/afni) (Cox, 2012) using standard procedures, including de-spiking, co-registration, normalization to MNI-space (MNI152 template) as well as smoothing using a 6-mm full-width half-maximum Gaussian kernel. Additionally images were band-passed filtered (0.008 – 0.15) and censored (euclidean norm > 0.3, outlier > 0.1). No subject reached the pre-defined cut-off for exclusion of 30% censored TRs. Motion parameters as well as tissue based regressors (ANATICOR; Jo et al., 2010), estimated from Freesurfer ventricles as well as white matter masks, were regressed out of the fMRI-time series.

Network Measures. DMN organizational changes at rest are obtained with the graph-theoretical measurement of network efficiency, being defined as the inverse of the sum of the shortest paths of a network (Fornito et al., 2016), indicating the efficiency of information exchange within a network and having been linked to the metabolic state of a network (Bullmore and Spoorns, 2012). Network Nodes were defined as 5-mm radius spheres around 12 pre-defined Default Mode Network regions (Fox et al., 2005; see Supplementary Table S1). For every subject the mean time-series of the voxels within every ROI-sphere was extracted and used to construct a 12 × 12 matrix. A general threshold of r = 0.25 (see Supplementary Figure S1 for a depiction of the stability of effect sizes over different thresholds and Supplementary Figure S2 for a depiction of the effects for proportional thresholds) was applied to all matrices to account for noise as well as to remove all negative correlations. DMN network efficiency (Latora and Marchiori, 2001, E_{DMN}), defined as the inverse of the sum of shortest paths (as implemented in the Brain Connectivity Toolbox, Rubinov and Spoorns, 2010), was calculated for each participant.

To obtain a more detailed understanding of regional DMN changes, additionally the node strength of each region (Fornito et al., 2016), i.e. the sum of all weights of each node within the DMN-network or, in other words, the sum of each z-transformed correlation of each region with all other regions of the DMN, was calculated for each participant using customized R-scripts (http://www.R-project.org). Additionally, to test a possible relationship between the sgACC and the DMN in relation to rumination, the node strength of an sgACC ROI (5-mm sphere) (Hamilton et al., 2015, see Supplementary Table S1) was calculated..

Furthermore - in order to explore if node degree changes of DMN regions were specific in regard to other DMN regions or of a more global nature – we investigated the node the degree changes of four additional control regions with DMN regions. None of these regions showed any significant change in node degree related to NA-inertia or rumination (see Supplementary Material 2).

2.3. Behavioral measures

Questionnaires. Subclinical depression symptoms were measured with the 20-item Center for Epidemiologic Studies Depression scale (CES-D; Redloff, 1977). Rumination was measured with the Rumination Responses Scale (RRS) (Treynor et al., 2003). I In order to make sure that the relation of rumination and depressive symptoms are not driven by similarity of the items in the RRS to items measuring depressive symptoms we used the 10 item version of the RRS (as proposed in Treynor et al., 2003), that has been constructed not to contain items similar to depression scales (see also Whitmer and Gotlib, 2011).

Daily Life Emotion Measurements (ESM). In the second part of the study (ESM-part) participants were given a research dedicated smartphone that was programmed to beep and present the participant with a short experience sampling questionnaire 10 times a day for 7 days. Beeps were programmed according to a stratified random interval scheme: The studied time of each day (between 10AM and 10PM) was divided into 10 equal intervals and a random beep was scheduled in each interval, resulting in participants being beeped on average every 72 minutes. This is consistent with previous ESM studies we and others have conducted (e.g. Brans et al., 2013; Pe et al., 2013). The questionnaire did not take more than a few minutes to complete. At each beep, current negative emotional experience was assessed by 4 negative (Stressed, Anxious, Angry, Sad) emotion-items in which participants had to indicate the extent to which they were currently experiencing the specific emotion on a sliding scale reaching from 0 [not at all] to 100 [very much]. The ESM questionnaire additionally included four positive affect items that were assessed in the same fashion but are were not included in the analyses of the present study (see Supplementary Material 3 for further information). Based on these items a momentary negative affect score (NA) was calculated for each subject at each time point by averaging across items, which was subsequently used for calculating person-levels scores of average NA and inertia of NA (see Supplementary Information Text for a more detailed description of the model).

2.4. Analysis

2.4.1. Aim 1: E_{DMN} and depression

To replicate the documented link between DMN organization and depressive symptoms we analyzed this relationship using multiple regression analysis in R with the CESD sum-score as dependent and E_{DMN} as independent variable. As additional information, we also investigated differences of DMN efficiency between a high risk group of developing MDD, defined by high levels of subclinical depressive symptoms (CESD > 16, see Redloff, 1977), and a lower risk group (CESD < 16). While individual differences in depression are more likely dimensional than categorical in nature (see, Haslam, et al., 2020; and see Vilagut et al., 2016 for criticism on the approach used here), it may be of interest to see the robustness of our findings in a categorical prediction according to a previously established and often used criterion. Age and gender were introduced into the model as variables of no interest.

2.4.2. Aim 2: NA-inertia and rumination as mediators of the relationship between E_{DMN} and depression

Emotional Inertia. As a next step we analyzed the relations between DMN Efficiency (E_{DMN}), subclinical depressive symptoms as well as risk for depression (as defined by a high level of subclinical depressive symptoms) and emotional inertia (autocorrelation) of negative affect in daily life using random-intercept random-slope multilevel models (nlme-package; Pinhero et al., 2018). In these models inertia was defined as the autoregressive effect between a negative affect (NA) score at time t and the subsequent NA-score at time t+1 (for a detailed description of the model see Supplementary Material 2). By means of cross-level interactions in the model, we then modeled how this autoregressive effect was a function of E_{EDM}, depressive symptoms, risk of depression and rumination (i.e. how those trait differences are associated with the relation between negative affect at a specific time-point with negative affect at the subsequent time-point). The second level variables of age, gender, the average negative affect score and the standard deviation of negative affect as well as the cross-level interaction effects of average negative affect and SD of negative affect with negative affect were introduced in all models as nuisance variables of no interest (cfr. Dejonckheere, et al., 2019). All between subject variables were grand-mean centered (for the relation between Inertia of single

negative affect Items and E_{DMN} see Supplementary Figure S3; for further information on the impact controlling for average negative affect as well as SD of negative affect on the relation of NA inertia and E_{DMN} see Supplementary Table S2; for the relationships between positive affect inertia and E_{DMN} as well as subclinical depressive symptoms and rumination see Supplementary Material 3).

Rumination. We investigated the relations between rumination and E_{DMN} as well as depressive symptoms by estimating multiple regression models in R in which rumination - along with gender and age as variables of no interest - acted as predictor for E_{DMN} and depressive symptoms. As additional information we further estimated a model on group differences in rumination between a high risk and lower risk group for depression. In the supplement we are also reporting the results of analyzing the Reflection and Brooding subscales of the Ruminative Response Scale individually (see Supplementary Table S3).

Multiple Mediation Analysis. We then tested for the existence of independent links between E_{DMN} to depressive symptoms over rumination and NA-inertia by fitting a multiple mediation model in R (lavaan-package; Rosseel, 2012), allowing to estimate separate indirect effects with NA-inertia and rumination as mediators in the same model, controlling for their possible shared effects (see Vander Weele and Vansteelandt, 2014). In addition to the covariance of the two mediators, the direct effect between E_{DMN} and subclinical depressive symptoms as well as the total effect are fitted within the model (also see figure 1).

2.4.3. Aim 3: Node Strength of DMN regions in relation NA-Inertia and Rumination

Further investigating the regional pattern of changes within the DMN connected to NA-inertia as well as rumination, for every region of the DMN two regression models including the node strength of this region as dependent and either NA-inertia or rumination as independent variable were estimated. Age and gender were additionally introduced into the models as variables of no interest. To control for multiple testing the resulting p-values are corrected using family-wise error correction (Holm-Bonferroni method; Holm, 1979). For rumination, an additional model on the node strength of the sgACC was estimated.

3.3. . Results

3.1. Behavioral measures

The participants showed a mean CES-D score of 12.03 (SD = 9.70) with 8 Subjects being at high risk of depression, defined as a CES-D score above 16 (Redloff, 1977). The mean Neuroticism score was 2.65 (SD = 0.77) and the mean rumination score was 18.17 (SD = 0.77).

Regarding the ESM measurements the mean negative affect score was 10.74 (SD = 7.41) and mean NA -inertia score was 0.36 (SD = 0.14). All measurements, including CES-D (r = 0.59, t(33) = 4.23, $p < 0.001$), inertia (r = 0.44, t(33) = 2.79, $p = 0.008$) as well as rumination (r = 0.51, t(33) = 3.39, $p = 0.002$) were positively correlated with neuroticism.

3.2. Aim 1: E_{DMN} and depression

DMN efficiency (E_{DMN}) was positively associated with subclinical depressive symptoms (β = 2.04 (0.84), t (30) = 2.44, $p = 0.02$, CI95% [0.34; 3.75]) as well as increased in a subgroup with high severity of subclinical depressive symptoms (CESD > 16, see Redloff, 1977) indicating high risk for clinical depression (β = 0.10 (0.04), t(30) = 2.58, $p = 0.02$, CI95% [0.02; 0.18]).

3.3. Aim 2: NA inertia and rumination as mediators of E_{DMN} and depression

NA Inertia. The relationship (i.e. autoregressive effect or inertia) between NA-scores with NA-scores at the preceding time-point significantly increased with increasing subclinical depressive symptoms (β =0.15 (0.07), t (1809) = = 2.15, $p = 0.03$, CI95% [0.11; 1.29]) as well as increasing E_{DMN} (β =0.92 (0.33), t (1809) = 2.84, $p = 0.005$, CI95% [0.28; 1.57]) and was higher in subjects at high risk for depression (β =0.18 (0.07), t (1809) = 2.72, $p = 0.01$, CI95% [0.05; 0.31]). In contrast there was no significant relationship with rumination (β = -0.01 (0.08), t (1809) = -0.06, $p = 0.989$, CI95% [-0.16;0.15]). As such higher levels of negative emotional inertia were related to both increased DMN efficiency and depressive symptoms but not to increased levels of rumination.

Rumination. Rumination was significantly positively associated with subclinical depressive symptoms (β =0.62 (0.15), t (30) = 4.11, $p < 0.001$, CI95% [0.31; 0.93]) as well as E_{DMN} (β =0.10 (0.03), t (30) = 2.95, $p = 0.006$, CI95% [0.03; 0.17]) (see Fig. 1) and significantly higher in group at risk of depression (as defined by strong subclinical depressive symptoms; β = 0.49 (0.18), t(30) = 2.70, $p = 0.01$, CI95% [0.12;0.86]). Results of additional analyses considering the Reflection and Brooding subscales of the Ruminative Response Scale individually can be found in Supplementary Table S3.

Multiple Mediation Analysis. The effect between E_{DMN} and depressive symptoms (c: β = 2.17 (0.79), t(30) = 2.74, $p = 0.01$, $CI_{95\%}$ [0.56; 3.79]) was fully mediated (c': β = -0.33 (0.85), z = -0.38, p =

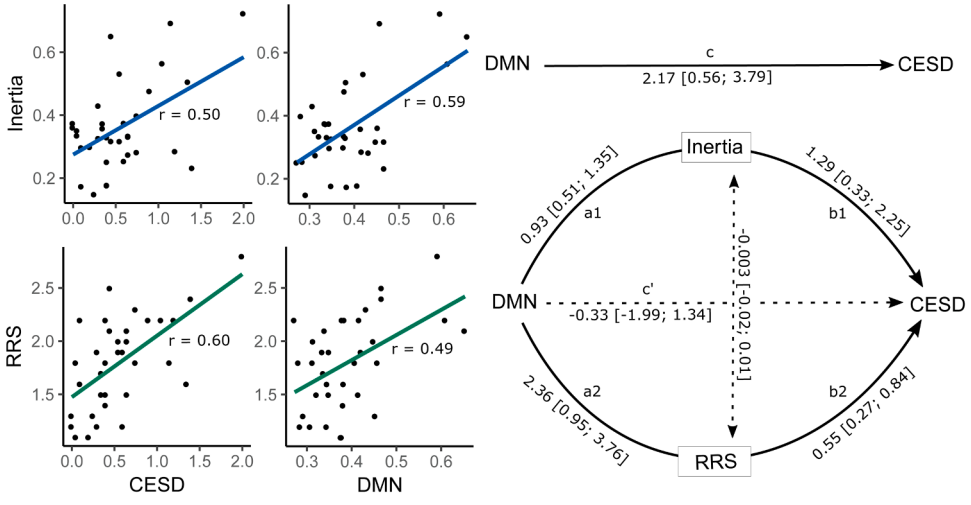

Fig. 1. Relation of NA-Inertia and rumination to DMN Efficiency and subclinical depressive symptoms. On the left panel (A) the relationships between NA-Inertia (Inertia) and rumination (RRS) as well as subclinical depressive symptoms (CESD) and DMN Efficiency (E_{DMN}) are presented. Additionally, simple correlation effect sizes have been added to the graph. On the right panel (B) a schematic depiction of the multiple mediation analysis is shown including the relation between E_{DMN} and subclinical depressive symptoms (c) as well as their estimated relation controlling for the indirect effects over NA-Inertia and rumination (c'). Additionally, the indirect effect from E_{DMN} over NA-Inertia (a1) to subclinical depressive symptoms (b1) as well as the relationship from E_{DMN} and rumination (RRS) (a2) to subclinical depressive symptoms (b2) are shown. Finally the covariance between Inertia and RRS, as estimated within the model, is depicted as an arrow between those two variables.

0.70, $CI_{95\%}$ [-1.99; 1.33]) by the indirect effects over NA-inertia (β = 1.20 (0.53), z = 2.25, $p = 0.024$, $CI_{95\%}$ [0.15; 2.24]) as well as rumination (β = 1.30 (0.53), z = 2.48, $p = 0.013$, $CI_{95\%}$ [0.27; 2.33]) while there was no significant covariation between the mediators (i.e. NA-inertia and rumination) (β = -0.003 (0.007), z = -0.39, $p = 0.700$, $CI_{95\%}$ [-0.02; 0.01]) (see also Fig. 1). This confirms that both emotional inertia and rumination uniquely contribute to explaining the link between DMN efficiency and depressive symptoms.

3.4. Aim 3: Node Strength of DMN regions in relation to NA-Inertia and rumination

NA-inertia in daily life was significantly associated to increases in node strength of the Posterior Cingulate Cortex (PCC; β = 0.49 (0.16), t(30) = 3.01, $p = 0.005$, $p_{FWE} = 0.044$, $CI_{95\%}$ [0.16; 0.82]) and medial Prefrontal Cortex (mPFC; β = 0.51 (0.15), t(30) = 3.52, $p = 0.001$, $p_{FWE} = 0.016$, $CI_{95\%}$ [0.21; 0.81]). Additionally, there were significant positive relationships between NA-inertia and the node strength in the left Superior Frontal Gyrus (SFG; β = 0.57 (0.15), t(30) = 3.69, $p < 0.001$, $p_{FWE} = 0.011$, $CI_{95\%}$ [0.25; 0.87]), left Inferior Temporal Lobe (ITL; β = 0.52 (0.16), t(30) = 3.22, $p = 0.003$, $p_{FWE} = 0.031$, $CI_{95\%}$ [0.19; 0.85]), right Parahippocampal Gyrus (PHG; β = 0.46 (0.15), t(30) = 3.03, $p = 0.005$, $p_{FWE} = 0.045$, $CI_{95\%}$ [0.14; 0.77]) as well as a trend-wise significant increase in the Retrosplenial Cortex (RSC; β = 0.44 (0.17), t(30) = 2.59, $p = 0.015$, $p_{FWE} = 0.088$, CI95% [0.09; 0.78]), left Lateral Parietal Cortex (LPC; β = 0.41 (0.17), t(30) = 2.41, $p = 0.022$, $p_{FWE} = 0.091$, CI95% [0.06; 0.76]), dorsomedial Prefrontal Cortex (dmPFC; β = 0.45 (0.16), t(30) = 2.77, $p = 0.008$, $p_{FWE} = 0.058$, $CI_{95\%}$ [0.12; 0.77]), right Superior Frontal Gyrus (SFG; β = 0.41 (0.16), t(30) = 2.50, $p = 0.018$, $p_{FWE} = 0.090$, CI95% [0.08; 0.75]) and the right Inferior Temporal Lobe (ITL; β = 0.40 (0.17), t(30) = 2.31, $p = 0.028$, $p_{FWE} = 0.091$, CI95% [0.05; 0.75]) .

Rumination was only a significantly related with the node-strength of the dmPFC (β = 0.54 (0.15), t(30) = 3.73, $p < 0.001$, $p_{FWE} = 0.009$, $CI_{95\%}$ [0.25; 0.84]) (all other $p_{FWE} > 0.14$) (see Fig. 2). An additional analysis including the sgACC did not show a significant relationship between the node strength of the sgACC and rumination (β = 0.23 (0.17), t(30) = 1.33, $p = .19$, CI95% [-0.12; 0.57]). The p-values corrected for multiple comparisons using family-wise error correction (Holm-Bonferroni method; Holm, 1979) are reported as p_{FWE}, the uncorrected p-values are reported – as additional information – as p.

4. Discussion

In the current study we investigated whether inflexible sustained emotional responding in terms of negative emotional inertia may provide an additional pathway linking DMN dysfunction to subclinical depressive symptoms and risk of depression.

In line with our hypothesis we showed that negative affect inertia (NA-inertia) was associated to increased DMN efficiency (E_{DMN}) and subclinical depressive symptoms, and that NA-inertia acted as a mediator linking E_{DMN} to subclinical depressive symptoms. Importantly, this mediation was found to be independent of rumination, which was also found to act as a mediator of this relation. As such, our results point to two independent pathways how DMN alterations can contribute to depressive symptoms: Aside from repetitive, inflexible internal cognitive processing, also inflexible emotional responding to the outside world (as measured in people's real lives) is linked to altered DMN organization and explains its relationship with depression.

Independently mediating the relationship between E_{DMN} and depressive symptoms might also point to emotional inertia and rumination representing different DMN-related processes. As discussed before, given the findings of inflexible elevated DMN connectivity and activity during emotional processing in MDD (Ho et al., 2015), NA-inertia might represent an increase in attributing resources to internal processes and decoupling from processing external emotional information. While this would point to a rather broad increase in functional connectivity between DMN regions especially involving the central midline hubs of the DMN (i.e. mPFC and PCC), rumination has been proposed to be connected to altered contributions of specific regions to DMN-related processes (for example Hamilton et al., 2015), especially including the subgenual Anterior Cingulate Cortex (sgACC) and dorsomedial Prefrontal Cortex (dmPFC). Such an altered contribution of single regions could indicate a changed engagement into DMN-related self-generated thought (DuPre and Spreng, 2018), resulting in an abnormally strong self-focus (Zhu et al., 2017; Sheline et al., 2009) as well as a stronger integration with negative emotionality (Hamilton et al., 2015) leading to thought patterns characteristic for rumination.

These hypothesized relations receive support from investigating the node strength of single DMN regions in relation to rumination and NA-inertia in the present study. NA-inertia was associated with a broad increase of node strength of DMN regions especially involving the midline DMN hub regions (PCC, mPFC) but also spanning over regions of the dorsal as well as ventral DMN-subnetwork (see also Andrew-Hanna et al., 2014).

It is important to point out that, in this study, rumination was measured with the 10-item Ruminative Response Scale (RRS) that, in contrast to the 22-item version, did not include items that are very similar to items in depression scales. This choice was made to ensure that there were no artefactual relationships between the rumination

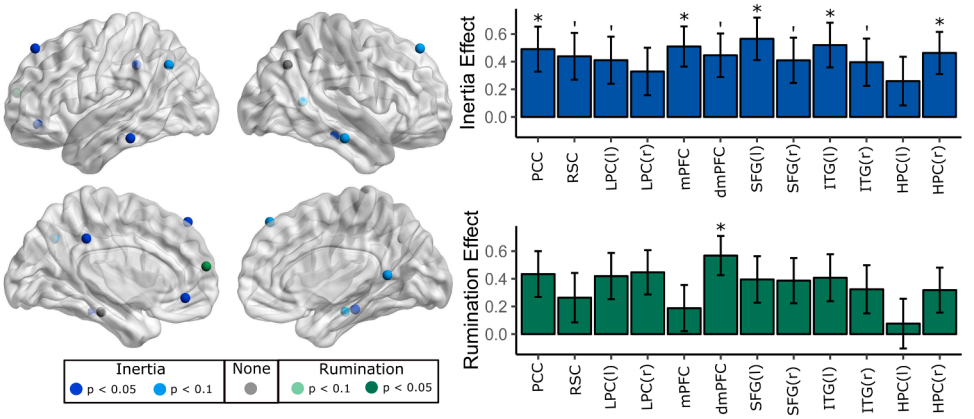

Fig. 2. Regional pattern of DMN associations with rumination as well as NA-Inertia. The relation of the node strength of single DMN regions with rumination and NA-Inertia is depicted on the left panel (A). Nodes significantly relating to NA-Inertia are shown in dark blue and trend-wise significant relations in light blue. Similarly significant relations with rumination are shown in dark green and trend-wise significant relations in light green. If there was no relation with wither NA-Inertia or rumination the nodes are shown in grey. In order to depict the significant relationship of rumination with the node strength of the dmPFC, the trend-wise significant relation of the dmPFC with Inertia is not shown in the graph. The depicted significant levels have been corrected for multiple comparisons. Additionally, the single relationships are shown as barplots (B) including error-bars for the standard deviations.

scores and depressive symptoms (Treynor et al., 2003; Whitmer and Gotlib, 2011). However, using this reduced version of the RRS scale might explain why we were not able to find a relation between rumination and negative emotional inertia as described by Koval et al. (2012).

Furthermore, in contrast to our hypotheses and previous results, we found no increase in node strength of the sgACC related to rumination. One explanation could be that the alterations of sgACC-DMN connectivity in subjects at risk of depression are, in contrast to currently depressed patients, very localized, having been mainly found to be specific to the connectivity between the sgACC and the Posterior Cingulate Cortex (Berman et al., 2011, Philippi et al., 2015). Indeed there are some indications that a broader pattern of abnormal sgACC-DMN connectivity found in clinical samples increases with increasing length of the current depressive episode (Greicius et al., 2007). Consequently such broad alteration might be more connected to currently suffering from MDD than being at risk of developing MDD.

More in general, negative emotional inertia (for example (Kuppens et al., 2012), rumination (for example McLaughlin and Nolen-Hoeksema, 2011) as well as aberrant DMN (Kaiser et al., 2015) connectivity are well-known risk-factors for MDD and the investigated relationships might be especially important for understanding risk and development of MDD. Accordingly, we explicitly focused in this study on a non-clinical sample targeting to understand how aberrant DMN organization is contributing to subclinical depressive symptoms and risk for depression rather than characterizing MDD. Moreover, our results are also important for understanding mechanisms associated with reduced well-being. Depression and depressive symptoms likely represent a continuum rather than clear-cut categories of "being depressed" and "not being depressed" (for example Hankin et al., 2005) and subclinical depressive symptoms have been shown to be associated with psycho-social deficits in the general population (Lewinsohn et al., 2000). However, focusing on such a sample also presents a limitation of the current study and investigating how the relation between inflexible emotional responding and aberrant DMN efficiency contributes to a wider range of depressive severity as observed in acutely depressed subjects will be an important future direction. Similarly, more research is needed to investigate to what degree the current findings extend to older age groups.

Our findings also have important implications for understanding the neural mechanisms underlying emotion dynamics in daily life. Based on the proposal that emotional inflexibility in daily life, as indicated by emotional inertia, represents decoupling from environmental stimulation (see Kuppens et al., 2010), we hypothesized that NA-inertia would be connected to a generally increased engagement into internal, DMN-related processes at rest. In line with this hypothesis we found NA-inertia to be associated with increased DMN efficiency as well as a broad increase in the node strength of DMN regions. Especially the strong effect sizes of these relations suggest a central role of aberrant DMN organization at rest in inflexibly sustained emotional responses in daily life. However, other studies investigating the neural correlates of emotional inertia have also described altered connectivity and activity of regions outside the DMN (Waugh et al., 2017; (Schwartz et al., 2019) and it remains unclear if and how those findings relate to each other. Accordingly, clearly more comprehensive studies are needed to further our understanding of the neural mechanisms of emotional inertia in daily life. In such future work it might be additionally interesting to investigate other aspects (of within and between) neural network organization and similarities and differences between positive affect and negative affect inertia.

Especially in regard to such future research, an important contribution of the current study is to put forward a clear hypothesis of the neural mechanisms underlying inflexible emotional responses observed in daily life. To further test this hypothesis future research is needed to examine whether the relation between NA-inertia and increased E_{DMN} at rest can also be observed during processing of emotional information and whether it is linked to a reduced sensitivity to emotional information.

5. Conclusion

In conclusion, we show that increased DMN efficiency, based on a broad increase in the coupling of DMN regions, is associated to increased emotional inertia in daily life, contributing to risk of depression. Furthermore we show that this link is independent from the rumination-related association between DMN organization and depressive symptoms, with rumination and inertia being associated with different patterns of regional DMN connectivity. These findings are contributing to our understanding of DMN related dysfunction in depression and risk of depression, by explicitly relating changes of DMN organization at rest to changed patterns of emotional experience in daily life. Further these results are indicating that the contribution of the DMN, being a complex, large scale and functionally heterogeneous network, to depression might not be unidimensional but involve multiple pathways.

Author Contributions

JP, PK, PF, PV designed and planed the study. ED assisted in the planing of the ESM part of the study. JP and ED conducted the data collection for the study. JP conducted the analysis. PF, PK and PV advised on the data analyses. JP, PF and PK wrote the manuscript. All the authors carefully reviewed and edited the article and approved the final draft.

Declaration of Competing Interest

The authors declare no competing financial 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.jad.2021.06.051.

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