Research Article

Affective Network Hyperconnectivity and Hypoconnectivity of Cognitive Control and Ventral Attention Networks in Adults with High Neuroticism Scores

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Abstract

Introduction: Subjects with high neuroticism are more likely to interpret ordinary situations as negative, and this might contribute to a predisposition toward mood and anxiety disorders. The aim of our study was to determine the localization of neuroticism-related Resting State Functional Connectivity (RSFC) differences between the two groups of high and low neuroticism, and to confirm our hypothesis that subjects with high neuroticism show hyper connectivity in the affective network and hypo connectivity in the cognitive control and attention networks.

Methods: Forty three healthy participants underwent resting state fMRI and completed the NEO Five Factor Personality Inventory. SPM8 and CONN software was used to pre-process and analyse resting state fMRI data. Correlation maps were produced between seed regions of the affective, cognitive control, attention and default mode networks and differences were analysed between groups fully corrected for multiple testing across the whole brain.

Results: Participants with high neuroticism scores displayed significantly greater functional connectivity in the affective network. There was significantly less functional connectivity in the cognitive control network and ventral attention network for participants with high neuroticism scores when compared to those with low neuroticism scores. Discussion: Affective network hyper connectivity might be related to emotional problems or mood disorders that are associated with high neuroticism. Additionally, the hypo connectivity seen in the cognitive control network might have to do with inattention and cognitive deficits that have consistently been found in major depression and anxiety disorders. Thus, oversensitivity in affective systems and at the same time reduced cognitive control might be in line with increased stress sensitivity and emotional liability in subjects with high neuroticism.

Introduction

Personality traits describe recurrent patterns of thoughts, feelings, and actions that occur in response to situational demands [1]. The Big Five Model is perhaps the most influential model to describe human personality through five main personality traits: Extraversion, Neuroticism, Agreeableness, Conscientiousness, and Openness to experience [2]. According to Eysenck’s (1967) theory of personality, neuroticism is interlinked with low tolerance for stress or aversive stimuli. Those subjects scoring higher in neuroticism are emotionally more reactive and vulnerable to stress [3]. Furthermore, high neurotic individuals express heightened emotional reactivity, especially to negative events [4]. They tend also to be more self-critical [5] and overly sensitive to criticism made by others [6]. They are more likely to interpret ordinary situations as threatening, and minor frustrations as hopelessly difficult, and these might contribute to a predisposition toward mood and anxiety disorders and thus present a risk factor towards these diseases [7,9]. At the other end of the scale, individuals who score low in neuroticism are less easily upset and are less emotionally reactive. They tend to be calm, emotionally stable, and free from persistent negative feelings [10,11].

Since subjects with high neuroticism are at risk to develop depressive and anxiety disorders and show low tolerance for stress, it is important to understand the biology of neuroticism. Neuroimaging may provide some insights into the neurobiological underpinnings of neuroticism. Most neuroticism-related functional MRI (fMRI) differences have been found in task-based studies [12-16]. It has been suggested that deficiencies in functional circuits in neuroticism may be associated to topographic characteristics of resting state networks [17]. A growing interest in the use of resting state fMRI, which does not require a task, has risen over the last few years. Resting state fMRI allows for the examination of large scale neural systems that exhibit spontaneous synchronous fluctuations during non-goal directed fluctuations, such as wakeful rest, sleep and anaesthesia [18]. Correlations between these low frequency (less than 0.1Hz) spontaneous fluctuations on Blood Oxygenated Level Dependent (BOLD) signal are considered to reflect interactions between adjacent
and non-adjacent brain areas that form spatially distributed networks of brain function [19]. Resting State Functional Connectivity (RSFC) is the observed correlation in spontaneous neural activity between brain areas at rest [17].

To improve understanding of RSFC in adults with high scores for neuroticism, the coordinates for regions of interest (ROIs) involved in neuroticism neuro-pathophysiology [12] from five neural networks were extracted [20,21]. These coordinates were used as correlates with all other time series in the brain to determine temporally coherent networks of RSFC [21].

The first network included in our study was the affective network. This network contains integrated regions of the affective sub-division of the Anterior Cingulated Cortex (ACC), amygdale, nucleus accumbens, hypothalamus, anterior insular, hippo campus and orbit frontal cortex with reciprocal connections to autonomic, visceromotor and endocrine systems [21]. This network is involved in emotional regulation and monitoring of salience of motivational stimuli [21]. A very recent fMRI resting state study showed significantly increased correlation in the bilateral amygdale in people with neuroticism [22]. Studies using cognitive-affective tasks found that activations in the frontal cortex, Dorsomedial Prefrontal Cortex (DMPFC), and amygdale are related to neuroticism [15,23,24]. Moreover, higher levels of neuroticism have been associated with a stronger interaction between the right amygdale and the right hippocampus as well as the right amygdala and prefrontal cortical regions, specifically ventromedial prefrontal cortex, dorsolateral prefrontal cortex, and ACC, in an aversive pavlovian conditioning task [25]. Since affective disorders are highly associated with neuroticism [26,27] it is important to take studies in the area of affective disorders into account. Previous resting state studies examining affective disorders have found altered connectivity of the above described structures [28,29]. Heightened functional connectivity for high neuroticism participants compared to low neuroticism participants was expected in our study.

The second network, the ventral attention network, uses the Temporoparietal Junction (TPJ) and Ventral Frontal Cortex (VFC) to reorient attention to salient behaviourally relevant stimuli [20]. No study to date has yet investigated this network in people with high neuroticism scores. However, Sylvester and colleagues have recently shown that children with a history of depression and/or anxiety had reduced RSFC among the regions of the ventral attention network compared to children with no psychiatric history [30]. Thus, hypo-connectivity in this network is to be expected in people with high scores for neuroticism.

Our third network is the bilateral dorsal attention network. This network uses regions such as the Intraparietal Sulcus (IPS) and the Frontal Eye Field (FEF) to enable the control of spatial attention through selection of sensory stimuli based upon internal goals or expectations and links them to appropriate motor responses, a top-down orienting of attention [20]. There is no study in the research literature looking at this network and neuroticism or mood disorders but we found a recent study by Sripada looking at an emotional regulation strategy of reappraisal. The authors showed that people who engaged in the task of reappraisal had increased connectivity in the dorsal attention and default networks [31]. We also expect alterations in connectivity within this network for the group with high levels of neuroticism.

The fourth network we included in our study was the cognitive control network which utilizes regions such as the bilateral Dorsolateral Prefrontal Cortex (DLPFC), pre-supplementary motor area, inferior frontal junction, anterior insular cortex, dorsal-premotor cortex, and posterior cortices [32]. These regions have been implicated in behavioural inhibition, suppression of unwanted thoughts, attention shifting, and efforts to reappraise emotional stimuli [33-35]. Recent work using resting state fMRI suggests that depression is associated with abnormalities in the functional connectivity between these regions, which comprise key nodes of the so-called cognitive control network [21,36,39]. Clasen and colleagues have shown in a very recent study that alterations within the cognitive control network predated the onset of depression in young women with familiar risk for depression. Cognitive control network connectivity could then be considered a viable risk factor for depression [40]. As we mentioned earlier the task-based study by Tzschoppe has shown that higher levels of neuroticism are associated also with a stronger interaction between the right amygdala and prefrontal cortical regions, specifically Ventromedial Prefrontal Cortex (VMPFC), DLPFC and ACC [25]. High neuroticism poses a risk for depression so we hypothesized that these individuals should also show an altered connectivity in the cognitive control network.

The fifth network that we have considered in the study is the default network. It contains the precuneus/posterior cingulated cortex, the medial prefrontal cortex, dorsal ACC, and acts as a form of functional connectivity baseline thought to reflect intrinsic brain activity [17]. It has been documented in the literature that patients with depression show altered default mode network connectivity at several regions [41,42]. Kunisato and colleagues have observed that neuroticism correlated negatively with regional activity in the middle frontal gyrus and the precuneus (the latter being part of the default network model) [43,44]. We expect to replicate this finding in our sample as there are no other studies on neuroticism and resting state fMRI.

The aim of our study is to explore the RSFC in individuals with high scores for neuroticism and to compare them with those scoring low neuroticism. We want to determine the localization and specificity of neuroticism-related connectivity differences between the two groups and to confirm our hypothesis that high neuroticism shows altered connectivity at several resting state network models that may resemble the changes found in depression (as neuroticism is a well-documented risk factor for depression).

**Methods**

**Participants and rating scales**

Forty five healthy participants were included in the study sample (28 females and 17 males). All participants were interviewed, and screened for any potential psychiatric diagnosis according to exclusion criteria and using the Structured Clinical Interview for DSM-IV (SCID-I) [45] by two psychiatrists. Exclusion criteria included: previous history of head injury or medical illness, previous history of mental illness, previous history of taking medication or substance/alcohol abuse. Handedness was obtained from the Edinburgh Handedness Inventory [46]. Self-administered and observer-rated scales were completed by all participants. The rating scales used were: the SCID-II personality questionnaire [45], the
Using CONN resting state software (http://www.nitrc.org/project/conn/) the data were temporally band-pass filtered (.009 < f < 0.08). Several sources of spurious variance along with their temporal derivatives were then removed from the data by linear regression, such as signal from regions cantered in the white matter, cerebrospinal fluid and movement. CONN implements the component-based noise correction method (CompCor) strategy for physiological and other noise source reduction. CompCor has the advantage of not requiring external monitoring of physiological fluctuations. Compared to methods that rely on global signal regression, the CompCor noise reduction method allows for interpretation of anti correlations as there is no regression of the global signal. This approach may enhance the sensitivity of positive correlations and produce comparable negative correlations. This regression procedure removes fluctuations unlikely to be involved in specific regional correlations.

Functional connectivity analysis of resting state activity

To compute functional connectivity maps corresponding to a selected seed Region of Interest (ROI), the region time course was correlated against all other voxels within the brain. Based on data from two previous resting state studies [20,21] connectivity within the affective network, ventral attention system, dorsal attention system, cognitive control network and default mode network were explored. Correlation maps were produced by extracting the BOLD time course from a seed region, then computing the correlation coefficient between that time course and the time course from all other brain voxels. The following seed ROIs with 5 mm radius were extracted for these 5 specific neural networks: the ACC (+/- x=10, y=-35, z=2) in the affective network; the TPJ (+/- x=53, y=-48, z=20) and VFC (+/- x=-37, y=-18, z=1) in the ventral attention system; the IPS (+/- x=-27, y=-58, z=49) and FEF (+/- x=24, y=-13, z=51) in the dorsal attention system, the DLPFC (+/- x=-36, y=27, z=29) in the cognitive control network and the precuneus (+/- x=7, y=-60, z=21) in the default mode network. For the ventral (TPJ, VFC) and dorsal (IPFC, FEF) attention network we thus extracted 2 connectivity maps. The principal techniques used were computation of whole brain voxel-wise intrinsic functional connectivity maps.

Statistical analysis

We analysed resting state functional MRI data in SPM8 using two-sample t-test to determine significant differences in functional connectivity between high and low neuroticism using the cut off points described above, and using a Family Wise Error (FWE) whole brain corrected threshold of P<0.01 (FWE corrected for the whole brain). The threshold was reduced to P<0.01 from P<0.05 because we analysed connectivity within the 5 different networks. Mean connectivity data were extracted from areas that showed significant differences between high and low neuroticism participants. Since Beck’s Depression Inventory and Hamilton Anxiety and Depression Rating Scales scores were different between participants with low and high neuroticism (but still all below the threshold for depression or anxiety disorder) these were added as covariates in additional ANCOVA analyses in SPM to observe the difference between participants with high neuroticism scores and participants with low neuroticism scores. Moreover, to assess for linear effects and associations between neuroticism as well as age and depression/ anxiety scores and brain connectivity we used Spearman’ rank test in regions that showed significant differences between individuals from the high neuroticism group versus those from the low neuroticism group in an additional analysis.

Results

Twenty eight female participants and 17 male participants entered the study. Ten participants scored high levels of neuroticism on the NEO Five Factor personality inventory. Compared to low neuroticism group, participants with high neuroticism scores...
displayed significantly greater functional connectivity in the right affective network (Table 1). We found significant differences at the right ACC. Participants with high neuroticism scores showed significantly greater functional connectivity between the right ACC and the left superior parietal lobe (x=-46, y=-56, z=56) as well as the right superior medial frontal lobe (x=-4, y=30, z=44) and the right inferior parietal lobe (x=54, y=-58, z=48) (Figure 1).

There was significantly less functional connectivity in the cognitive control network for participants with high neuroticism scores when compared to those with low neuroticism scores (Table 2). We found significant differences between the right DLPFC with the right middle temporal lobe (x=60, y=-34, z=2) and the right insula (x=36, y=-16, z=16) (Figure 2). There was also less functional connectivity in the ventral attention network for participants with high neuroticism scores when compared to those with low neuroticism scores (Table 2). Here significant differences between the right TPJ and the left inferior parietal lobe were detected (x=-46, y=-52, z=40) (Figure 3).

We should also mention that all group comparison results held true when Beck’s Depression Inventory and Hamilton Anxiety and Depression Rating Scales scores were included as co-variates in the analysis.

No significant correlations were found between RSFC and age, depression or anxiety scores (Table 3).

### Discussion

To the best of our knowledge, this is the first time the affective, cognitive control and attention networks were explored together with the default mode network to determine the localization and specificity of neuroticism-related RSFC differences in adults with high and low neuroticism scores.

A main finding within our study was as hypothesized the significantly higher RSFC within the affective network for participants with high neuroticism scores when compared to those with low neuroticism scores. As we said earlier, this network is involved in emotional regulation and monitoring the salience of motivational stimuli [21].Our finding is in line with findings that subjects with high neuroticism are more emotional reactive and stress sensitive. We found that participants with high neuroticism displayed more RSFC between the right ACC of the affective network and the left superior parietal lobe, the right inferior parietal lobe and the right superior medial frontal lobe (DMPFC).

### Table 1: Between group resting state connectivity differences: high neuroticism vs low neuroticism.

<table>
<thead>
<tr>
<th>Networks and regions</th>
<th>FWE-Corr</th>
<th>K value</th>
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<th>x</th>
<th>y</th>
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<td>Affective network</td>
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<tr>
<td>R ACC-left sup parietal lobe</td>
<td>0.025</td>
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<td>0.001</td>
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<tr>
<td>R ACC-right inferior parietal lobe</td>
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<td>48</td>
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<tr>
<td>R ACC-right sup medial frontal lobe</td>
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<td>0.000</td>
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<td>4</td>
<td>30</td>
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<td>Dorsal attention network</td>
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<tr>
<td>Cognitive control network</td>
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<td>Default mode network</td>
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### Table 2: Between group resting state connectivity differences: low neuroticism vs high neuroticism.

<table>
<thead>
<tr>
<th>Networks and regions</th>
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<th>K value</th>
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<tr>
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<td>-52</td>
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<tr>
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</tr>
<tr>
<td>Cognitive control network</td>
<td>R DLPFC-right mid temporal lobe</td>
<td>0.004</td>
<td>235</td>
<td>0.000</td>
<td>60</td>
<td>-34</td>
</tr>
<tr>
<td>R DLPFC-right insula</td>
<td>0.025</td>
<td>163</td>
<td>0.001</td>
<td>36</td>
<td>-16</td>
<td>16</td>
</tr>
<tr>
<td>Default mode network</td>
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Figure 1: Participants with high neuroticism scores showed significantly greater functional connectivity between the right ACC and the right inferior parietal lobe (x=54, y=-58, z=48) in comparison to participants with low neuroticism scores (1A). The individual BOLD activity is depicted in relation to neuroticism scores on the right side of the figure (1B).

Figure 2: Significant differences between the right DLPFC with the right middle temporal lobe (x=60, y=-34, z=2) and the right insula (x=36, y=-16, z=16) were found in the study. Participants with high neuroticism show significantly lower RSFC in these areas compared to participants with lower neuroticism (2A). The individual BOLD activity is depicted in relation to neuroticism scores on the right side of the figure (2B).
The ACC has been very much associated with emotional regulation [51-54], the experience of sadness and anxiety [55,56] and with depression [57]. The dorsal part of the ACC is connected with the prefrontal and parietal cortices as well as the motor system and the frontal eye fields making it a central station for processing top-down and bottom-up stimuli and assigning appropriate control to other areas in the brain [58]. Thus, our findings that functional connectivity between ACC and prefrontal and parietal cortices is relevant for neuroticism is in line with these anatomical connections. Interestingly, resting state studies examining affective disorders have also found altered connectivity of the affective network, in particular in the ACC and DMPFC [28,29]. FMRI BOLD responses in the frontal cortex, DMPFC and amygdala have also been associated with neuroticism in cognitive-affective task studies [12,15,24,59,60] as superior parietal lobe is known to be involved in body part localization [61], writing [62] and manipulation of information in working memory [63]. The right superior medial frontal lobe is involved in theory of mind processes [64] and inhibitory control [65]. These parietal and frontal areas of the brain have been closely related to anxiety and mood disorders [66,67] and high neuroticism seems to predispose to mood and anxiety disorders [7,8,9].

The cognitive control network showed also interesting and novel results. The brain areas included in this network have been implicated in behavioural inhibition, suppression of unwanted thoughts, attention shifting, and efforts to reappraise emotional stimuli [33-35]. Participants with high neuroticism scores exhibited significantly less attention shifting, and efforts to reappraise emotional stimuli [33-35]. The individual BOLD activity is depicted in relation to neuroticism scores on the right side of the figure (3B). The cognitive control network showed also interesting and novel results. The brain areas included in this network have been implicated in behavioural inhibition, suppression of unwanted thoughts, attention shifting, and efforts to reappraise emotional stimuli [33-35]. Participants with high neuroticism scores exhibited significantly less attention shifting, and efforts to reappraise emotional stimuli [33-35]

The ventral attention network reorients attention to salient behaviourally relevant stimuli [20]. We found that individuals with high neuroticism scores showed less RSFC between the right TPJ and the left inferior parietal lobe. The right TPJ is pivotal in analysing signals from self-produced actions as well as from external environment [75]. The right TPJ is involved also in the identification and processing of social cues [76]. The inferior parietal lobe seems to be associated with detection of salient new events in the environment [77,78] and with sustained attention on task goals [79-81]. Problems with attention focus and distractibility are some of the core symptoms of major depression and anxiety [45]. Sylvester and colleagues have recently showed that children with a history of depression and/or anxiety had reduced RSFC among the regions of the ventral attention network compared to children with no psychiatric history [30].

The DLPFC has been linked with adaptive control [32] working memory [68] and emotional regulation [69]. The middle temporal lobe was found to be less connected with the DLPFC in our study. Previous neuroimaging studies have suggested that the middle temporal lobe is associated with language (Brodmann area 21) and semantic memory processing [70,72]. A study by Kennedy et al., 2007 using PET scans found that depressed patients treated with venlafaxine showed increased metabolism in the Brodmann 21 area. An opposite pattern was found for patients treated with cognitive behavioural therapy [73].

| Table 3: Spearman correlations between extracted RSFC, Ham-D, Ham-A, BDI and neuroticism scores. |
|------|-------|-------|-------|-------|
|      | Age   | NEO   | FFI   | HAM_D | HAM_A | BDI   |
| RACC_left sup parietal lobe | Corr_coef | .061 | .443 | .086 | .289 | .186 |
| Sig. | .197 | .000 | .739 | .058 | .155 |
| RACC_right inferior parietal lobe | Corr_coef | -.197 | .514 | -.197 | .358 | .351 |
| Sig. | .107 | .001 | .205 | .020 | .021 |
| RTPJ_left inferior parietal lobe | Corr_coef | .200 | .567 | .113 | .150 | .127 |
| Sig. | .199 | .000 | .471 | .342 | .418 |

The insulin was also significantly disconnected to the DLPFC in individuals with high neuroticism scores. The insulin is instrumental in integrating disparate functional system involved in processing affect, sensory-motor processing, and general cognition and is well suited to provide an interface between feelings, cognition and action [74]. This hypo connectivity is relevant as other fMRI resting state studies have shown hypo activation of cognitive control network predating the onset of depression in young women with familiar risk for depression. Cognitive control network connectivity could be then considered a potential risk factor for depression [40].

Our findings must be considered in light of limitations. The rating scale that we use to assess level of neuroticism is a self-rated one which despite of being reliable and validated tool is not free from recall bias. The cross-sectional design did not involve follow-up with research participants. Therefore, we were not able to determine if differences in connectivity predate depression or anxiety disorder onset, reflecting neuroticism as a risk factor for development of mood anxiety disorders. Including longitudinal follow up is a critical feature of future research to directly assess the extent to which differences in connectivity predict depression onset, particularly in the context of life stress. The sample size was large enough to look at differences between participants with high and low neuroticism scores. We chose this procedure, since neuroticism might not be a linear function of...
brain function that would be the requirement for a linear regression analysis. Strength of our study is that our results are valuable as they were corrected for multiple comparisons and strong enough to survive conservative Bonferroni testing, which reduced type 1 errors.

Conclusion

In conclusion, our findings shed light upon the neuroticism related RSFC and its role as a risk factor for the development of major depression. High neuroticism was associated with affective network hyper connectivity and cognitive control and ventral attention network hypo connectivity. Affective network hyper connectivity might be related to emotional problems or mood disorders that are associated with high neuroticism. Additionally, the hypo connectivity seen in the cognitive control might have to do with the inattention and cognitive deficits that have consistently been found in major depression and anxiety disorders. Thus, oversensitivity in affective systems and at the same time reduced cognitive control might be in line with increased stress sensitivity and emotional liability in subjects with high neuroticism.

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