Views on vulnerability

Cognitive and neurobiological vulnerability during remission of Major Depressive Disorder
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Default mode network dominance over the task positive network is not increased in remitted depressed patients at high risk for recurrence

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INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disease burden worldwide. Among the harmful aspects of MDD is its chronic nature, as more than 50% of patients experience recurrence, and the risk thereof increases with every episode. Unfortunately, data on recovered-state MDD is scarce. In order to improve preventative strategies, it is necessary to identify vulnerability factors that persist in remitted patients at high risk of recurrence. Rumination, defined as the tendency to obsessively focus attention on depressive symptoms and consequences, has been identified as a psychological risk factor for recurrence. The DMN is a neural network that processes introspective, self-generated thought such as mind-wandering, autobiographical memory and future planning. DMN activity is anti-correlated with brain areas that are activated during attention demanding tasks, including planning and problem solving, which are conceptualized as the ‘Task Positive Network’ (TPN). The TPN consist of the dorsal attention system and prefrontal regions. In MDD, studies have shown failures to deactivate DMN regions in MDD subjects during tasks and impaired DMN deactivation was associated with self-reported rumination in MDD. Further, in depression dominance of the ‘Default Mode Network’ (DMN) over the Task Positive Network (TPN) during rest has been linked to rumination. A recent review hypothesized that dominance of the Default Mode Network might persist in remitted MDD, and through its correlation with rumination, predisposes to vulnerability for another recurrence. However, this hypothesis has not yet been well examined. The aim of this study was to determine (1) whether DMN Dominance was increased in remitted MDD-patients at high risk for recurrence compared to controls (2) whether DMN dominance was associated with rumination in remitted MDD. If so, DMN Dominance, through its association with rumination, might serve as a neural vulnerability factor for recurrence.

METHODS

We first created masks of the DMN and TPN, using seed based functional connectivity correlation analysis. In line with a study by Hamilton et al. (2011), we defined the DMN as all areas that correlated positively with seed regions in the Posterior Cingulate Cortex (PCC) and Medial Lateral Prefrontal Cortex (MLPFC): key areas of the DMN. We defined the TPN as all areas that correlated negatively with seed regions in the PCC and MLPFC (Figure 1). Second, using the validated method by Hamilton we estimated dominance of the DMN over the TPN in blood oxygenation level dependent resting state fMRI scans. DMN-dominance was defined as the percentage of scans (out of 220 scans in total) that the DMN BOLD signal was greater than TPN BOLD signal (figure 2). We examined 61 remitted depressed patients with more than two previous episodes, who were in stable remission and free of medication and 40 never-disordered matched controls. We compared levels of DMN dominance between patients and controls using independent samples.
T-tests (p = 0.05, 2-tailed). Furthermore, we determined the correlation between DMN dominance and rumination by the Ruminative Responses Scale in the past week.

Figure 1. Spatial distribution of BOLD signal fluctuations at rest, representing the anticorrelated Task Positive Network (TPN; blue) and Default Mode (DMN; yellow-orange) networks. The DMN (yellow-orange) consist of the Medial Prefrontal Cortex (MPFC), Posterior Cingulate Cortex (PCC) and parietal cortex areas; the TPN (blue) of the dorsal attention system including the Intra-parietal cortex (IPC) and prefrontal regions including the dorsolateral prefrontal cortex (DLPFC). Adapted from Marchetti et al. 2011 and Andrews-Hanna et al (2014).

Figure 2. Calculation of DMN-dominance (% scans DMN BOLD signal >TPN BOLD signal). Blue line is DMN BOLD signal change, green line is TPN BOLD signal change. Red line is DMN dominance (+1: DMN is dominant, -1: TPN is dominant).
RESULTS

DMN dominance did not differ between remitted patients and controls (49.4±3.22% vs. 50.0±2.86%, respectively p = 0.32). Remitted depressed patients had significantly higher levels of rumination than controls (p > 0.001). However, there was no significant association between DMN dominance and rumination in remitted-MDD (p=0.28, r=0.15; Figure 3); nor in controls (p=0.13, r=-0.25).

CONCLUSION

Our study investigated the neurobiological background of remitted MDD. Contrary to our expectations, we did not find that depression related DMN dominance persists in remitted MDD-patients at high risk for recurrence. Furthermore, DMN dominance was not associated with rumination in remitted MDD. Therefore, in this sample, it is unlikely that the DMN dominance will account for vulnerability to recurrence in recovered depression. Future studies should assess functioning of the DMN in remitted-MNDD using different fMRI measures (i.e. task based and more common FC-analysis methods). Furthermore, DMN dominance could also be assessed during emotional tasks, as differences might only become apparent during sad mood states. If this finding is replicated, emerging theory should be revised.
REFERENCES