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Polygenic risk for depression and the neural correlates of working memory in healthy subjects

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ABSTRACT

Introduction: Major depressive disorder (MDD) patients show impairments of cognitive functioning such as working memory (WM), and furthermore alterations during WM-fMRI tasks especially in frontal and parietal brain regions. The calculation of a polygenic risk score (PRS) can be used to describe the genetic influence on MDD, hence imaging genetic studies aspire to combine both genetics and neuroimaging data to identify the influence of genetic factors on brain functioning. We aimed to detect the effect of MDD-PRS on brain activation during a WM task measured with fMRI and expect healthy individuals with a higher PRS to be more resembling to MDD patients.

Method: In total, n = 137 (80 men, 57 women, aged 34.5, SD = 10.4 years) healthy subjects performed a WM n-back task [0-back (baseline), 2-back and 3-back condition] in a 3 T-MRI-tomograph. The sample was genotyped using the Infinium PsychArray BeadChip and a polygenic risk score was calculated for MDD using PGC MDD GWAS results.

Results: A lower MDD risk score was associated with increased activation in the bilateral middle occipital gyri (MOG), the bilateral middle frontal gyri (MFG) and the right precentral gyrus (PCG) during the 2-back vs. baseline condition. Moreover, a lower PRS was associated with increased brain activation during the 3-back vs. baseline condition in the bilateral cerebellum, the right MFG and the left inferior parietal lobule. A higher polygenic risk score was associated with hyperactivation in brain regions comprising the right MFG and the right supplementary motor area during the 3-back vs. 2-back condition.

Discussion: The results suggest that part of the WM-related brain activation patterns might be explained by genetic variants captured by the MDD-PRS. Furthermore we were able to detect MDD-associated activation patterns in healthy individuals depending on the MDD-PRS and the task complexity. Additional gene loci could contribute to these task-dependent brain activation patterns.

1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders with a lifetime prevalence of 14.6% in high-income countries (Bromet et al., 2011) affecting various symptoms such as mood, behavioral factors or cognitive functioning. Since cumulative cases of depression could be observed more often in families and especially in close relatives, research proposes a strong impact of genetic factors contributing to the genesis of MDD (McGuffin and Katz, 1989; Schulte-Körne and Allgaier, 2008). Early twin-studies revealed a heritability of

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depressive symptoms of about 30% (e.g. McGue and Christensen, 2003). Nevertheless stressful environmental factors, such as critical life events, increase the probability for developing MDD. Therefore Sullivan et al. (2000) suggested a mixed model for the etiology of MDD by considering both genetic and environmental influences, with the heritability of genetic risk being estimated as high as 40% (Sullivan et al., 2000).

1.1. Genetic nature of MDD and the advantage of polygenic risk scoring

Genome-wide association studies (GWAS) revealed some significant single markers explaining heritability for various psychiatric disorders or particular traits, but have been only partially successful in discovering single nucleotide polymorphisms (SNPs) that achieve genome-wide significance for MDD (Ripke et al., 2013). More precisely several candidate genes – such as the serotonin transporter gene SLC6A4/5HTT (e.g. Caspi et al., 2010; Uher and McGuffin, 2010) or the brain-derived neurotrophic factor (BDNF) gene (e.g. Duncan et al., 2009) – are discussed to influence the genesis of MDD or at least MDD-associated symptoms. Nevertheless research failed to find single genetic variation that increases the risk for MDD substantially (Lohoff, 2010). Hence there is evidence that the multitudinous markers that did not reach genome-wide significance might explain genetic variance in predicting diseases if they were summarized to a combined score (Dudbridge, 2013). Thus examining the connection between a wide array of SNPs might help to predict individuals genetic risk for developing a psychiatric disorder.

The calculation of a polygenic risk score (PRS) – which is basically an accumulation of various risk variants – is a comparatively new method and a further step in the exploration of genetic disposition for different psychiatric disorders such as MDD. For calculating the PRS a number of SNPs are chosen from a GWAS training sample according to their ranked p-values (Dudbridge, 2013), considering large sample sizes and different descriptions of the phenotype. Hence individually computed PRSs might help to predict the risk for several diseases, respectively (Wray et al., 2007, 2014). The high potential of polygenic risk scoring in MDD has been confirmed in several studies (Byrne et al., 2014; Levine et al., 2014; Middeldorp et al., 2011; Mullins et al., 2015; Musliner et al., 2015; Peyrot et al., 2014).

1.2. Working memory impairments in MDD & their neural correlates

MDD patients exhibit impairments in several cognitive domains (Hasselbalch et al., 2011; Marazziti et al., 2010; Porter et al., 2003; Roca et al., 2015). A cognitive core dimension in executive functioning is working memory (WM), which is a system to memorize, retrieve and utilize information (Rottschy et al., 2012) to process extensive cognitive tasks in daily life such as reasoning or deduction. A reliable, valid and often used instrument to determine WM is the n-back version of the Continuous Performance Task (CPT) (Cohen et al., 1994). Although literature suggests impairments of WM in MDD patients (Bourke et al., 2012; Christopher and MacDonald, 2005; Dumas and Newhouse, 2014; Rose and Ebmeier, 2006), many investigations failed to find differences in the behavioral performance in crude WM paradigms between MDD and healthy controls (HC) (Harvey et al., 2005; Matsuo et al., 2007; Norbury et al., 2014; Schöning et al., 2009; Walsh et al., 2007). Nevertheless, differences on a functional MRI level during WM tasks were commonly observed in MDD patients (Fitzgerald et al., 2008; Goethals et al., 2005; Opmeer et al., 2013; Vasic et al., 2009; Wang et al., 2015). FMRI studies indicated the activation of bilateral fronto-parietal networks (Kondo et al., 2004; Krug et al., 2008; Rottschy et al., 2012; Wager and Smith, 2003; Wang et al., 2015), but regarding differences between MDD vs. HC research suggests discrepancies especially on the direction of the brain activation (hypo- or hyperactivation); however there is no consensus yet (Fitzgerald et al., 2008; Matsuo et al., 2007; Rottschy et al., 2012). While most of the studies indicated hypoactivation in MDD patients during WM tasks (Bartova et al., 2015; Brooks et al., 2015; Goethals et al., 2005; Pu et al., 2012), others in contrast found hyperactivation in depressed subjects (Matsuo et al., 2007; Vasic et al., 2009). Regarding these results Harvey et al. (2005) suggested the theory of hyperfrontality – which has also been observed in other mental diseases such as schizophrenia (e.g. Callicott et al., 2003) – stating that depressed subjects need greater activation in respective brain areas compared to HC for comparable behavioral performance modulated by the complexity of task.

1.3. Imaging genetics with WM

Imaging genetic studies combined MRI data and genetic variables to gain a deeper understanding of the etiology and epidemiology of mental disorders (e.g. Domschke et al., 2008; Krug et al., 2014, 2013; Opmeer et al., 2014). A crucial issue in imaging genetic studies is to detect the degree to which observed brain alterations are affected and triggered by genetic factors.

To date, several MDD-related single genetic variants in combination with memory functioning have been assessed (e.g. LeMoult et al., 2015). However, studies combining SNP's, fMRI and working memory in particular are very rare. Egan et al. (2003) examined the 5′ region of BDNF in combination with the n-back task and found poorer behavioral performance and altered hippocampal activation during memory load in methionine allele homozygotes compared to valine-allele homozygotes. Furthermore Mannie et al. (2010) reported functional differences in occipital, parietal and temporal regions in subjects with increased familial risk of depression during the n-back task. On the other hand Opmeer et al. (2013) found a positive association of the number of met-alleles of the val158met polymorphism in the catechol-O-methyltransferase (COMT) gene and the activation of the right inferior frontal gyrus during emotional processing, but not during working memory. However, former studies only assessed the effect of single genetic variants and often failed to find an association between SNP's and working memory functioning (Mannie et al., 2009; Opmeer et al., 2015). Hence this illustrates the necessity of applying a PRS, as it consists a cumulative number of various genetic risk variants and might be a better proxy for genetic risk per se.

Due to the novelty of this method, only few approaches combined fMRI data and polygenic risk scores for mental disorders, and most of them engaged the PRS for schizophrenia (e.g. French et al., 2016; Kauppi et al., 2015; Walton et al., 2014). To our knowledge only very few investigations combined neuroimaging data and PRS for depression (Holmes et al., 2012; Whalley et al., 2013), but none of them used functional MRI data, and particularly did not probe cognitive functions such as WM. Although there are several non-MRI-investigations (Mullins et al., 2015; Musliner et al., 2015; Peyrot et al., 2014), there is an overall lack of fMRI studies combining working memory and MDD-PRS. These difficulties make existing PRS-studies additionally difficult to compare to our present study. However, a relationship between WM-related brain activation and genetic factors is assumable as many investigations reported a connection between polygenic heritability and cognitive domains (e.g. Davies et al., 2011; Deary et al., 2009), polygenic scores and brain activation (e.g. Whalley et al., 2015) and cognitive load and brain activation (e.g. Backes et al., 2014), although no investigation has used the present study design before.

1.3.1. Hypotheses

The aim of the present study was to examine the impact of cumulative risk for MDD on WM-related brain activations in healthy subjects. First, we expect the typical fronto-parietal activation cluster as often described in prior WM-studies. Following current research (e.g. Lee et al., 2013; Schöning et al., 2009; Wang et al., 2015) we expect especially the middle frontal gyrus, precentral gyrus, angular gyrus and precuneus to be affected during WM load. We furthermore hypothesize an association of MDD-PRS and altered BOLD-signal in HC similar to