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Hippocampal volume correlates with attenuated negative psychotic symptoms irrespective of antidepressant medication

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ABSTRACT

Background: Individuals with at-risk mental state for psychosis (ARMS) often suffer from depressive and anxiety symptoms, which are clinically similar to the negative symptomatology described for psychosis. Thus, many ARMS individuals are already being treated with antidepressant medication.
Objectives: To investigate clinical and structural differences between psychosis high-risk individuals with or without antidepressants.
Methods: We compared ARMS individuals currently receiving antidepressants (ARMS-AD; n = 18), ARMS individuals not receiving antidepressants (ARMS-nonAD; n = 31) and healthy subjects (HC; n = 24), in terms of brain structure abnormalities, using voxel-based morphometry. We also performed region of interest analysis for the hippocampus, anterior cingulate cortex, amygdala and precuneus.
Results: The ARMS-AD had higher 'depression' and lower 'motor hyperactivity' scores than the ARMS-nonAD. Compared to HC, there was significantly less GMV in the middle frontal gyrus in the whole ARMS cohort and in the superior frontal gyrus in the ARMS-AD subgroup. Compared to ARMS-nonAD, the ARMS-AD group showed more gray matter volume (GMV) in the left superior parietal lobe, but less GMV in the left hippocampus and the right precuneus. We found a significant negative correlation between attenuated negative symptoms and hippocampal volume in the whole ARMS cohort.
Conclusion: Reduced GMV in the hippocampus and precuneus is associated with short-term antidepressant medication and more severe depressive symptoms. Hippocampal volume is further negatively correlated with attenuated negative psychotic symptoms. Longitudinal studies are needed to distinguish whether hippocampal volume deficits in the ARMS are related to attenuated negative psychotic symptoms or to antidepressant action.

1. Introduction

The clinical high-risk state of psychosis (at-risk mental state, hereafter ARMS) is defined by attenuated positive psychotic symptoms, genetic liability and functional deterioration or brief and self-remitting psychotic symptoms (Fusar-Poli et al., 2013; Yung et al., 1998). However, affective symptoms, including depressive and anxiety symptoms, are also highly prevalent in these individuals (Salokangas et al., 2012). A recent meta-analysis, conducted in 1683 high-risk subjects, confirmed that the baseline prevalence of comorbid depressive and anxiety disorder is 41% and 15%, respectively (Fusar-Poli et al., 2014a). Depressive and anxiety symptoms can precede the onset of attenuated positive psychotic symptoms (Fusar-Poli et al., 2013). Some studies indicate that co-occurrence of depressive disorders can predict subsequent transition to psychosis in ARMS individuals (Salokangas et al., 2012). However, other studies have not confirmed this finding (Fusar-Poli et al., 2014a). Additionally, a large study on 3349 twins suggests an association between depressive and/or anxiety symptoms and psychosis-like traits (schizotypy) and emphasizes a major role for genetics, especially as regards positive symptoms (Macare et al., 2012). The comorbidity of psychotic and depressive disorders in the ARMS population is associated with specific psychopathological features at the time of the presentation to high risk services and with low functional level (Fusar-Poli et al., 2013). Because of these problems, clinical high-risk individuals

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often receive antidepressant medication (e.g. 42% of ARMS individuals in our previous study (Smieskova et al., 2012a)).

Negative psychotic symptoms are a major source of disability in the psychosis spectrum and are refractory to any effective treatment (Fusar-Poli et al., 2014b). Negative symptoms group into two factors, one involving diminished expression of affect and alogia and the second involving avolition, including anhedonia and asociality (Fusar-Poli et al., 2014b). Antidepressants may have a potential benefit for ARMS individuals, as they may target their negative attenuated psychotic symptoms (Cornblatt et al., 2007; Fusar-Poli et al., 2007). These studies indicate that antidepressant treatments in ARMS individuals can impact their longitudinal outcomes. However, it is not clear if these improvements are associated with underlying neurobiological changes (Wood et al., 2011).

Neuroimaging studies using magnetic resonance imaging (MRI) have indicated that ARMS showed brain alterations in the prefrontal (Borgwardt et al., 2006; Borgwardt et al., 2008; Koutsouleris et al., 2009; Mechelli et al., 2011; Wood et al., 2010), cingulate (Fornito et al., 2008; Koutsouleris et al., 2009), superior (Takahashi et al., 2009; Takahashi et al., 2010) and medial temporal (Borgwardt et al., 2007b; Tognin et al., 2014), insular (Smieskova et al., 2010) and cerebellar regions when compared to healthy controls. Furthermore, ARMS individuals with subsequent transition to psychosis showed volumetric reductions in the prefrontal, insular and cingulate cortex compared to those without transition (Smieskova et al., 2010).

Similar alterations were found in depressive disorders. Reductions in gray matter volume (GMV) in the anterior cingulate gyrus, hippocampus, amygdala (Koolschijn et al., 2009) and prefrontal cortex (Lorenzetti et al., 2009) were associated with major depression. The only available study directly testing the effect of comorbid depressive disorders on the neurobiology of ARMS uncovered a significant impact on the anterior cingulate region (Modinos et al., 2014). On the other hand, long-term antidepressant medication can be neuroprotective and some studies have linked the use of antidepressants to an increase in hippocampal volume in patients with major depressive disorder (Amico et al., 2011; Malykhin et al., 2010). It has been shown that antidepressants increase hippocampal neurogenesis (Anacker et al., 2011). Thus, both affective symptoms (Baynes et al., 2000) and antidepressant medication (Kraus et al., 2014) are known to impact brain structure.

In the present study, we addressed for the first time the effect of antidepressant treatment and attenuated negative psychotic symptoms on the neurobiology of ARMS. Firstly, we hypothesized that ARMS individuals without current antidepressant treatment (ARMS-nonAD) would manifest more severe attenuated negative symptoms than ARMS subjects currently receiving antidepressants (ARMS-AD). Secondly, we hypothesized that ARMS-AD individuals would have increased GMV in regions associated with depressive symptoms and/or antidepressant medication (hippocampus, anterior cingulate gyrus, amygdala and precuneus) compared to the ARMS-nonAD individuals. Thirdly, we hypothesized that the volumetric abnormalities in gray matter between ARMS-AD and ARMS-nonAD would be associated with attenuated negative symptoms.

2. Materials and methods

2.1. Subjects

MRI data were collected within the framework of a research program on the early detection of psychosis. The subjects were recruited in our specialized clinic for the early detection of psychosis (FEPSY) at the Psychiatric Outpatient Department, Psychiatric University Clinics Basel, Switzerland (Riecher-Rössler et al., 2006).

The entire group of ARMS individuals (n = 49) conforms to Yung's criteria (Yung et al., 1998) and overlaps with previously published data (Borgwardt et al., 2007a; Borgwardt et al., 2007b; Smieskova et al., 2012a; Smieskova et al., 2012b). All the ARMS individuals were antipsychotic-free and were assessed prior to the neuroimaging session. ARMS inclusion required one or more of the following:

(a) attenuated psychotic symptoms that do not reach full psychosis threshold
(b) brief limited intermittent psychotic symptoms (lasting less than a week with spontaneous remission)
(c) a first degree relative with a psychotic disorder plus at least two indicators of a clinical change, such as a marked decline in social or occupational functioning.

We assessed the subjects using the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008), the Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) and the Global Assessment of Functioning (GAF) (Endicott et al., 1976). Attenuated negative psychotic symptom severity was investigated with the cluster 'negative symptoms', calculated from the BPRS as a sum of blunted affect, emotional withdrawal, and motor retardation (BPRS16, BPRS17 and BPRS18) (Fusar-Poli et al., 2014b; Velligan et al., 2005). Additionally, we calculated 'mood disturbance' BPRS cluster as a sum of anxiety, depression, suicidality and guilt (BPRS02, BPRS03, BPRS04 and BPRS05) (Thomas et al., 2004), as well as depression (BPRS03) and motor retardation (BPRS18) scores alone. We used these scores for stepwise regression analysis with backward elimination.

In a second step, we divided the ARMS individuals into two subgroups, based on whether they were currently being treated with antidepressants (ARMS-AD, n = 18) or not (ARMS-nonAD, n = 31) (Table 1). Antidepressant medication within the AD subgroup included: fluoxetine (SSRI; n = 2), escitalopram (SSRI; n = 5), sertraline (SSRI; n = 1), mirtazapine [NaSSA (noradrenergic and specific serotonergic antidepressant); n = 4], venlafaxine [SSNRI (selective serotonin–norepinephrine reuptake inhibitor), n = 2], duloxetine (SSNRI; n = 2), fluoxetine plus trazodone [SSRI, SARI (serotonin antagonist and reuptake inhibitor); n = 1] and St. John's Wort (n = 1). Antidepressant therapy had a mean duration of 50 ± 47 days (range 4–170 days). In order to exclude possible biases through antipsychotic therapy, we confirmed that all individuals were antipsychotic-free. In addition, current and previous psychotropic medication, alcohol, nicotine, cannabis, and other illegal drug consumption were assessed using a semi-structured interview, as adapted from the Drug and Alcohol Assessment Schedule of the Early Psychosis Prevention and Intervention Centre (EPPIC).

Participants were excluded from the study if they presented with a history of previous psychotic disorder, psychotic symptomatology secondary to an organic disorder, substance abuse, affective psychosis, borderline personality disorder, age under 18 or over 40, inadequate knowledge of the German language or IQ less than 70 (assessed by multiple-choice vocabulary intelligence test) (Lehrl et al., 1995).

Healthy controls (n = 24) were from the same geographical area as the other groups (Table 1). All participants provided written informed consent. The study was approved by the local ethics committee.

2.2. Magnetic resonance imaging acquisition

For structural imaging, a whole brain 3D T_1-weighted MPRAGE (magnetization prepared rapid acquisition gradient) sequence was applied using a 3 T magnetic resonance imaging scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) and a 12-channel radio frequency head coil. The acquisition was based on a sagittal matrix of 256 × 256 × 176 and 1 × 1 × 1 mm^3 isotropic spatial resolution, with an inversion time of 1000 ms, repetition time of 2 s, echo time of 3.4 ms, flip angle of 8° and bandwidth of 200 Hz/pixel. All images were reviewed by trained neuroradiologists for radiological abnormalities.