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# Classifying individuals at high-risk for psychosis based on functional brain activity during working memory processing

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ABSTRACT

The psychosis high-risk state is accompanied by alterations in functional brain activity during working memory processing. We used binary automatic pattern-classification to discriminate between the at-risk mental state (ARMS), first episode psychosis (FEP) and healthy controls (HCs) based on n-back WM-induced brain activity. Linear support vector machines and leave-one-out-cross-validation were applied to fMRI data of matched ARMS, FEP and HC (19 subjects/group).

The HC and ARMS were correctly classified, with an accuracy of 76.2% (sensitivity 89.5%, specificity 63.2%, $p = 0.01$) using a verbal working memory network mask. Only 50% and 47.4% of individuals were classified correctly for HC vs. FEP ($p = 0.46$) or ARMS vs. FEP ($p = 0.62$), respectively. Without mask, accuracy was 65.8% for HC vs. ARMS ($p = 0.03$) and 65.8% for HC vs. FEP ($p = 0.0047$), and 57.9% for ARMS vs. FEP ($p = 0.18$). Regions in the medial frontal, paracingulate, cingulate, inferior frontal and superior frontal gyri, inferior and superior parietal lobules, and precuneus were particularly important for group separation.

These results suggest that FEP and HC or FEP and ARMS cannot be accurately separated in small samples under these conditions. However, ARMS can be identified with very high sensitivity in comparison to HC. This might aid classification and help to predict transition in the ARMS.



## 1. Introduction

Working memory deficits are considered to be a central manifestation of the pathophysiology of schizophrenia (Forbes et al., 2009) and behavioural deficits in working memory processing (Pflueger et al., 2007) are already evident before the onset of the disorder in individuals with an at-risk mental state (ARMS) (Fusar-Poli et al., 2012d). Alterations in functional brain activity (Smieskova et al., 2012a) during working memory processing have been reported in ARMS subjects. In comparison to healthy controls (HCs), subjects at high risk for psychosis exhibited reduced prefrontal and parietal activation during the n-back task (Fusar-Poli et al., 2010).

There is increasing evidence that vulnerability to psychosis is associated with dysfunctional connectivity (Schmidt et al., 2013b). For example, Crossley et al. (2009) demonstrated a progressive increase in dysfunctional frontotemporal connectivity during a working memory task from HC to ARMS individuals and further to patients with FEP. Beyond connectivity, ARMS is also associated with abnormalities of regional brain structure (Fusar-Poli et al., 2012e; Smieskova et al., 2010), activity (Broome et al., 2010), and neurochemistry (Allen et al., 2012; Fusar-Poli et al., 2011b) that are qualitatively similar to but less severe than those in patients with overt psychosis (Fusar-Poli et al., 2007b). There is also evidence suggesting that within ARMS individuals, prefrontal dysfunction during WM is related to grey matter abnormalities in the same regions (Fusar-Poli et al., 2011a).

However, it is still unclear whether functional brain activity during working memory processing can be used for the individual classification and prognosis of patients at high clinical risk.

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At present, individuals considered at high-risk for psychosis are clinically identified according to the PACE (Personal Assessment and Crisis Evaluation Clinic, Melbourne) criteria if they present with "attenuated" psychotic symptoms, full-blown psychotic symptoms that are brief and self-limiting (Riecher-Rossler et al., 2007a; Riecher-Rössler et al., 2009; Yung et al., 2004), or a significant decrease in functioning in the context of a family history of schizophrenia (Fusar-Poli et al., 2012b). This can lead to the correct prediction of a subsequent transition to a first psychotic episode in only 29% (Fusar-Poli et al., 2012a) of ARMS individuals after 2 years and in 35 (Nelson et al., 2013)–49% (Klosterkotter et al., 2001) after 3–10 years. Thus, in practical terms, it is difficult to predict which subjects with an ARMS will later develop psychosis on the basis of their presentation of clinical features and neuropsychological markers (Fusar-Poli et al., 2012c).

Multivariate automatic pattern classification of individuals at high-risk may be a promising approach to predicting the development of psychoses in individuals with ARMS (Lao et al., 2004; Mandl et al., 2013a). These methods categorise individuals by identification of the multivariate statistical properties of the data that discriminate between groups of subjects (Klöppel et al., 2008b; Lao et al., 2004). In this context, support vector machines (SVMs) have emerged as a powerful tool, as these machines can learn to categorise complex, high dimensional training data and to generalise the learned classification rules to new data (Koutsouleris et al., 2012; Noble, 2006). SVMs use information from all available voxels, which are combined to reflect differences between groups (Klöppel et al., 2008a), in order to create classifiers that allow the clinician to make predictions for newly acquired (or unseen) data (Klöppel et al., 2008b; Rizk-Jackson et al., 2011). SVMs have been successfully applied to structural MRI data and can distinguish between ARMS subjects and healthy controls (HCs) with high accuracy (Borgwardt et al., 2013b; Koutsouleris et al., 2012; Koutsouleris et al., 2009a). A limited number of studies have employed MRI data to investigate neurofunctional classifiers in individuals at risk of psychosis, in order to demonstrate that subtle differential functional patterns subserving emotional processing may make a major contribution towards identifying individuals who tend towards psychosis (Modinos et al., 2012; Modinos et al., 2013).

## 2. Aims of the study

Despite substantial evidence of working memory deficits both, at the time of first episode of the disease (Mesholam-Gately et al., 2009), and predating the onset of psychosis (Fusar-Poli et al., 2012c), so far it has not been assessed if discriminative information regarding vulnerability for psychosis resides in working memory alterations. In this study, we sought to examine whether subjects with an ARMS can be identified on the basis of their individual response within a working memory network of regions activated in a verbal identity-monitoring variant of the n-back task (Owen et al., 2005). We used previously collected contrast images of fMRI data (Smieskova et al., 2012a) and applied pattern classification using linear SVMs and leave-one-out cross-validation (Klöppel et al., 2008b, 2009).

Based on previous structural (Borgwardt et al., 2013b; Koutsouleris et al., 2009a, 2012) and functional (Modinos et al., 2012, 2013) SVM MRI studies of subjects with an ARMS, we hypothesised that prefrontal activations could make a predominant contribution to the classification of the ARMS. On the assumption that increasing task demand increases the magnitude of neurofunctional abnormalities in ARMS (Fusar-Poli et al., 2007b), we expected robust discrimination of ARMS and HC, with high classification accuracies. On the other hand, we expected that it would be much more difficult to differentiate ARMS and FEP patients on the basis of their working memory activations (Borgwardt et al., 2013a).

## 3. Methods

### 3.1. Participants

Subjects with an ARMS and FEP patients were assessed at the time of MRI scan. Inclusion required one or more of the following: (a) "attenuated" psychotic symptoms, (b) brief limited intermittent psychotic symptoms (BLIPS), or (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. All ARMS individuals were antipsychotic-naive. Subjects were assessed using the 'Basel Screening Instrument for Psychosis' (BSIP) (Riecher-Rossler et al., 2007b), 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). The BSIP evaluates "prodromal" symptoms occurring in the previous 5 years; nonspecific "prodromal" signs (Riecher-Rossler et al., 2007b) occurring in the previous 2 years; previous or current psychotic symptoms, psychosocial functioning over the last 5 years, substance dependency; and psychotic disorders in first and second degree relatives (Riecher-Rossler et al., 2008). The group of individuals with an ARMS corresponds to the Personal Assessment and Crisis Evaluation (PACE) criteria by Yung et al. (1998). The FEP patients met the operational criteria for FEP according to Breitborde et al. (2009). Current and previous psychotropic medication, alcohol, nicotine, cannabis, and consumption of other illegal drugs were investigated by using a semi-structured interview adapted from the Early Psychosis Prevention and Intervention Centre (EPPIC) Drug and Alcohol Assessment Schedule (http://www.eppic.org.au). The exclusion criteria for these subjects were: history of previous psychotic disorder treated with antipsychotics; psychotic symptomatology secondary to an "organic" disorder; substance abuse according to the ICD-10 research criteria; psychotic symptomatology associated with an affective psychosis or a borderline personality disorder; age under 18 years; insufficient knowledge of the German language; and IQ less than 70 (Lehrl et al., 1995).

In ARMS subjects, clinical follow-up occurred on average 4.8 ± 8.6 months (range = 0–24 months) after their baseline MRI scans. During the follow-up period, 4 ARMS subjects (21%) made a transition to a first episode of psychosis, according to the PACE criteria (Yung et al., 1998). HCs were recruited from the same geographical area as the other groups. All subjects were representative of the local population of individuals presenting with an ARMS or FEP in terms of age, sex, handedness, and alcohol and cannabis consumption. These individuals had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, substance abuse, and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical semi-structured interview. All participants provided written informed consent, and the study was approved by the Research Ethics Committee.

### 3.2. MR image acquisition

Functional data were acquired on a 3 T scanner (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany) using an echo planar sequence with a repetition time of 2.5 s, echo time of 28 ms, matrix 76 × 76, 126 volumes and 38 slices with 0.5 mm interslice gap, that gave a resolution of 3 × 3 × 3 $mm^3$, and a field of view of 228 × 228 $cm^2$.

### 3.3. n-back working memory task

A well-established n-back working memory task (Smieskova et al., 2012a) was administered to patients and controls. With an interstimulus interval of 2 s, all subjects were presented with a series of black letters on a white background in a prismatic mirror. Each stimulus was presented for 1 s. The size of the letters was 8 cm projected onto the