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Use of neuroanatomical pattern regression to predict the structural brain dynamics of vulnerability and transition to psychosis

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ABSTRACT

Background: The at-risk mental state for psychosis (ARMS) has been associated with abnormal structural brain dynamics underlying disease transition or non-transition. To date, it is unknown whether these dynamic brain changes can be predicted at the single-subject level prior to disease transition using MRI-based machine-learning techniques.
Methods: First, deformation-based morphometry and partial-least-squares (PLS) was used to investigate patterns of volumetric changes over time in 25 ARMS individuals versus 28 healthy controls (HC) (1) irrespective of the clinical outcome and (2) according to illness transition or non-transition. Then, the baseline MRI data were employed to predict the expression of these volumetric changes at the individual level using support-vector regression (SVR).
Results: PLS revealed a pattern of pronounced morphometric changes in ARMS versus HC that affected predominantly the right prefrontal, as well as the perisylvian, parietal and periventricular structures ($p<0.011$), and that was more pronounced in the converters versus the non-converters ($p<0.010$). The SVR analysis facilitated a reliable prediction of these longitudinal brain changes in individual out-of training cases (HC vs ARMS: $r=0.83$, $p<0.001$; HC vs converters vs non-converters: $r=0.83$, $p<0.001$) by relying on baseline patterns that involved ventricular enlargements, as well as prefrontal, perisylvian, limbic, parietal and subcortical volume reductions.
Conclusions: Abnormal brain changes over time may underlie an elevated vulnerability for psychosis and may be most pronounced in subsequent converters to psychosis. Pattern regression techniques may facilitate an accurate prediction of these structural brain dynamics, potentially allowing for an early recognition of individuals at risk of developing psychosis-associated neuroanatomical changes over time.

1. Introduction

The at-risk mental state for psychosis (ARMS) has been associated with subtle brain abnormalities (Borgwardt et al., 2007a,b; Koutsouleris et al., 2009a,b; Lawrie et al., 1999; Meisenzahl et al., 2008b; Pantelis et al., 2003; Seidman et al., 2003) qualitatively similar to those found in established schizophrenia (Gaser et al., 2004; Honea et al., 2005; Koutsouleris et al., 2008; Meisenzahl et al., 2008a). Recent

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studies suggested that these alterations are neither confined to single cortical regions nor dispersed across the entire brain, but rather involve interconnected neural systems spanning prefrontal, perisylvian, parietal, limbic and cerebellar regions (Borgwardt et al., 2008; Koutsouleris et al., 2009b; Pantelis et al., 2003; Sun et al., 2009b). Additionally, investigations of longitudinal neuroanatomical changes in clinically defined ARMS individuals (Borgwardt et al., 2008; Pantelis et al., 2003; Sun et al., 2009b; Takahashi et al., 2009) and genetically defined high-risk subjects (Job et al., 2005, 2006; Lawrie et al., 2002) mainly found progressive volume losses within this "prodromal" pattern that primarily affected individuals with a subsequent illness transition. These findings have been interpreted within the concept of a "late neurodevelopmental disturbance", evolving on the basis of a pre-existing neurobiological predisposition when cortical association areas are placed under increasing functional demand in late adolescence and early adulthood (Pantelis et al., 2005).

It is, however, unclear whether this process is *exclusively* active in those who ultimately develop the disease. Alternatively, the neurobiology of the ARMS may be characterized by a *gradual* progression of structural changes that reaches its full expression across disease transition, but that can also be traced to a lesser extent in vulnerable subjects without subsequent illness (DeLisi, 2008; Koutsouleris et al., 2009b; Takahashi et al., 2009). Thus, in the context of a possible neuroimaging-aided early recognition of psychosis (Bray et al., 2009; Koutsouleris et al., 2009a; Linden and Fallgatter, 2009; Sun et al., 2009c), it has to be evaluated (1) whether *spatiotemporal* neuroanatomical patterns underlying the ARMS can be deconstructed into specific illness-associated trajectories and trajectories conferring an unspecific vulnerability, and (2) whether these trajectories can be predicted at the individual level prior to disease transition.

The existing data suggest that ARMS-associated structural abnormalities are subtle and likely to occur within multicollinear patterns involving networks of interconnected brain regions. Therefore, univariate statistics may be limited in detecting these morphological signatures and in measuring their expression at the single-subject level for the purpose of an individualized early recognition, because these methods degrade these complex patterns into largely overlapping voxel-by-voxel measurements (Davatzikos, 2004). However, these limitations may be overcome by a methodological shift to multivariate analysis methods capable of tracing the high-dimensional structure of ARMS-associated morphological profiles at baseline and over time.

Therefore, we used deformation-based morphometry and partial least squares (PLS) (Gilboa et al., 2005; Kawasaki et al., 2007; McIntosh et al., 1996; Menzies et al., 2007; Nestor et al., 2002; Tura et al., 2008) (1) to investigate system-level covariance patterns of longitudinal structural brain changes in clinically defined ARMS individuals versus healthy controls, and (2) to examine whether these patterns were *exclusively* driven by ARMS individuals subsequently developing a schizophrenia spectrum disorder or, alternatively, whether subjects without disease transition expressed similar brain dynamics, albeit to a lesser degree. We expected these trajectories (1) to involve patterns of volumetric losses covering prefrontal, perisylvian, parietal, limbic and cerebellar structures, and (2) to be differentially expressed according to illness transition or non-transition. Furthermore, we explored whether the expression of these trajectories could be predicted at the *individual level* using only the MRI data acquired at study inclusion. For this purpose, we employed support-vector regression (SVR) (Schölkopf and Smola, 2002), a multivariate machine-learning technique, due to its good generalization properties. We expected the SVR predictions to rest upon a neuroanatomical baseline pattern covering those brain regions that were subsequently affected by abnormal morphometric change.

2. Materials and methods

2.1. Participants

A prospective study of 28 healthy volunteers (HC; age at baseline (SD): 25.1 (3.6), 39% females) and 25 ARMS individuals (age at baseline (SD): 23.1 (4.7), 28% females) was conducted using structural MRI scanning and clinical assessments at baseline and after a mean (SD) of 3.7 (1.3) years. All followed subjects were part of a baseline population of 75 HC and 46 ARMS individuals (Koutsouleris et al., 2009a,b) who were recruited using previously described operationalized criteria employed by our and other research groups to study the neurobiology of the ARMS (Frommann et al., 2008; Hurlemann et al., 2008; Koutsouleris et al., 2009a,b; Meisenzahl et al., 2008b; Quednow et al., 2008; Schultze-Lutter et al., 2007). Briefly, different types of prodromal symptoms, including cognitive/perceptive basic symptoms taken from the Bonn Scale for Assessment of Prodromal Symptoms (Kojoh and Hirasawa, 1990; Klosterkötter et al., 2001), as well as the subthreshold psychotic symptoms closely corresponding to the PACE criteria (Yung et al., 2003, 2004), including Attenuated Psychotic Symptoms (APS) as well as Brief Limited Intermittent Psychotic Symptoms (BLIPS) were used to define an ARMS for psychosis (Table 1).

Study inclusion required *either* (1) a positive global functioning & trait marker, *or* (2) at least one positive psychopathological state marker fulfilling specific duration criteria (Table 1). Exclusion criteria (Table 1) were assessed by obtaining the personal and familial history using a semi-structured clinical interview as well as the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). Subjects were excluded from the study if they met the following criteria, including (1) disease transition as defined by Yung et al., (1998), (2) a past or present diagnosis of schizophrenia spectrum and bipolar disorders, as well as delirium, dementia, amnestic or other cognitive disorders, mental retardation and psychiatric disorders due to a somatic factor, following the DSM-IV criteria, (3) alcohol or drug abuse within three months prior to examination, (4) past or present inflammatory, traumatic or epileptic diseases of the central nervous system and (5) any previous treatment with antipsychotics. All participants provided their written informed consent prior to study inclusion. The study was approved by the Local Research Ethics Committee of the Ludwig-Maximilians-University.

Included ARMS individuals were seen weekly in the first month, monthly in the first year, quarterly in the second year and thereafter annually to detect a possible transition to psychosis as defined by Yung et al. (1998). All followed ARMS