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Prediction of outcome in the psychosis prodrome using neuroanatomical pattern classification

Lana Kambeitz-Ilankovic [a,*], Eva M. Meisenzahl [a], Carlos Cabral [a], Sebastian von Saldern [a], Joseph Kambeitz [a], Peter Falkai [a], Hans-Jürgen Möller [a], Maximilian Reiser [b], Nikolaos Koutsouleris [a]

[a] Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany
[b] Department of Radiology, Ludwig-Maximilian-University, Munich, Germany

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ABSTRACT

To date, research into the biomarker-aided early recognition of psychosis has focused on predicting the transition likelihood of clinically defined individuals with different at-risk mental states (ARMS) based on structural (and functional) brain changes. However, it is currently unknown whether neuroimaging patterns could be identified to facilitate the individualized prediction of symptomatic and functional recovery.

Therefore, we investigated whether cortical surface alterations analyzed by means of multivariate pattern recognition methods could enable the single-subject identification of functional outcomes in twenty-seven ARMS individuals. Subjects were dichotomized into 'good' vs. 'poor' outcome groups on average 4 years after the baseline MRI scan using a Global Assessment of Functioning (GAF) threshold of 70.

Cortical surface-based pattern classification predicted good (N = 14) vs. poor outcome status (N = 13) at follow-up with an accuracy of 82% as determined by nested leave-one-cross-validation. Neuroanatomical prediction involved cortical area reductions in superior temporal, inferior frontal and inferior parietal areas and was not confounded by functional impairment at baseline, or antipsychotic medication and transition status over the follow-up period. The prediction model's decision scores were correlated with positive and general symptom scores in the ARMS group at follow-up, whereas negative symptoms were not linked to predicted poorer functional outcome.

These findings suggest that poorer functional outcomes are associated with non-resolving attenuated psychosis and could be predicted at the single-subject level using multivariate neuroanatomical risk stratification methods. However, the generalizability and specificity of the suggested prediction model should be thoroughly investigated in future large-scale and cross-diagnostic MRI studies.

1. Introduction

Recent univariate and multivariate Magnetic Resonance Imaging (MRI) studies investigating volumetric and surface-based cortical abnormalities in individuals at high risk for psychosis have confirmed that some of the alterations are already present during the at-risk mental state for psychosis (ARMS) (Fusar-Poli et al., 2011) and may be predictive of a later transition to the frank disorder (Smieskova et al., 2010). Moreover, recent proof-of-concept applications of multivariate pattern classification methods suggested that a subsequent disease transition might be predicted at the individual level using structural MRI in populations at clinical risk of developing the illness (Koutsouleris et al., 2009a, 2009b; Koutsouleris et al., 2014). Nevertheless, reliable imaging predictors of symptomatic and functional recovery among non-converting high risk individuals who represent the majority of the ARMS populations have not been investigated yet. It is noteworthy that recent studies emphasized that ARMS individuals, who ultimately did not convert to psychosis, remained at a lower level of functioning compared to non-psychiatric comparison subjects (Addington et al., 2011; Gee and Cannon, 2011). Furthermore, several studies investigating cost-effective treatments in psychosis indicated that intensive early intervention programs may not only improve the clinical course of psychotic disorders (Cullberg et al., 2006; Mihalopoulos et al., 2009) but also improve their global level of functioning compared to standard treatment or no treatment (Hastrup et al., 2013; Stafford et al., 2013). Thus, the elucidation of the determinants and potential modifiers of functional outcome trajectories in early stages of psychosis has increasingly moved into the focus of international research efforts (Yung et al., 2012).

* Corresponding author at: Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Nussbaumstr. 7, 80336 Munich, Germany. Tel.: +49 89 4400 53447.
E-mail address: Lana.Kambeitz-Ilankovic@med.uni-muenchen.de (L. Kambeitz-Ilankovic).

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The growing knowledge about enduring functional impairment and disability in ARMS patients (Cornblatt et al., 2007; Velthorst et al., 2010) encourages the search for prognostic biomarkers to individually predict functional outcome independent of a subsequent transition to full-blown psychosis. While neuroimaging investigations on different ARMS populations provided converging evidence for a pattern of distributed, but regionally specific reductions of gray matter (Pantelis et al., 2003; Meisenzahl et al., 2008; Takahashi et al., 2009; Mechelli et al., 2011) and cortical thickness alterations (Jung et al., 2011; Ziermans et al., 2012; Benetti et al., 2013), with particular foci located in frontal, cingulate and temporal brain areas (Borgwardt et al., 2007; Witthaus et al., 2009; Jung et al., 2012), structural brain alterations have scarcely been related to the functional outcome dimension. Although a majority of studies suggests that cortical changes in temporal, parietal and cingulate areas are shared by unaffected relatives of psychotic patients (Honea et al., 2005; Goghari et al., 2007; Calabrese et al., 2008; Goldman et al., 2009; Yang et al., 2010), the literature remains unclear which structural brain components specifically map to the vulnerability, transition likelihood and functional outcome dimensions. Importantly, it has been suggested that converters and non-converters indeed share a common ground of cortical alterations that amplifies during transition to psychotic illness (Cannon et al., 2015). Along this line of research recent studies using sensitive analysis of cortical surface contraction (Sun et al., 2009a, 2009b; Takahashi et al., 2009) provided further insight into alterations of prefrontal regions during illness transition, while others (Tognin et al., 2014) suggested that there were no significant differences in cortical thickness alterations between ARMS subjects who later developed psychosis and those who did not. The aim of the present study was to investigate whether cortical surface changes analyzed by means of multivariate pattern recognition methods can individually predict subsequent functional outcome in individuals with different ARMS for psychosis. To the best of our knowledge, this is the first study to explore structural brain markers for individualized outcome prediction beyond the classical categorization of clinical outcome into conversion and non-conversion to psychosis. The detection of individuals with specific brain alterations associated with poorer outcome at follow-up may help in identifying a critical group of at-risk persons, who irrespective of diagnostic thresholds require clinical treatment and therapeutic support. Thus, such tools for an outcome-based and biologically-founded stratification of the ARMS could pave the way towards early interventions aiming at mitigating the disability associated with enduring attenuated psychosis.

2. Methods

2.1. Participants

Twenty-seven individuals in an ARMS for psychosis (Table 1) were recruited at the Early Detection and Intervention Centre for Mental Crises, Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Germany, using operationalized criteria as detailed in series of previous work (Koutsouleris et al., 2009a, 2009b; Koutsouleris et al., 2010b). These criteria were based on a two-stage concept of the ARMS, distinguishing between (1) an "early" ARMS (ARMS-E), mainly defined by the presence of basic symptoms and associated with an increased, but not imminent risk of psychosis, and (2) a "late" ARMS (ARMS-L), characterized by an ultra-high risk for psychosis following the Personal Assessment of Crisis Evaluation (PACE) criteria (Yung et al., 1998). In summary, potential ARMS subjects meeting defined sets of state and/or trait markers were included in the study. Inclusion based on global functioning & trait factors required a ≥30 point reduction in the DSM-IV Global Assessment of Functioning (GAF) Scale and (1) a familial history of psychotic disorders in the first-degree relatives, or (2) a personal history of pre-/perinatal complications. Inclusion based on psychopathological state markers required at least 1 positive item in the basic symptoms, attenuated psychotic or brief limited intermittent psychotic symptom categories of the Inclusion Criteria Checklist following specific time and duration criteria (Koutsouleris et al., 2009a). Nine/eighteen ARMS individuals fulfilled criteria for the ARMS-E/ARMS-L state at study inclusion.

Table 1
Demographic and clinical parameters of the ARMS samples.

Sociodemographic variables	GAF− group	GAF+ group	T/χ2	P
N	14	13		
Mean age at follow-up [years] (SD)	23.5 (4.7)	23.2 (5.2)	.89	ns
Handedness (right)	13	11	.46	ns
Sex (male)	11	8	.94	ns
Years of education	11.7 (1.5)	11.8 (1.2)	−.10	ns
Mean verbal IQ [MWT-B, Z score]* (SD)	−0.85 (1.2)	0.25 (1.9)	1.23	ns
Medication				
Antidepressants (yes/no)	4/10	2/11	1.95	ns
Mood stabilizers (yes/no)	2/12	1/12	0.30	ns
Clinical variables				
Baseline T0				
Mean PANSS positive symptoms score (SD)	9.8 (2.0)	11.1 (3.4)	−.86	ns
Mean PANSS negative symptoms score (SD)	12.3 (4.4)	13.4 (8.7)	−.28	ns
Mean PANSS general score (SD)	24.8 (3.5)	28.6 (9.0)	−.99	ns
Mean PANSS total score (SD)	47 (7.4.)	53.2 (19.1)	−.76	ns
Mean MADRS score (SD)	13.4 (10.4)	12.6 (5.7)	.20	ns
Follow-up T1				
Mean PANSS positive symptoms score (SD)	15 (5.4)	8.6 (2.1)	3.73	.005
Mean PANSS negative symptoms score (SD)	20.6 (8.1)	13.7 (6.8)	2.16	.044
Mean PANSS general score (SD)	37.6 (10.7)	23.5 (4.5)	4.12	.002
Mean PANSS total score (SD)	73.2 (21.4)	45.9 (10.8)	3.87	.003
Mean MADRS score (SD)	9.6 (7.6)	7.0 (5.2)	1.02	ns

Candidate ARMS individuals were carefully screened for exclusion criteria by evaluating the personal and familial history using a semi-structured clinical interview and the Structured Clinical Interview for DSM-IV. More specifically, subjects were excluded if they met criteria for (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. Besides the assessment of global functioning, the ARMS individuals were evaluated using the Positive and Negative Symptom Scale (PANSS; Kay et al. (1987)) and the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg (1979)). The present sample largely overlapped (93%) with the ARMS group analyzed in Koutsouleris, Gaser et al. (2010a). All participants provided their written informed consent prior to study inclusion. The study was approved by the Local Research Ethics Committee of the Ludwig-Maximilian-University.

Included ARMS individuals were seen weekly in the first month, monthly in the first year, quarterly in the second year and annually thereafter to detect a possible transition to psychosis as defined by Yung et al. (1998). The mean (SD) follow-up interval measured 3.8 (1.2) years. All followed ARMS individuals were offered supportive counselling and clinical management. At follow-up, a complete re-examination was performed and the ARMS individuals were subgrouped either into an ARMS non-transition (ARMS-NT, n = 15) or a transition (ARMS-T, n = 12) group, if they met the transition criteria during the follow-up period and had a confirmed diagnosis of schizophrenia spectrum disorder according to DSM-IV criteria one year after transition. The mean (SD) time to transition measured 7.3 (8.7) months. Fourteen subjects received atypical antipsychotics during the follow-up period (9 ARMS-T, 5 ARMS-NT). For the present analysis,