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Functional and structural correlates of abnormal involuntary movements in psychosis risk and first episode psychosis

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ABSTRACT

Background: Abnormal involuntary movements (AIM) may occur throughout the course of psychosis. While AIM are thought to indicate striatal abnormalities, the functional and structural correlates of increased AIM remain elusive. Here, we examined the prevalence of AIM in patients with clinical high risk for psychosis (CHR), first episode psychosis (FEP) and clinical controls (CC). Furthermore, we tested the association of AIM with regional cerebral blood flow (rCBF), grey matter volume (GMV), and premorbid IQ.
Methods: We conducted a video-based analysis of AIM in patients with CHR ($n = 45$), FEP ($n = 10$) and CC ($n = 39$), recruited in the Early Detection and Intervention Center, Bern. Premorbid intelligence was evaluated using the Peabody Picture Vocabulary test. Additionally, arterial spin labeling MRIs and structural MRIs were acquired in a subgroup of the sample to investigate the association of AIM with rCBF and GMV.
Results: Higher total AIM scores were detected in CHR ($p = 0.02$) and FEP ($p = 0.04$) as compared to CC. When separated for different muscle groups, lips and perioral movements were significantly increased in CHR patients as compared to CC ($p = 0.009$). AIM scores correlated positively with rCBF in the premotor cortex, Brodmann area 6 ($p < 0.05$, FWE corrected). Negative correlations were found between AIM and GMV of the corresponding caudal middle frontal gyrus ($p = 0.04$, FWE corrected) and premorbid intelligence ($p = 0.02$).
Conclusions: AIM were more frequent in the psychosis spectrum than in clinical controls. Neuroimaging findings indicate an involvement of cortical motor areas in abnormal motor behavior, instead of pure basal ganglia pathology.

1. Introduction

Early detection and intervention of psychotic disorders has been widely recognized for its potential to alter the course of psychotic disorders (Fusar-Poli et al., 2013; Schmidt et al., 2015; Schultze-Lutter et al., 2015).

For the assessment of clinical high-risk (CHR) criteria of psychosis (Fusar-Poli et al., 2015; Schmidt et al., 2015; Schultze-Lutter et al., 2015), two major approaches are currently used (Fusar-Poli et al., 2013; Fusar-Poli et al., 2015; Schultze-Lutter et al., 2015): the ultra-high risk (UHR) criteria and the basic symptom (BS) criteria (Schultze-Lutter et al., 2015; Schultze-Lutter et al., 2012). Meta-analyses report CHR conversion rates of 18% after six months and 36% after 3 years (Fusar-Poli et al., 2012).

However, because of the considerable rate (~65%) of CHR patients not converting to psychosis, additional clinical and neurobiological predictors have been suggested to improve the prognostic value of CHR criteria (Cannon, 2016; Hirjak et al., 2018a; Khoury and Nasrallah, 2018; Mikanmaa et al., 2019; van Harten et al., 2017).

A promising clinical marker in early detection research is the presence of motor abnormalities. Motor system pathology in psychosis is increasingly acknowledged (Hirjak et al., 2018a; van Harten et al., 2017; Walther and Mittal, 2017). Motor symptoms occur frequently in first episode psychosis (FEP) and CHR subjects. Moreover, motor abnormalities can be readily and objectively assessed (van Harten et al., 2017). Furthermore, recent evidence suggests that motor biotypes exist among CHR subjects delineating distinct clinical and

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cognitive profiles, neurobiology, and transition risk (Dean et al., 2018). In psychosis, motor symptoms have been detected in 66% of the first-episode, never-medicated patients and in 80% of the chronically medicated schizophrenia patients (Walther and Strik, 2012).

Abnormal involuntary movements (AIM) have received increasing interest due to their potential use as markers for psychosis risk. Indeed, AIM are found in CHR patients (Callaway et al., 2014) and unaffected first-degree relatives of schizophrenia patients (Koning et al., 2010). AIM can appear as dyskinetic, choreoathetoid movements in neck or extremities, as tics or facial grimacing (Whitty et al., 2009). For the clinical assessment of AIM, several scales are available; one is the abnormal involuntary movement scale (AIM scale) (Guy, 1976). A random-sampling community study on the link of AIM to CHR state has revealed that AIM were more frequent in unmedicated children and adolescents who fulfilled CHR criteria compared to those who did not (Kindler et al., 2016). Thus in both, persons with schizophrenia and those with increased risk for psychosis AIM are increased (Mittal et al., 2011b). Neuroimaging studies have indicated a link between dyskinetic movements and reduced striatal grey matter volume in CHR patients (Mittal et al., 2010a).

The pathophysiology of motor symptoms involves a widely distributed brain network including the thalamus, basal ganglia, cerebellum and motor and premotor cortical areas (van Harten et al., 2017; Walther and Mittal, 2017). Studies consistently suggest that different types of motor symptoms involve distinct and, thus, specific network loops (Mittal et al., 2017; Viher et al., 2019; Walther et al., 2017b). In AIM, the loop between motor cortex and basal ganglia seems to be critical, indicated by studies on neurological disorders (Fennema-Notestine et al., 2004). However, knowledge on brain structure or function related to AIM in psychiatric and particularly in psychotic disorders is sparse (Walther, 2015). Altered grey matter volume (GMV) was detected in motor areas in patients with schizophrenia with concurrent motor symptoms (Stegmayer et al., 2014). One study reported reduced GMV in the superior frontal gyrus in chronic schizophrenia patients with dyskinesia, suggesting a role of the premotor cortex (Li et al., 2013).

Cortico-subcortical loops of motor domains are contributing to cognitive performance and studies have reported associations between cognitive symptoms and AIM (Waddington et al., 1987). Previously, a negative correlation between premorbid IQ and AIM has been reported in a community-based sample of neuroleptic-naïve minors (Magulac et al., 1999) and in patients with schizophrenia (Fenton et al., 1994; Manschreck et al., 1990). A recent study showed the clustering of impaired motor performance with reduced cognitive performance in CHR patients, and also the highest probability of conversion to psychosis (Dean et al., 2018). Thus, the combination of motor symptoms and cognitive deterioration might bring additional predictive value.

Regional cerebral blood flow (rCBF) as measured with arterial spin labeling (ASL) magnetic resonance imaging (MRI) reflects localized metabolic activity. ASL-rCBF has successfully been applied in different stages of psychosis measuring functional cortical pathologies (Kindler et al., 2013; Kindler et al., 2015; Squarcina et al., 2015), plus providing the potential to measure changes in striatal neuronal activity (Allen et al., 2018; Allen et al., 2016; Kindler et al., 2018).

In light of these initial findings, the first aim of the present study was to investigate whether the occurrence of AIM was higher in individuals with CHR and FEP as compared to CC using an observer-based assessment from videos collected from clinical interviews. The second aim was to search for both functional and structural brain correlates of observed AIM in this sample. According to the Research Domain Criteria (RDoC) framework that recently included a motor domain and suggests investigating dimensions of behaviors across diagnoses (Bernard and Mittal, 2015), brain correlates of AIM were evaluated in the total sample (Garvey and Cuthbert, 2017). Our hypothesis was to find a positive association between the occurrence of AIM and rCBF especially in motor areas (basal ganglia, premotor areas) in patients with CHR, FEP and CC. Further, we hypothesized to additionally find a negative association between AIM and GMV in fronto-striatal motor areas. Finally, we expected to find negative correlations between premorbid intelligence and AIM.

2. Methods

2.1. Participants

In total, 45 CHR patients, 10 FEP patients and 39 non-psychotic/non-CHR clinical controls (CC) were included in this study (Table 1A).

All patients (CHR, FEP, CC) were recruited at the Bern Early Recognition and Intervention Center (FETZ Bern), which serves the whole Canton of Bern with a catchment area of about 1.5 million inhabitants. Approximately 80 patients (age 8–40 years) are examined each year for a CHR state according to state-of the art guidelines (Schmidt et al., 2015; Schultze-Lutter et al., 2015). Routine assessments include in-depth psychopathological evaluation, a cognitive test battery, MRI and blood screening. In the current sample (n = 94), 59 (62.8%) patients were below age 18. For the current study, we included all patients from the FETZ Bern who had presented between 2011 and 2016, had been subjected to AIM assessment and had given informed consent and, in minors, parental informed consent. The ethics committee of the Canton of Bern had generally approved this procedure.

A subset of the sample also had undergone standardized cerebral MR imaging: altogether N = 34 had a functional measure of rCBF (CHR n = 21, FEP n = 4, CC n = 9) and N = 38 had structural grey matter MR images (CHR n = 23, FEP n = 5, CC n = 10) (Table 1B).

Table 1
Sample demographics.

A) AIMS - video analysis

	CHR	FEP	CC	n	Test-value	p
Age [yrs.]	18.4 ± 0.8	17.7 ± 1.7	18.5 ± 0.8	94	0.10	0.90
Sex	23m/22f	5m/5f	25m/14f	94	1.6	0.45
Nationality	39S/6O	9S/1O	36S/3O	94	1.2	0.87
PPVT	56.7 ± 14.9	49.4 ± 16.7	54.7 ± 21.6	89	0.60	0.55
SOFAS	62.10 ± 11.1	50.3 ± 12.3	62.7 ± 12.0	94	4.4	0.015*
wo/w AP	39/6 (13.3%)	5/5 (50%)	32/7 (17.9%)	94	7.1	0.029*
CPZ	21.6 ± 93.1	110.8 ± 246.8	18.1 ± 50.0	94	3.3	0.041*

B) AIMS - MR analysis

	CHR	FEP	CC	n	Test-value	p
Age [yrs.]	18.6 ± 5.0	16.4 ± 1.1	19.0 ± 5.0	38	0.57	0.57
Sex	10m/13f	2m/3f	7m/3f	38	2.2	0.33
Nationality	20S/3O	4S/1O	10S/0O	38	2.6	0.63
PPVT	60.3 ± 14.5	42.8 ± 14.7	59.0 ± 23.4	38	2.1	0.14
SOFAS	61.9 ± 12.0	49.0 ± 9.8	61.1 ± 7.9	38	2.4	0.11
rCBF GM	70.0 ± 11.9	72.1 ± 6.9	67.6 ± 8.4	34	0.25	0.78
GMV cmf	13,077.4 ± 2126.7	11,513.0 ± 262.0	13,663.8 ± 1685.1	38	2.2	0.13
wo/w AP	21/2 (8.7%)	1/4 (80%)	9/1 (10%)	38	14.4	0.001*
CPZ	6.9 ± 28.1	211.7 ± 333.3	10.0 ± 31.6	38	6.7	0.003*

Mean ± standard deviation. N = sample size. Sex m = male, f = female. Nationality S = Swiss, O = other. PPVT = Peabody Picture Vocabulary Test, age and sex adjusted percent range. SOFAS = social and occupational functioning score. rCBF GM = regional cerebral blood flow in total grey matter [ml/100 g/min]. GMV cmf = grey matter volume caudal middle frontal [μl]. Patients without (wo)/with (w) antipsychotic medication (AP) in total numbers and percentage of subjects on AP. CPZ = chlorpromazine equivalents. P-values refer to ANOVAs and chi-square tests comparing patient groups.

* Significant at $p < 0.05$.