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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 $p < 0.05$.

2.2. Diagnostic assessments

CHR criteria were defined by both UHR and BS criteria (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015). UHR criteria (Yung et al., 1998) were assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2010). The SIPS assesses the presence of attenuated psychotic symptoms, brief intermittent psychotic symptoms, and genetic risk and functional decline criterion. BS criteria (Klosterkotter et al., 2001; Schultze-Lutter et al., 2016; Schultze-Lutter et al., 2012) including Cognitive Disturbances (COGDIS) and Cognitive-Perceptive Basic Symptoms (COPER) were assessed using the Schizophrenia Proneness Instrument, Adult version (SPI-A) (Schultze-Lutter et al., 2007) and the Schizophrenia Proneness Instrument, Child & Youth Version (SPI-CY) (Schultze-Lutter and Koch, 2010) in minors. For their spontaneous, immediate recognition by patients as disturbances of their own (mental) processes, BS are distinct from the symptoms that define the UHR criteria (i.e., attenuated psychotic symptoms (APS) or brief intermittent psychotic symptoms (BIPS)) and from frank psychotic symptoms, in which reality testing is disturbed, at least to some degree. The BS concept considers a benign course if everyday situations and demands do not overstrain the patient's already pathologically vulnerable information processing capacity. However, (attenuated) psychotic symptoms are considered to arise from BS, when there is an unfavourable environment or the symptom load is too high (Schultze-Lutter, 2009). All interviewers underwent intensive training for 3 months prior to diagnosing patients according to the respective criteria and continuing supervision of ratings during the diagnostic process by F.S.-L.

Additionally, the Mini-International Neuropsychiatric Interview (MINI) for adults (Sheehan et al., 1998) and its version for children (Sheehan et al., 2010) were used to assess DSM-IV diagnoses.

CC did not fulfil any CHR criterion nor did they have a history of past or present psychosis. FEP patients were diagnosed as schizophrenia ($n = 4$), schizoaffective disorder ($n = 3$), schizophreniform disorder ($n = 2$) and brief psychotic disorder ($n = 1$). Patients with attention deficit disorders were not excluded from this study. Further information on MINI diagnoses is provided in Table S1 (supplementary data).

To assess premorbid verbal intelligence the Peabody Picture Vocabulary Test (PPVT) (Dunn and Dunn, 2007), was applied, providing age- and gender-adjusted normative data.

Psychosocial functioning was evaluated with the Social and Occupational Functioning Assessment Scale (SOFAS) (APA, 1994).

Current antipsychotic medication was converted to chlorpromazine equivalents (CPZ) according to standard guidelines (Leucht et al., 2003).

2.3. Assessment of abnormal involuntary movements

AIM were assessed using videos recorded during the routine clinical diagnostic examination and rated without sound by 2 independent raters (J.K, G.F.), who were blinded for diagnoses (CHR, FEP, CC). AIM were assessed using the AIMS (Guy, 1976) that rates facial, oral, extremity, and trunk movements during a standard setting on seven items (Table S2, supplementary data). The investigation strictly followed the AIMS examination procedure. Our primary parameter was the total AIMS score (mean sum score of items 1–7 of two raters). Secondary, we used a threshold for presence of AIM of ≥ 2 for AIMS total score to define the presence or absence of AIM, as reported in previous studies (Kindler et al., 2016). A total score of 2 implies either one item rated as “mild,” or two items rated as “minimal.” The raters were trained and instructed with training videos (AIMS training) and live interviews and received supervision of S.W. to ensure high data quality. Inter-rater reliability met intra-class correlations of 0.95.

2.4. Structural and functional brain imaging

Magnetic resonance imaging (MRI) was performed using a 3.0 T Magnetom Verio scanner (Siemens Medical Systems, Erlangen, Germany) using a standard 12-channel radio frequency head coil. High-resolution structural images were obtained using 3D T1-weighted modified driven equilibrium Fourier transform (MDEFT) scans [176 sagittal slices, 256×256 matrix, 1 mm slice thickness, $1 \times 1 \times 1\ mm^3$ voxel size, repetition time (TR) = 7.92 ms, 2.48 ms echo time (TE), 16° flip angle (FA)]. rCBF was measured using a pseudo Continuous ASL (pCASL) sequence [220 mm^2 field of view; 64×64 matrix; 25° FA; 1600 ms tagging duration; 1250 ms post-labeling delay; 4000 ms/13 ms TR/TE] acquiring 100 functional images (Wang et al., 2005).

2.4.1. Functional analysis: regional cerebral blood flow

Image processing was done using MATLAB® (MATLAB version 8, release 14; MathWorks, Inc., Natick, MA, USA) and statistical parametric mapping (SPM 8, Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk/spm8). ASL data analysis was conducted with ‘aslm’ (Homan et al., 2012). First, data were visually screened for motion (>3 mm in x, z or z direction or >3° rotation) and scanner artifacts. Motion parameters of rCBF data revealed no significant differences between groups ($p > 0.05$). Voxelwise mean rCBF for each subject was calculated from flow-time series, subtracting labeled and non-labeled images (Federspiel et al., 2006). After realignment and co-registration to the grey matter (GM)-segmented T1 images, normalization was conducted using the SPM Montreal Neurologic Institute T1 template. Spatial smoothing was done with an 8-mm full-width at half maximum kernel. Mean rCBF data were finally normalized [z = (voxel rCBF — global GM rCBF)/SD across individual brain voxels] and GM corrected using GM segments as inclusive masks.

2.4.2. Structural analysis: grey matter volume

Grey matter MRI image analysis was performed on a Mac OSX 10.8 workstation using FreeSurfer version v6.0. software. All data sets were screened for anatomical abnormalities, excessive motion, successful normalization and artifacts. Images were next run through a first-level autoreconstruction in FreeSurfer. The skull-stripped brains were checked for remaining dura, sinuses or other artifacts that could interfere with successful segmentation. When artifacts were found, images were edited manually. When deemed sufficiently clean for segmentation, images were run through second- and third-level autoreconstruction, in which grey matter surface area, thickness, and volume measures were extracted. Finally, automated cortical parcellation was performed using a separate processing pipeline included in the FreeSurfer software package.

2.5. Statistics

Using SPSS 21.0, frequencies and percentages of sociodemographic, clinical and AIMS data were compared by chi-square tests, means of normally distributed interval data by two-sample *t*-tests, and non-normally distributed interval or ordinal data by Kruskal-Wallis and Mann-Whitney *U* tests. Statistical distribution was examined with Kolmogorov-Smirnov tests. Statistical significance of two-sided tests was set at $p < 0.05$.

The association between rCBF and AIMS total scores was investigated in the total sample (CHR, CC and FEP) with a linear regression model in SPM 8 using a grey matter mask and chlorpromazine equivalents as covariate. Results were family wise error (FWE) peak level corrected for multiple testing ($p < 0.05$).

Additionally, we investigated whether areas involved in a fronto-striatal motor-network loop showed associations between

GMV and AIMS total score using a region of interest (ROI) approach [bilateral ROIs (Freesurfer parcellation, Desikan-Killiany Atlas): caudal middle frontal (cmf), supplemental motor area (SMA, paracentral), striatum (putamen & caudate), primary motor cortex (precentral)]. Results are reported after family wise error (FWE) correction ($p < 0.05$) (Nichols and Hayasaka, 2003).

Spearman rank correlations were calculated to assess the association between AIM and premorbid intelligence using the PPVT.

Secondary, exploratory correlational tests were run separately in each group (CC, CHR, FEP) on extracted rCBF and GMV of significant regions and cognition. Results are reported at $p < 0.05$, two-sided.

3. Results

3.1. Patient characteristics

Patients of the AIM video sample (Table 1A) did not differ in age, sex, nationality or premorbid intelligence. Of the CHR patients, 17 fulfilled UHR criteria, 15 fulfilled BS criteria and 13 fulfilled both (UHR + BS). A significantly lower SOFAS score was detected in FEP as compared to both CHR ($p = 0.007$) and CC ($p = 0.005$), with no difference between CHR and CC ($p = 0.82$) (Table 1A). The distribution of AIMS scores is shown in Fig. S1 (supplementary data). Moreover, significantly higher CPZ equivalents were detected in FEP as compared to both CHR ($p = 0.018$) and CC ($p = 0.015$), with no difference between CHR and CC ($p = 0.88$).

In the MR sample (Table 1B), FEP patients were treated with significantly higher doses of antipsychotics as compared to CHR ($p = 0.001$) and CC ($p = 0.003$), whereas no other differences were detected.

3.2. Frequency of AIM

AIMS total scores differed significantly between the three groups (Kruskal Wallis test: $\chi^2(2) = 7.7$, $p = 0.021$; Fig. 1). Post-hoc Mann-Whitney tests showed significantly higher total AIMS scores in CHR as compared to CC ($p = 0.017$, $z = 2.4$) and significantly higher AIMS total scores in FEP as compared to CC ($p = 0.037$, $z = 2.1$) but no difference between FEP and CHR ($p = 0.504$, $z = 0.7$).

Similarly, a significant difference between groups was detected in percentage of AIMS ≥2 [CHR 34/45 (75.6%); FEP 9/10 (90.0%); CC 19/39 (48.7%); $\chi^2(2) = 9.6$, $p = 0.008$], with significantly higher percentage of AIMS ≥2 in CHR as compared to CC ($\chi^2(1) = 6.5$, $p = 0.01$) and in FEP as compared to CC ($\chi^2(1) = 5.5$, $p = 0.02$), and no difference between FEP and CHR ($\chi^2(1) = 1.0$, $p = 0.32$).

When different muscle groups were considered, a significant difference was found only in the "lips and perioral area" ($p = 0.026$, $\chi^2(2) = 7.7$, Fig. S2, supplementary data) with significantly higher AIMS scores in CHR as compared to CC ($p = 0.009$, $z = 2.6$) and no other group differences (FEP vs CC, $p = 0.14$, $z = 1.5$; FEP vs CHR, $p = 0.75$, $z = 0.3$). Table S3 (supplementary data) shows AIMS scores by body region. No significant associations were detected between AIMS scores, separated for muscle groups, and antipsychotic medication (Table S4, supplementary data).

3.3. Functional correlates — AIM and rCBF

In the total ASL sample ($n = 34$), a significant positive correlation between rCBF and AIMS total score was detected in the middle frontal gyrus extending to the precentral gyrus (x/y/z = −56/0/40, BA 6, $t = 5.2$, $z = 4.4$, CS = 49, FWE whole brain corrected at $p < 0.05$; Fig. 2).

When separated for diagnostic groups, this effect was statistical significant in CHR patients ($n = 21$, $R = 0.77$, $p < 0.001$), whereas for CC ($n = 9$, $R = 0.56$, $p = 0.11$) and FEP ($n = 4$, $R = 0.14$, $p = 0.86$), no significant correlations were detected.

No correlations were detected between AIM and rCBF in the striatum ($R < 0.5$, $p > 0.05$). Further information on the impact of antipsychotic medication on rCBF is provided in the Supplement.

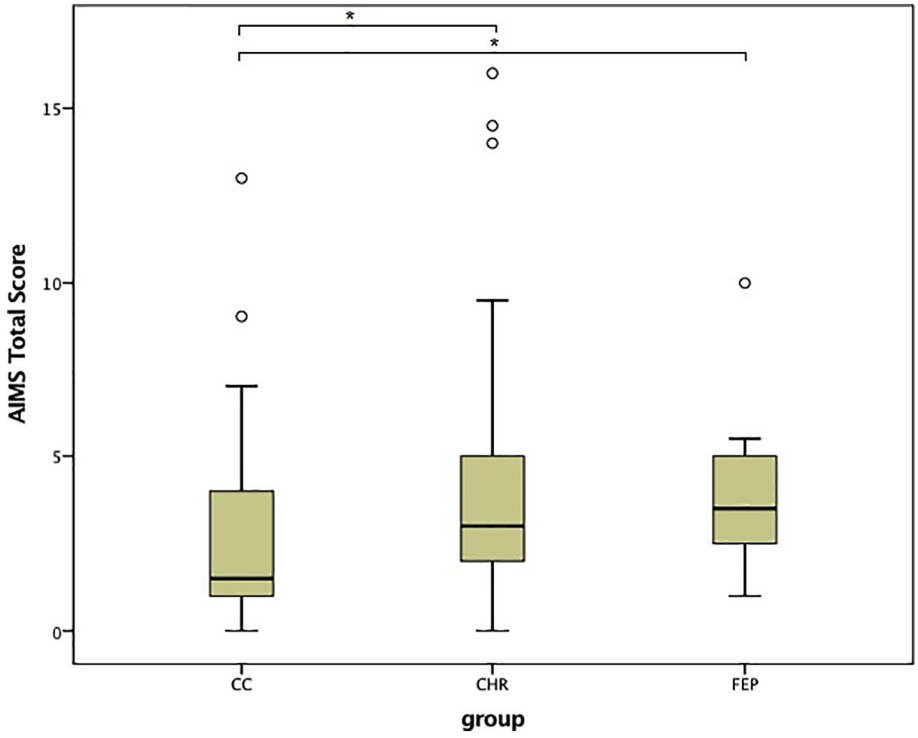

Fig. 1. Boxplots of abnormal involuntary movement scale (AIMS) total scores (sum of items 1–7) in clinical controls (CC), clinical high-risk patients (CHR) and first episode psychosis (FEP). Patients with CHR and FEP had significantly higher AIMS scores as compared to CC. * significant at $p < 0.05$.

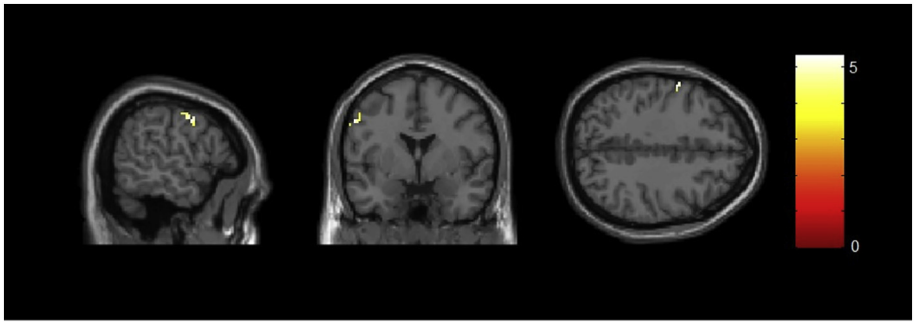

Fig. 2. A significant positive association between rCBF and AIM scale total score was detected in the Brodmann area 6, premotor cortex, left middle frontal gyrus (yellow area, x/y/z = −56/0/40, t = 5.2, z = 4.4, cluster size = 49, FWE whole brain corrected, $p < 0.05$, n = 34), corresponding to hand/face area.

3.4. Structural correlates − AIM and GMV

In the total structural MRI sample (n = 38), AIMS scores correlated negatively with caudal middle frontal volume (R = −0.41, p = 0.04, FWE corrected, Fig. 3). No other significant correlations were detected (R < 0.3, p > 0.05).

When separated for diagnostic groups, a significant correlation was found only in CC (n = 10, R = −0.86, p = 0.003), whereas no significant results were detected in CHR (n = 23, R = −0.33, p = 0.133) or FEP (n = 5, R = 0.88, p = 0.13).

3.5. Cognitive correlates − AIM and premorbid verbal IQ

In the total sample (n = 89), AIMS total scores correlated negatively with premorbid verbal intelligence as measured with PPVT (Spearman's Rho = −0.24, p = 0.024).

When separated for diagnostic groups, a correlation at trend level was found in CHR (Spearman Rho = −0.28, p = 0.078), and no other significant correlations were detected (CC Spearman Rho = −0.14, p = 0.44; FEP Spearman Rho = −0.37, p = 0.32).

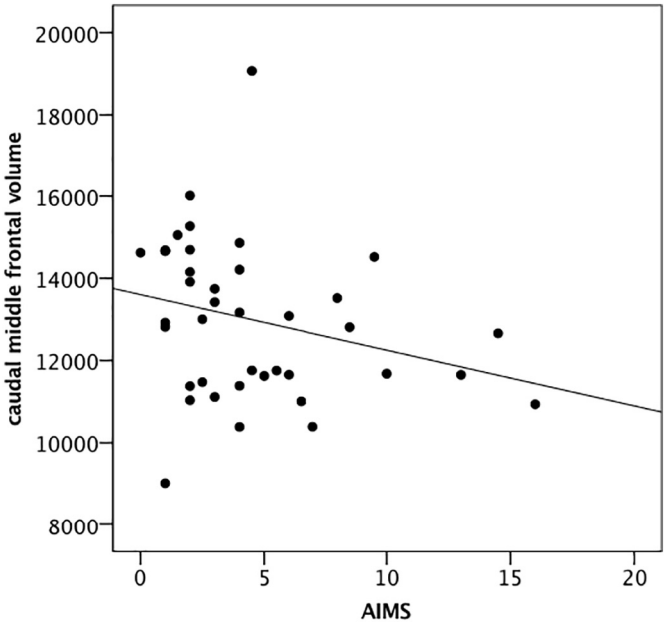

Fig. 3. Correlation of AIM scale total score with caudal middle frontal volume in μl (Desikan-Killiany Atlas). A significant negative correlation (R = −0.41, p = 0.04, FWE corrected) was found in the total sample.

4. Discussion

In this study, we explored the prevalence of AIM in CHR and FEP patients and their association with brain structure, function and cognition. We found significantly higher AIM severity in CHR and FEP as compared to CC, in line with previous studies (Callaway et al., 2014; Mittal et al., 2011a; Mittal et al., 2011b), using observer-based video ratings as a different but particular readily available method that is considered highly reliable (Schiffman et al., 2004). To date, only a few studies have used video assessments to investigate motor symptoms in psychosis risk (Dean et al., 2013; Macmanus et al., 2012; Mittal et al., 2007; Mittal et al., 2010b; Schiffman et al., 2009; Schiffman et al., 2004; Walker et al., 1994). To our knowledge, this is the first video based analysis directly comparing help-seeking CHR, FEP and CC patients from an early detection center. The assessment of AIM in CHR might in future be used as an additional predictor for the symptomatic assessment of psychosis risk (Dean and Mittal, 2015; Kindler et al., 2016; Mittal et al., 2008; van Harten et al., 2017).

Furthermore, we report for the first time a significant association between AIM and rCBF in the lateral premotor cortex, Brodmann area (BA) 6, indicating increased neuronal resting state activity in that area (Wong, 2014). In addition to this positive association between rCBF and AIM, GMV of the corresponding brain region, the caudal middle frontal gyrus, correlated negatively with AIM. Thus, evidence from two different neurobiological parameters, a functional and a structural one, suggests that the premotor cortex, which is responsible for planning and controlling movements, is involved in AIM.

The area BA 6 that showed the strongest correlations between rCBF and AIM matches the perioral area according to the functional topography of the motor cortex (Brown et al., 2008; Pulvermuller et al., 2006). This topographic position fits well to our clinical observation of increased lips and perioral movements in CHR patients of the present study.

BA 6 is part of the frontal cortex situated anterior to the primary motor cortex (BA 4). It is composed laterally of the premotor cortex and medially of the supplementary motor area. BA 6 plays a major role in sequencing and planning of complex, coordinated movements (Saugstad, 2008). Also it is one of the most intensively connected areas. The motor functions involve the control of muscles, as well as planning and guiding movements (Vogt and Vogt, 1919; Vogt and Vogt, 1926). Moreover, the premotor cortex seems to play an important role in cognitive functions like cognitive space perception, action understanding and imitation, the learning of associations between stimuli and responses and the control of executive functions (e.g. task switching) (Rizzolatti et al., 2002).

Aberrant premotor cortex structure and function have been implicated in altered motor behavior in schizophrenia. For

example, structural alterations in the BA 6 (Stegmayer et al., 2014) and connecting fibers (Bracht et al., 2013; Walther et al., 2011) were associated with the severity of motor impairments appearing with the disorder. Finally, increased rCBF in premotor areas, correlated with higher objectively assessed motor activity in schizophrenia (Walther et al., 2011). These findings correspond with the results of the present study, keeping in mind that probably the whole motor system is contributing to abnormal motor behavior in psychosis, of which the premotor cortex is a major hub (Strik et al., 2017).

Most importantly, one recent study has found increased resting state perfusion of the supplementary motor area, BA 6, in patients with catatonia (Walther et al., 2017a). From a clinical point of view, there are overlapping symptoms in the AIMS scale and catatonia rating scales. Catatonia is prevalent in patients with schizophrenia and may also be associated with other psychiatric conditions such as affective disorders or under certain medical conditions (Walther et al., 2017a; Walther et al., 2019b; Walther and Strik, 2012). The latter study (Walther et al., 2017a) emphasizes the importance of premotor areas in motor symptoms of chronic psychoses. The authors claimed motor symptoms may emerge through the use of cortical pathways involving the premotor areas in patients to compensate insufficient or inhibitory basal ganglia output (Walther, 2015).

Our study demonstrates that AIM are prevalent in the psychosis spectrum. While there is some specificity to psychosis, AIM are considered a dimensional feature (Kent et al., 2018). Along this line the sensorymotor domain of the Research Domain Criteria (RDoC) is a dimensional, transdiagnostic system, spanning the range from normal to abnormal and transgressing conventional categorical diagnostic approaches (Bernard and Mittal, 2015; Walther et al., 2019a). We found potentially relevant biological correlates when applying a dimensional approach to AIM. Yet, when separated for diagnoses, the correlation between rCBF and AIM was clearly driven by CHR individuals, whereas the negative association between GMV and AIM was stronger in CC. However, the sample size of the analysis of diagnostic subgroups was too small to provide adequately powered results and therefore these findings have to be interpreted with caution. Even though, these associations might be pronounced in specific diagnoses, dimensional approaches such as the RDoC motor domain clearly aid in unraveling pathological processes underlying motor phenomena.

Interestingly, the negative correlation between premorbid IQ and AIM is consistent with several previous studies (Fenton et al., 1994; Magulac et al., 1999; Manschreck et al., 1990). PPVT is a measure of receptive vocabulary. In line, a negative association between verbal comprehension and AIM has been previously also demonstrated in CHR patients (Mittal et al., 2010b). Moreover, one recent study reported the highest conversion rates in CHR patients with concurrent motor symptoms and cognitive deficits (Dean et al., 2018). Cortico-striato-cortical loops are involved in the regulation of both motor behavior and different neurocognitive functions, potentially explaining these findings.

AIM have previously been attributed to antidopaminergic drugs. In contrast, this view has been challenged by recent findings of heterogeneous contributions to AIM in medication naïve first episode patients (Hirjak et al., 2018b; Peralta and Cuesta, 2010; Walther and Mittal, 2017). Along this line, there was no difference in chlorpromazine equivalents between CHR and CC, higher AIM scores in CHR of the present study seem to be unrelated to antipsychotic medication and must have other causes. The clinical control group of the present study consisted of patients suffering from psychiatric disorders other than psychosis and were closely matched to factors like age, level of psychosocial functioning or premorbid intelligence with CHR patients.

The most important limitation of this study is its modest sample size, which restricts the statistical significance and prevented us from comparing subgroups with e.g. specific patterns of motor symptoms. Another weakness is the absence of healthy controls as a completely uninfluenced reference group. Additionally, the group differences in variance of both the covariate (CPZ) and the dependent variables can compromise power.

In the present study, we demonstrate that patients fulfilling CHR criteria and those already suffering from FEP can be differentiated from CC based on their AIM scale scores, which might be used as an additional predictor for clinical psychosis risk detection. Further, we show for the first time associations between AIM and biological markers such as rCBF and GMV in a psychiatric sample, indicating a pathophysiological involvement of the associated motor cortex. The correlation between AIM, rCBF and GMV in the premotor cortex revealed by the present study suggests a dysfunction in areas responsible for planning, initializing and controlling of motor functions in patients developing AIM. Thus, our study is in line with several previous studies on schizophrenia patients with motor symptoms. However, it demonstrates that those dysfunctions, though to a lesser degree, might already be present before the onset of psychosis.

Contributors

J.K. analysed the data and wrote the manuscript.

C.M. and F.S.-L. were responsible for psychopathology and cognitive assessments.

G.F. rated video-based data (abnormal involuntary movements).

M.H. was conducting and supervising MR data assessments and analysis.

B.G.S. was conceptualizing and organizing the study.

M.K. was providing scientific input in study design, drafting and writing the manuscript.

D.H. was conducting and supervising MR data assessments and analysis, study design and writing of manuscript.

S.W. was conceptualizing the study, supervising video-based ratings and drafting and writing of the manuscript.

Declaration of Competing Interest

The authors report no biomedical financial interests or potential conflicts of interest relevant to this project.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.032.

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