# Aberrant functional connectivity within the salience network is related to cognitive deficits and disorganization in psychosis

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**Abstract**

In schizophrenia and schizoaffective disorder cognitive deficits are a reliable characteristic predicting a poor functional outcome. It has been theorized that both the default mode network (DMN) and the salience network (SN) play a crucial role in cognitive processes and aberrant functional connectivity within these networks in psychotic patients has been reported. The goal of this study was to reveal potential links between aberrant functional connectivity within these networks and impaired cognitive performance in psychosis.

We chose two approaches for cognitive assessment, first the MATRICS Consensus Cognitive Battery (MCCB) combined into a global score and second the disorganization factor derived from a five-factor model of the Positive and Negative Syndrome Scale (PANSS) known to be relevant for cognitive performance. DMN and SN were identified using independent component analysis on resting-state functional magnetic resonance imaging data.

We found significantly decreased connectivity within the right supplementary motor area (SMA) and bilateral putamen in patients with psychosis (n=70; 27F/43M) compared to healthy controls (n=72; 28F/44M). Within patients, linear regression analysis revealed that aberrant SMA connectivity was associated with impaired global cognition, while dysfunctional bilateral putamen connectivity predicted disorganization. There were no significant changes in connectivity within the DMN.

Results support the hypothesis that SN dysfunctional connectivity is important in the pathobiology of cognitive deficits in psychosis. For the first time we were able to show the involvement of dysfunctional SMA connectivity in this context. We interpret the decreased SN connectivity as evidence of reduced functionality in recruiting brain areas necessary for cognitive processing.

## 1. Introduction

Schizophrenia is characterized by positive symptoms like delusion and hallucinations, as well as negative symptoms, such as blunted affect, apathy and anhedonia (Andreasen, 1985). Schizoaffective disorder also shows this symptomatology with the addition of mood symptoms for a substantial portion of the duration of the illness (Malaspina et al., 2013). For both diseases neuropsychological tests have shown a similar degree of impairment in cognition (Bora et al., 2009; Lewandowski et al., 2011; Lynham et al., 2018). These cognitive deficits are associated with deficient functioning in the outside world together with a poor functional outcome (Green et al., 2004), and therefore constitute a core aspect of the disease's symptomatology. The goal of our study was to identify neuronal causes for this cognitive impairment. In this paper we are going to summarize both disorders under the more general term psychosis.

The neuronal basis of psychotic symptoms is still poorly understood and a vast range of hypotheses exist on how they emerge. Some focus on a dysregulation of neurotransmitters, most prominently dopamine (Carlsson, 1988; Howes and Kapur, 2009), while others concentrate on structural or functional aberrations of certain brain areas (Fannon et al., 2000; Kühn and Gallinat, 2013; Olabi et al., 2011). Another popular hypothesis is that psychotic symptoms are best understood as aberrations of neural connectivity between different brain areas (Friston and Frith, 1995; Khadka et al., 2013). More recently, there has been increasing interest in examining resting-state networks (RSNs) in patients and healthy controls. These networks can be identified when participants do not engage in a particular task. Analysing this data reveals spatially segregated brain areas that have strong functional connections to one another and work as an RSN (Beckmann et al., 2005; Fox et al., 2005). RSNs can be reliably detected across different individuals (Damoiseaux et al., 2006; De Luca et al., 2006), and include networks also active during cognitive processes (Corbetta and Shulman, 2002; Fox et

al., 2006) or even during different states of consciousness (Boly et al., 2008; Greicius et al., 2008). This suggests that RSNs represent a general intrinsic organization of the human brain, and they are thought to play a crucial role in cognitive processes (Bressler and Menon, 2010).

The most studied RSN in psychosis is the Default Mode Network (DMN), which primarily consists of the medial prefrontal cortex, angular gyrus, as well as the posterior cingulate gyrus (Andrews-Hanna et al., 2014). It is more active during rest than during cognitive task performance and therefore most likely relevant for task-independent brain functions (Greicius et al., 2003; Gusnard and Raichle et al., 2001). Many studies detected aberrations in the connectivity of the DMN in psychotic patients and an association to symptom severity (Forlim et al., 2020; Rotarska-Jagiela et al., 2010; Whitfield-Gabrieli and Ford, 2012; Woodward et al., 2011). A failure to suppress DMN activation during cognitive tasks may interfere with task specific neural processes and has been theorized to contribute to cognitive deficits in psychosis (Fryer et al., 2013; Pu et al., 2016; Whitfield-Gabrieli et al., 2009).

Another important RSN is the salience network (SN), which consists of paralimbic structures, most prominently the bilateral anterior insula and dorsal anterior cingulate cortex (dACC), and which has also strong associations with the dorsolateral prefrontal cortex, supplementary motor area (SMA)/pre SMA, frontal, temporal, and parietal opercular regions, as well as the subcortical striatopallidum and amygdala (Seeley et al., 2007). The SN's primary function is likely to identify relevant stimuli among the continuous flow of inputs the brain has to deal with (Seeley et al., 2007). Many studies have built on and expanded this hypothesis. Menon and Uddin (2010) propose that the SN represents the final point of a number of hierarchically ordered saliency filters in the central nervous system. Once a relevant stimulus has passed those filters and triggers the SN, the network engages specific attentional or cognitive networks to further process the information (Menon and Uddin, 2010). Palaniyappan and Liddle (2012) propose that a dysregulation of the SN in psychosis can cause inappropriate

attribution of salience to non-relevant internal and external stimuli, which in turn results in deficits in information processing, self-monitoring errors, and inappropriate associations, leading to disorganization, hallucination and delusion. Aberrant SN connectivity has been linked to both positive and negative symptomatology (Manoliu et al., 2014; Orliac et al., 2013; Pu et al., 2012), and there have been reports of an influence of functional SN connectivity on cognitive performance in schizophrenia (Moran et al., 2013; Tu et al., 2012).

Building on the existing literature, we hypothesize that aberrant connectivity within the DMN and SN might contribute to cognitive deficits in psychotic patients. This study aims at analysing the link between aberrant DMN and SN connectivity and deficits in cognition in patients diagnosed with schizophrenia or schizoaffective disorder. We used resting-state functional magnetic resonance imaging (rs-fMRI) data, standardized methods for testing cognitive capacity, as well as clinical ratings to measure a disorganization score closely related to cognition. We performed a two-step analysis. In the first step, we identified parts of the networks which exhibit aberrant intrinsic connectivity in patients when compared to healthy individuals. In the second step, we searched for relations between this aberrant connectivity and cognitive capacity, revealing a possible neuronal basis for cognitive deficits in psychosis.

## 2. Methods

### *2.1 Participants*

Participants were recruited within the study "Augmentation of neuronal network plasticity in schizophrenia", a preregistered randomized training study (https://clinicaltrials.gov/ct2/show/NCT03522220) carried out at the University Medical Centre Hamburg-Eppendorf. The local ethics review board (https://www.aerztekammer-hamburg.org/ethikkommission.html) approved of the study and all participants gave written

consent before starting with the study. The study included participants aged from 18 to 55 years, who were either diagnosed with schizophrenia or schizoaffective disorder based on the criteria of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) or healthy individuals with no history of psychiatric disorders. To be included in the study, patients needed be clinically stable, but still show residual symptoms by scoring three points or above on at least one item of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Within patients, comorbid psychiatric diseases as well as alcohol and substance use disorders within the last year were excluded using the German version of the Mini International Neuropsychiatric Interview (MINI) (Ackenheil et al., 1998). Within the healthy control group, comorbid psychiatric diseases including alcohol and substance use disorders were excluded using the screening questionnaire of the MINI (Ackenheil et al., 1998). Due to the nature of the preregistered randomized training study, participants that had played more than one hour of video games per day in the last six months, or had previously finished the games Super Mario Bros. or Super Mario 64 DS were excluded from the study. Furthermore, any participants with a significant somatic or neurological disease or MRI contraindication were excluded. Analyses for this work were performed solely with data of participants acquired before the intervention. In total we included data of 152 participants in this work, of which 78 were diagnosed with schizophrenia or schizoaffective disorder and 74 were healthy controls.

*2.2 Procedure*

MR scans, PANSS ratings and cognitive testings were done in two to three sessions spanning two to four hours. Sessions took place within an average span of 1.7 days in the healthy control group (SD=1.4), and 4.7 days in the patients group (SD=6.5). Cognitive testings were not done after MR scanning to exclude potential negative effects on concentration.

*2.3 Assessment of disorganization symptoms*

The severity of symptoms of all participants within the patient group was rated using the PANSS (Kay et al., 1987). The rating was carried out by two clinically trained individuals, whose ratings were averaged (arithmetic mean) for the final score. The intraclass correlation coefficient between rater 1 and 2 regarding the Total PANSS score was ICC = 0.95. The PANSS evaluates schizophrenia symptoms using 30 items and groups them into three categories: a Positive scale (7 items), a Negative scale (7 items), and a General Psychopathology scale (14 items). Factor analyses have shown that a five factor model is better suited to categorize PANSS data (van der Gaag et al., 2006). These models include a cognitive/disorganization factor, which has been reported to be closely associated with neuropsychological tests measuring cognition (Bell et al., 1994; Dominguez et al., 2009). To evaluate the influence of SN connectivity on cognitive capacity we therefore chose to focus on this cognitive/disorganization factor, since it has been most closely associated with cognitive capacity (Bell et al., 1994).

For our analysis, we decided to use the model described by van der Gaag et al. (2006), who used a ten-fold cross validation on a large data set (N=5769) to identify stable factors. The model described by the authors consists of the factors: positive symptoms, negative symptoms, disorganization symptoms, excitement and emotional distress. The disorganization factor includes the items *conceptual disorganization*, *difficulty in abstraction*, *stereotyped thinking*, *poor attention* and *disorientation.*

PANSS data was missing from three subjects of the patient group due to dropout. These subjects were excluded from all calculations including PANSS data.

*2.4 Assessment of global cognition*

All study participants were tested using the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein and Green, 2006), a standardized tool for testing cognitive capacity especially

in schizophrenia patients. It includes a total of ten tasks, testing for seven different cognitive domains: *speed of processing*, *attention/vigilance*, *working memory*, *verbal learning*, *visual learning*, *reasoning and problem solving*, and *social cognition*. In line with the battery's guidelines, a sum score of all cognitive domains (global cognition) was calculated and corrected for age and gender.

MCCB data was missing from eight subjects of the patient group and from two subjects of the control group due to dropout. These subjects were excluded from all calculations including MCCB data. The data acquisition of the MCCB took on average 2 hours. Participants were able to take breaks between tasks if needed.

*2.5 MRI Data acquisition*

Brain images were acquired on a 3 Tesla Siemens Magneton Skyra MRI scanner system. Structural images were obtained via a three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) (TR=2500ms; TE=2.12ms; TI=1100ms; acquisition matrix=256×256×192; flip angle=9˚; FOV=240 mm; voxel size=0.8mm×0.8mm×0.9mm). Functional images were collected during rest while participants were asked to fixate a cross with their eyes, using a T2*-weighted echo planar imaging (EPI) sequence sensitive to blood oxygen level dependent (BOLD) contrast (TR=2000ms; TE=30ms, image matrix=72×72, voxel size=3.0mm×3.0mm×3.0mm, flip angle=80°, FOV=216mm, 36 axial slices).

*2.6 Preprocessing of resting-state fMRI data*

To reduce initial fluctuation of the MRI signal, the first ten images of every subject were discarded, leaving 200 images per subject. The standard preprocessing pipeline of the SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) based CONN functional connectivity toolbox version 18.b (www.nitrc.org/projects/conn) (Whitfield-Gabrieli and Nieto-Castanon, 2012) was used. It includes motion realignment, slice timing correction, coregistration, segmentation into grey

and white matter and cerebrospinal fluid tissue classes, normalization to Montreal Neurologic Institute (MNI) space as well as smoothing with an 8 mm FWHM-Gaussian filter. It furthermore incorporates an ART-based identification of outliers, which creates variables depicting the amount of motion observed and global BOLD signal changes. To minimize the impact of motion and artefacts, all subjects whose motion or global signal change parameters deviated more than two standard deviations from the mean value were excluded from all further analyses. This resulted in an exclusion of eight subjects from the patients group (final sample: n=70) and two subjects from the control group (final sample: n=72).

*2.7 Independent component analysis (ICA)*

ICA was performed using the GIFT toolbox (http://trendscenter.org/software/gift/) (Calhoun et al., 2001). The optimal number of independent sources was estimated by the software using MDL criteria (Li et al., 2007), with a result of n=28. We used the Infomax algorithm to estimate independent sources. The ICASSO function of the toolbox was used to run the ICA 20 times and cluster the results (minimal cluster size=16, maximal cluster size=20, methods used RandInit and Bootstrap). Only components with ICASSO stability index >0.9 were used for further analysis. The DMN and SN were identified via spatial correlation analysis using predefined network templates provided by the toolbox (http://findlab.stanford.edu/functional_ROIs.html) (Shirer et al., 2012).

The spatial maps of the DMN and SN were thresholded as described by Allen et al. (2011) to focus on the most relevant voxels of the network. The thresholded spatial maps were taken into second level analysis. We performed a group comparison by calculating voxel-wise two-sample t-tests with a significance threshold of $p<0.001$ at a voxel level. The resulting clusters were corrected for multiple comparisons using a FWE corrected threshold of $p<0.05$. Bonferroni correction was used to control for analysing both the DMN and SN, resulting in a FEW corrected threshold of $p<0.025$ on cluster-level. Since age, gender and antipsychotic

medication of individuals are reported to influence network connectivity (Allen et al., 2011; Lui et al., 2010), all three variables were used as covariates of no interest. Values for antipsychotic medication were calculated using Olanzapine equivalence doses (Leucht et al., 2016). Anatomical areas were identified based on the peak voxel location of significant clusters using the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). All reported coordinates by our study correspond to the Montreal Neurological Institute coordinate system. For visualisation, we superimposed the significant clusters on an averaged normalized structural image of all participants.

*2.8 Correlation of intrinsic network connectivity with disorganization and global cognition*

We extracted the mean ICA values of each subject for each cluster that was significant in the group comparison. These values depict how strong the voxels of the cluster are connected to the extracted RSN component, therefore resembling intrinsic network connectivity.

Linear regression models were calculated using the stats package (https://www.R-project.org/) (R Core Team, 2018) of the statistical software R (version 1.2.5042). We calculated two models, one with the disorganization factor of the PANSS as the dependent variable, another one with the global cognition score of the MCCB. As independent variables, we chose the mean ICA values of the significant clusters. Bonferroni correction was used to control for analysing both disorganization and global cognition, resulting in a significance threshold of $p<0.025$. Because age, gender, educational years and antipsychotic medication are reported to influence the symptomatology of schizophrenia (Cámara et al., 2021; Galderisi et al., 2009; Kahn et al., 2008; Schultz et al., 1997), we included these variables in our linear models as covariates of no interest. To meet criteria of normal distribution, we log-transformed the disorganization factor. After data transformation, linear models met all assumptions of ordinary least square linear regression.

For exploratory purposes, we additionally investigated which subscores of the PANSS disorganization factor and which tasks from the global cognition score drive the correlation in our regression models. Therefore, we calculated Spearman correlation coefficients between the above mentioned subscores or tasks and ICA values of clusters significantly predicting either global cognition or disorganization symptoms in our regression models. Spearman correlation was used, because many subscores were not normally distributed. Due to the exploratory nature of this additional analysis, we decided to not correct for multiple comparisons.

## 3. Results

### *3.1 Clinical data*

Demographics and clinical variables of interest for the final sample of 72 healthy controls and 70 psychotic patients are shown in table 1. Within the patients group, 62 (89%) individuals were diagnosed with schizophrenia, 8 (11%) with schizoaffective disorder. 59 patients (84%) were receiving antipsychotic medication, with 13 of them (19%) receiving a first generation antipsychotic, while 54 (77%) were medicated with a second generation antipsychotic. Additionally, 3 (4%) were medicated with anticholinergics, 14 (20%) with antidepressants, 13 (19%) with benzodiazepines, and 4 (6%) with mood stabilizers. Data on medication taken was missing for 4 patients (6%). Additional information regarding the medication is given in the supplement.

### *3.2 Intrinsic network connectivity group comparison*

DMN and SN ICA components of our final sample were identified via spatial correlation analysis using predefined network templates provided by the GIFT toolbox. The DMN component showed a correlation of r=0.651, the SN component of r=0.479. Group comparison revealed no significant aberrations in the DMN component, while the SN

component had decreased functional connectivity within the right supplementary motor area (SMA) and bilateral putamen in psychotic patients when compared to healthy controls (fig. 1+ table 2). These results are still significant after Bonferroni correction for analysing both the DMN and SN.

*3.3 Correlations between functional connectivity and disorganization factor*

Due to high correlation of ICA values between the two putamen clusters (r=0.552), we decided to combine them into one cluster for further analysis. The linear model predicting disorganization is summarized in table 3. SMA intrinsic connectivity did not predict disorganization ($t(60)=0.479$; $p=0.633$), but putamen did ($t(60)=-2.502$; $p=<0.05$) (fig. 2). The putamen variable stays significant after Bonferroni correction for analysing both our global cognition score and disorganization factor.

We further explored which items of the disorganization factor significantly correlated with ICA values of the putamen cluster. Note that many items of the disorganization factor were not normally distributed and had low variability, making this a highly exploratory analysis. We observed a significant correlation only between putamen intrinsic connectivity and *difficulty in abstraction* (rho=-0.314; p = 0.01), but not for *stereotyped thinking* (rho=-0.202; p=0.101), *disorientation* (rho=-0.199; p=0.106), *conceptual disorganization* (rho=-0.138; p=0.264) or *poor attention* (rho=-0.041; p=0.742).

Due to missing data regarding the disorganization factor for a total of three participants, the sample for this analysis consisted of a total size of 67 patients.

*3.4 Correlation between functional connectivity and global cognition*

The linear model predicting global cognition is summarized in table 3. SMA connectivity did predict global cognition ($T(55)=2.819$; $p<0.05$), while putamen did not ($T(55)=-0.182$;

p=0.856) (fig. 2). The SMA variable stays significant after Bonferroni correction for analysing both our global cognition score and disorganization factor.

For exploratory purposes, we further examined which domains of the global cognition score significantly correlated with ICA values of the SMA cluster. We observed significant correlations between SMA intrinsic connectivity and *verbal learning* (rho=0.285; p=0.023) and *working memory* (rho=0.256; p=0.043). Correlations with r*easoning and problem solving* (rho=0.227; p=0.074) and *speed of processing* (rho=0.223; p=0.079) were significant at a trend level. There were no significant relations between SMA connectivity and *visual learning* (rho=0.203; p=0.111), *social cognition* (rho=0.089; p=0.489) or *attention/vigilance* (rho=0.005; p=0.967).

Due to missing data regarding the global cognition score for a total of eight participants, the sample for this analysis consisted of a total size of 62 patients.

**Table 1.** Means and group comparisons of demographic data, PANSS and MCCB results

| | Healthy control (n = 72) | SZ patients (n = 70) | T Value | P Value |
|---|---|---|---|---|
| Gender | 28F/44M | 27F/43M | | |
| Age (years) | 29.52 | 31.61 | -1.458 | 0.147 |
| OLA (mg) | | 15.31 | | |
| EDU Years | 16.52 | 15.31 | 1.977 | 0.05 |
| Onset Age | | 22.60 | | |
| Duration Psychosis (years) | | 10.55 | | |
| Episodes per Year since Onset | | 1.21 | | |
| Pack Years | 2.33 | 16.93 | -3.236 | 0.002 |
| PANSS Total Score | | 65.03 | | |
| PANSS Positive Score | | 16.32 | | |
| PANSS Negative Score | | 15.19 | | |
| Disorganization | | 10.93 | | |
| Conceptual Disorganization | | 2.63 | | |
| Difficulty in Abstraction | | 2.32 | | |
| Stereotyped Thinking | | 1.99 | | |
| Disorientation | | 1.13 | | |
| Poor Attention | | 2.86 | | |
| Global Cognition | 47.97 | 37.95 | 5.912 | <0.001 |
| Speed of Processing | 46.99 | 37.35 | 6.017 | <0.001 |

| | | | | |
|---|---|---|---|---|
| Attention/Vigilance | 49.04 | 39.39 | 5.181 | <0.001 |
| Working Memory | 52.97 | 46.49 | 3.332 | 0.001 |
| Verbal Learning | 47.97 | 43.60 | 2.670 | 0.009 |
| Visual Learning | 44.23 | 40.79 | 2.115 | 0.037 |
| Reasoning and Problem Solving | 49.10 | 42.49 | 3.710 | <0.001 |
| Social Cognition | 50.36 | 43.70 | 3.440 | <0.001 |

SZ patients=schizophrenic/schizoaffective patients; F=female; M=male; OLA=olanzapine equivalence doses of antipsychotic medication; EDU Years= educational years; Pack Years=tobacco packs smoked per day multiplied by years as smoker; note: the PANSS Total Score consists of 30 items, the PANSS Negative and Positive Sores of 7 items each, the Disorganization Factor of 5 items

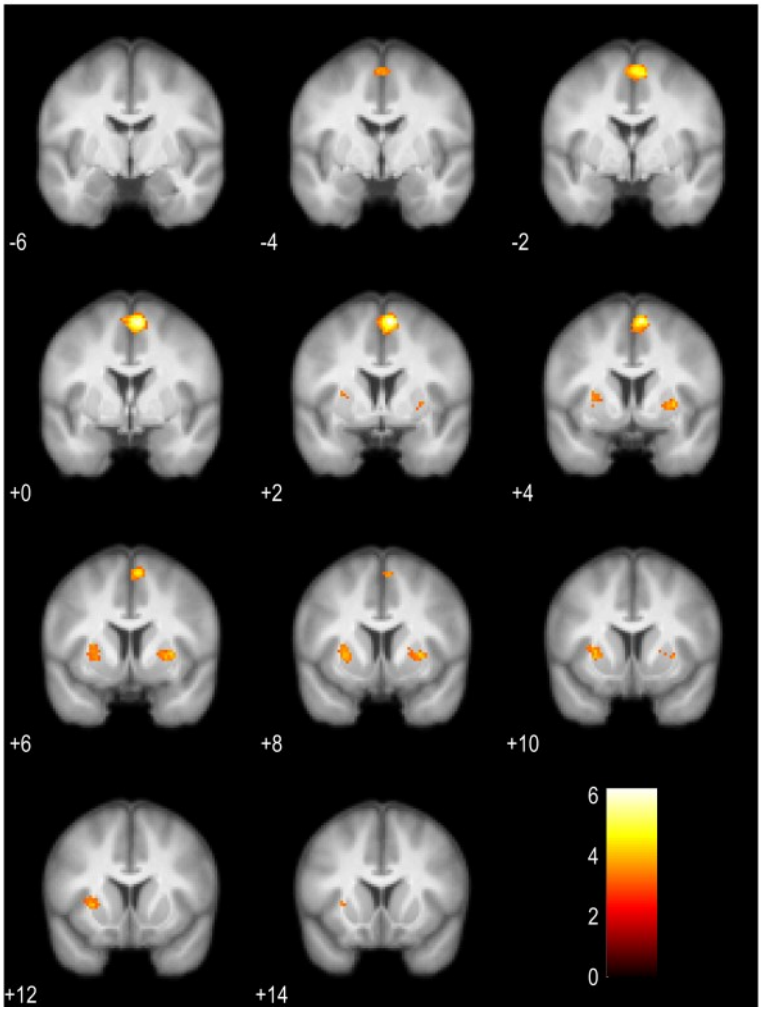

Figure 1. Group differences in functional connectivity between healthy controls and schizophrenic/schizoaffective patients in the salience network. Patients showed decreased functional connectivity in the right SMA and bilateral putamen.

**Table 2.** Group comparison of functional connectivity in the salience network between healthy controls and psychotic patients

| | **SMA right** | **Putamen left** | **Putamen right** |
|---|---|---|---|
| *MINI coordinates* | 6 2 60 | -26 12 2 | 28 8 2 |
| *Clustersize* | 204 | 100 | 67 |
| *T peak-level* | 6.23 | 4.2 | 4.33 |
| *P FEW corrected cluster-level* | <0.001 | 0.003 | 0.016 |

**Table 3.** Linear models predicting disorganization and global cognition

| | **Disorganization** | | | **Global cognition** | | |
|---|---|---|---|---|---|---|
| *Predictors* | *Estimates* | *CI* | *p* | *Estimates* | *CI* | *p* |
| (Intercept) | 2.25 | 1.77 – 2.72 | **<0.001** | 14.78 | -5.02 – 34.58 | 0.140 |
| SMA right | 0.03 | -0.09 – 0.14 | 0.633 | 6.56 | 1.90 – 11.23 | **0.007** |
| Putamen | -0.17 | -0.30 – -0.03 | **0.015** | -0.49 | -5.92 – 4.94 | 0.856 |
| Age | 0.01 | 0.00 – 0.02 | **0.007** | 0.24 | -0.08 – 0.55 | 0.135 |
| Gender | 0.11 | -0.03 – 0.25 | 0.120 | -0.51 | -6.08 – 5.06 | 0.856 |
| Medication | 0.00 | -0.00 – 0.00 | 0.468 | -0.06 | -0.16 – 0.05 | 0.293 |
| EDU Years | -0.02 | -0.04 – 0.00 | 0.054 | 0.15 | -0.65 – 0.96 | 0.706 |
| | $R^2$ / adjusted $R^2$ = 0.244 / 0.168 | | | $R^2$ / adjusted $R^2$ = 0.152 / 0.059 | | |

*Note.* The disorganization variable was log-transformed to meet criteria of normal-distribution; Medication refers to Olanzapine equivalence doses of antipsychotic medication; EDU Years refers to educational years

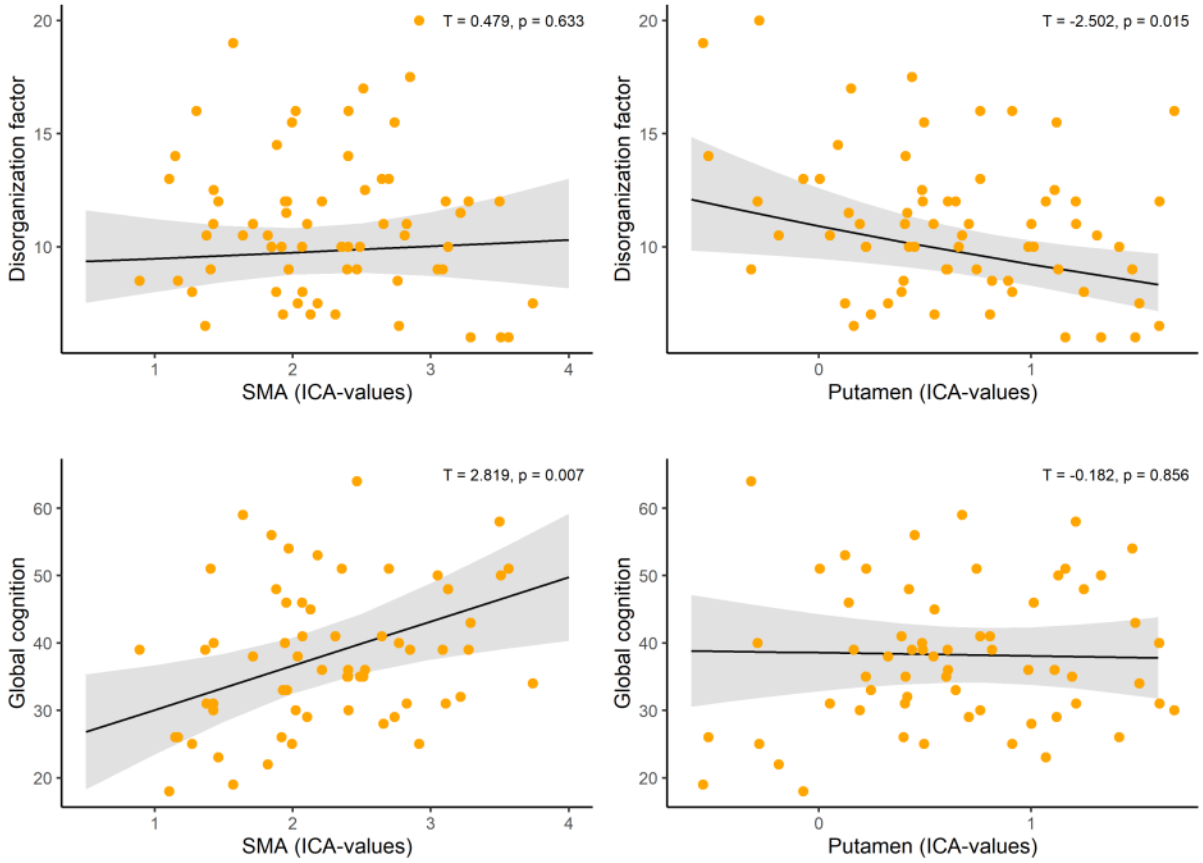


**Figure 2.** Visualization of linear models predicting psychotic symptomatology based on intrinsic connectivity values in psychotic patients (see, table 2). Upper panel: Prediction of disorganization symptoms based on SMA (left) or Putamen (right) ICA values. Lower panel: Prediction of global cognition based on SMA (left) or Putamen (right) ICA values. Predicted values were obtained using the ggeffects package in R (Lüdecke, 2018).

## 4. Discussion

In this study, we investigated the hypothesis that aberrant intrinsic DMN and SN connectivity in psychosis contributes to the cognitive deficits commonly described for this patient group. We used ICA to extract the DMN and SN from a group of psychotic patients and individuals with no psychiatric disorder. ICA is a powerful data-driven method that can be used to analyse RSN connectivity without an *a priori* definition of regions of interest (Cole et al., 2010). To identify areas that show aberrant functional connectivity within the networks, we performed a voxel-wise two sample t-test between the groups using intrinsic connectivity values. In the DMN, we found no significant changes in psychotic patients. In the SN, functional connectivity was reduced within bilateral putamen, as well as within the SMA in the patient group. Reduced connectivity within bilateral putamen was predictive of a higher degree of disorganization symptoms, while reduced connectivity within the SMA was predictive of a reduction in global cognition in patients.

Finding no significant aberrations in intrinsic DMN connectivity is in contrast to our initial hypothesis. However, it is in line with previous results demonstrating that the DMN is affected very heterogeneously by the disease. DMN connectivity in psychosis has been reported to be increased (Galindo et al., 2018), decreased (Manoliu et al., 2014; Orliac et al., 2013; Rotarska-Jagiela et al., 2010), both increased and decreased (Mannell et al., 2010; Ongür et al., 2010), as well as not being affected at all (Chahine et al., 2017; Wolf et al., 2011), even when using the same method for network-identification (ICA). This might be due to the very heterogeneous nature of the disease itself. It is also noteworthy that in order to avoid type one errors in our exploratory voxel wise connectivity analysis, our significance threshold was chosen rather conservatively. This may be another explanation for missing aberrations within the DMN.

In accordance with our hypothesis we found aberrant functional connectivity within the SN in psychotic patients. This is consistent with previous studies reporting decreased connectivity within the SN (Du et al., 2017; Manoliu et al., 2014; Ohta et al., 2018; Orliac et al., 2013; Pu et al., 2012; Tu et al., 2011). Interestingly, both the SMA and putamen are not regarded as part of the SN's key hubs. It is however not uncommon for them to be identified as part of the network in ICA (Orliac et al., 2013; Seeley et al., 2007), and they have therefore been described as regions closely associated with the network (Seeley et al., 2007). Previous studies analysing intrinsic SN connectivity have reported both reduced connectivity in the core nodes of the network, namely the anterior insula and the anterior cingulate cortex (Manoliu et al., 2014, Pu et al., 2012), as well as in other, less prominent areas of the network, namely the putamen, pallidum and thalamus (Du et al., 2017; Ohta et al., 2018; Orliac et al., 2013; Tu et al., 2011). The aberrant linkage of these less prominent areas within the SN in psychosis could represent a dysregulation of one of the main functions of the SN as described by Menon and Uddin (2010): the recruitment of specific attentional and cognitive networks to process information. Impairment of this function in schizophrenia is also reported by Manoliu et al. (2014), who found deficits in the dependence of the interaction between the central executive network and the DMN on SN activity in patients. We propose the decreased intrinsic SN connectivity found in our study is evidence of reduced functionality of the SN in recruiting brain areas necessary for cognitive processing, as in our case the putamen and SMA.

Our finding of reduced putamen connectivity within the SN in psychotic patients is in line with previous results (Karcher et al., 2019; Orliac et al., 2013; Tu et al., 2012). The putamen is a central part of the striatum, which is known for its role in motor function and cognitive tasks (Alexander et al., 1986; Simpson et al., 2010). In schizophrenia, structural and functional abnormality within the putamen is well documented (Brandt and Bonelli, 2008;

Menon et al., 2001), and there is vast evidence of reduced cortico-striatal connectivity often associated with symptom severity (Avram et al., 2018; Fornito et al., 2013; Koch et al., 2014). Cortico-striatal connectivity is reported to have an important role in the pathogenesis of cognitive symptoms in psychosis (Avram et al., 2018; Simpson et al., 2010). A possible mechanism for this role is the mediation of "incentive salience" attribution to stimuli via dopamine release within the striatum, a process that marks a stimulus as highly attractive and desirable (Robinson and Berridge, 1993). Aberrations in this process might cause otherwise non-relevant stimuli to be falsely attributed with "incentive salience", marking them inappropriately as desirable, causing abnormal learning processes (Heinz and Schlagenhauf, 2010; Kapur, 2003). Psychotic patients have been shown to demonstrate abnormal activation in midbrain regions like the striatum in response to reward prediction error (Murray et al., 2008), which may be evidence of difficulties in reward based learning. This mechanism may explain our correlation between aberrant putamen connectivity and disorganization symptoms in patients.

Interestingly the basal ganglia have been described as part of a system gradually learning based on positive and negative outcomes (Frank and Claus, 2006; Knowlton et al., 1996), as opposed to a more frontally centred rapid learning system based on recent information (Gold et al., 2008). This might explain why we found no significant correlation between putamen connectivity and global cognition, as the MCCB tasks mostly depend on fast learning processes and not as much on slower gradual learning.

To our knowledge, we are the first to report aberrant SMA connectivity within the SN in psychosis. Similar to the putamen the SMA is a brain area known to be highly relevant for motor tasks (Brinkman, 1981; Cunnington et al., 2003). Interestingly it has also been consistently associated with both verbal and spatial working memory (Awh et al., 1995; Chung et al., 2005; Reuter-Lorenz et al., 2000; Ricciardi et al., 2006; Smith and Jonides et al.,

1998). While the specific role of the SMA in working memory is still up for debate, it has been proposed to contribute to a rehearsal process that refreshes stored content (Awh et al., 1995, Smith and Jonides et al., 1998). These findings fit well with our result of an association between SMA connectivity within the SN and global cognition, which was mainly driven by significant correlations with *working memory* and *verbal learning.* Similar to the working memory tasks of the MCCB, the verbal learning task requires the retrieval of items from working memory, making intact working memory capacity crucial for both subscores. This is also indicated by a correlation between *working memory* and *verbal learning* (r=0.421). We propose our results resemble aberrations in the recruitment of the SMA by the SN, which results in deficits of SMA functions like verbal and spatial working memory.

It has been reported that verbal working memory processes are more closely associated with left-hemispheric activation, while spatial working memory processes are primarily right-hemispheric (Reuter-Lorenz et al., 2000; Smith et al., 1996). We found no sign of such lateralization, as our SMA cluster lies close to the interhemispheric fissure and was associated with both verbal and spatial working memory. It has already been suggested that the described lateralization is reduced in schizophrenia (Walter et al., 2003), and our results might be further evidence of this process.

*Limitations*

A common limitation when analysing basal ganglia in psychosis is the influence of medication on dopamine sensitive neurons. Most of the patients within our study were medicated with antipsychotics, which may have influenced striatal connectivity (Lui et al., 2010; Sarpal et al., 2015). We tried to minimize this influence by including olanzapine equivalence doses as a covariate in our t-test as well as in our linear models. Some patients were also medicated with antidepressants, anticholinergics, benzodiazepines or mood

stabilizers. These substances may have influenced fMRI data as well (Chhatwal et al., 2019; Dandash et al., 2018; McCabe and Mishor, 2011; Pflanz et al., 2015).

Furthermore, our study only consisted of resting-state fMRI data. While resting-state data is well suited to calculate connectivity between functionally related brain areas (Biswal et al., 1995; Greicius et al., 2003), it is noteworthy that we did not identify our clusters based on activation during cognitive tasks, and that there might be other explanations for the correlation of aberrant connectivity and cognitive symptom scores, than a direct influence of these clusters on cognitive processing.

*Conclusions*

In summary, the results of the present study support the hypothesis that aberrant intrinsic SN connectivity in psychosis may be a basis for the well-described cognitive deficits of the disease. Future studies can build upon our findings and further analyse the link between aberrant SN connectivity and cognitive capacity in psychosis. In order to more directly link functional connectivity to cognitive deficits, the use of a combination of resting-state and task-based fMRI data might be beneficial. In the long run, it will be particularly interesting whether aberrant SN connectivity could potentially be a treatment target for psychosis.

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All authors report no financial interests or conflicts of interest.

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