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Aberrant striatal coupling with default mode and central executive network relates to self-reported avolition and anhedonia in schizophrenia

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A B S T R A C T

Background: Avolition and anhedonia are common symptoms in schizophrenia and are related to poor long-term prognosis. There is evidence for aberrant cortico-striatal function and connectivity as neural substrate of avolition and anhedonia. However, it remains unclear how both relate to shared or distinct striatal coupling with large-scale intrinsic networks. Using resting state functional magnetic resonance imaging (rs-fMRI) this study investigated the association of large-scale cortico-striatal functional connectivity with self-reported and clinician-rated avolition and anhedonia in subjects with schizophrenia.

Methods: Seventeen subjects with schizophrenia (SZ) and 28 healthy controls (HC) underwent rs-fMRI. Using Independent Component Analysis (ICA), we assessed Independent Components (ICs) reflecting intrinsic connectivity networks (ICNs), intra intrinsic functional connectivity within the ICs (intra-iFC), and intrinsic functional connectivity between different ICs (inter-iFC). Avolition and anhedonia were assessed using the Self Evaluation Scale for Negative Symptoms and the Brief Negative Symptom Scale.

Results: ICA revealed three striatal components and six cortical ICNs. Both self-rated avolition and anhedonia correlated with increased inter-iFC between the caudate and posterior Default Mode Network (pDMN) and between the caudate and Central Executive Network (CEN). In contrast, clinician-rated avolition and anhedonia were not correlated with cortico-striatal connectivity. Group comparison revealed trend-wise decreased inter-iFC between the caudate and Salience Network (SN) in schizophrenia patients compared to HC.

Discussion: Self-rated, but not clinician-rated, avolition and anhedonia was associated with aberrant striatal coupling with the default mode and the central executive network. These findings suggest that self-reported and clinician-rated scores might capture different aspects of motivational and hedonic deficits in schizophrenia and therefore relate to different cortico-striatal functional abnormalities.

1. Introduction

Schizophrenia (SZ) is a severe and disabling mental disorder (Whiteford et al., 2013) characterized by positive symptoms, negative symptoms, cognitive deficits (Szoeke 2008), structural brain alterations (Asami 2012; Köse 2018; Van Erp 2016, 2018; Kos 2016), and functional disconnections in large-scale brain networks (Dong 2018). Up to 60% of patients with schizophrenia suffer from negative symptoms (Correll 2020), which have been further conceptualized into two dimensions: A motivation and pleasure dimension including the domains asociality, avolition, and anhedonia and a diminished expression dimension including the domains blunted affect, and alogia (Kaiser 2017; Blanchard 2005; Foussias 2010). Both dimensions have been linked to different behavioural and neurobiological mechanisms (Marder 2017; Galderisi 2018; Bègue 2020). However, recent psychometric studies provide support for a more granular differentiation into the five negative symptom domains and suggest that neural mechanism should be examined individually (Strauss 2018; Ahmed 2019). In this regard, avolition, a reduced motivation to initiate or persist in goal-directed activity and anhedonia, a reduced ability to experience pleasure, are of particular interest (Galderisi 2018; Bègue 2020). Both domains are highly prevalent in patients with schizophrenia and are associated with reduced quality of life, reduced real-life functioning and poor clinical outcome (Faerden 2010; Galderisi 2013, 2014; Strauss 2013; Konstantakopoulos 2011; Cuesta 2020), yet effective treatments are still lacking (Kirkpatrick 2006; Fusar-Poli 2015; Correll 2020). At the same time, while neuroscientific frameworks for these domains are emerging (Galderisi 2018; Husain 2018), the identification of distinct neural

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signatures of avolition and anhedonia remains to be established.

With respect to anhedonia, a specific deficit in anticipatory pleasure (Gard 2007; Horan 2006; Mote 2014) has been proposed in schizophrenia, while consummatory in-the moment pleasure has been suggested to be relatively intact (Strauss 2013). In addition, it has been proposed that anhedonia reflects a deficit in sustained hedonic response (Kring 2013a), which has received further support in a recent computational ecological momentary assessment (EMA) study (Strauss et al., 2020). The reported discrepancy between self-reported anticipatory and consummatory in-the moment anhedonia has been challenged by a meta-analysis (Visser 2020) reporting no significant differences in self-ratings of anticipatory compared to consummatory pleasure in the schizophrenia spectrum (observer-rating were not included in this meta-analysis). Taken together, the complexity of avolition and anhedonia as well as the putatively distinct contribution of anticipatory and consummatory pleasure deficits are far from clear and a comprehensive phenotyping combining self-reports and interview-based assessments is needed (Marder 2017; Galderisi 2018; Bègue 2020) to understand the neural substrates of both domains.

In this regard, neuroimaging has begun to uncover the functional brain signatures related to motivational (avolition) and hedonic/pleasure deficits (anhedonia) in schizophrenia. Studies using resting-state functional magnetic resonance imaging (rs-fMRI) showed a relationship between striatal dysconnectivity and global negative symptom severity (Tu 2012; Fornito 2013; Shukla 2018), whereas task-related fMRI studies found consistent evidence for an association between blunted ventral striatal activation and negative symptoms (Radua 2015). This aberrant striatal activation was observed in particular during reward processing including prediction error coding (Waltz 2018; Dowd 2012, 2016) and reward anticipation (Simon 2010; Kirschner 2016; Mucci 2015; Stepien 2018), but also during cognitive processes (Ehrlich 2012). In addition a large-scale network approach from Abram et al. (2017) showed a relationship between reduced medial-fronto-temporal networks and the motivation and pleasure dimension measured with the combined global ratings of avolition and anhedonia from the Scale for the Assessment of Negative Symptoms (SANS). However, most of these studies either used total negative symptoms scores or combined avolition and anhedonia in one single factor, which limits the identification of potential distinct striatal mechanisms.

In contrast, only few studies directly employed specific measures for either avolition and/or anhedonia to explore shared or dissociable striatal correlates. Mucci and colleagues (2015a) reported a specific negative association between avolition (avolition-apathy factor, Schedule for the Deficit Syndrome (SDS), Kirkpatrick 1989) and blunted dorsal but not ventral caudate activation, and Morris (2015) found that reduced caudate activation (not specifying ventral and dorsal) was correlated with avolition (avolition-apathy score from the SANS). In addition, one diffusion tensor imaging study observed an association between avolition (SDS) and dysconnectivity in motivation-related brain circuits including the amygdala, ventral striatum (VST) and insula (Amodio 2018). Correspondingly, a recent rs-fMRI study found that avolition (SDS) is associated with reduced connectivity of the ventro-tegmental area with the right ventro-lateral prefrontal cortex, bilateral insular cortex and the right occipital complex (Giordano 2018). Regarding anhedonia, studies showed a relationship of blunted ventral striatal and ventromedial prefrontal cortex (vMPFC) reward signals (Dowd 2012; Arrondo 2015), and dysconnectivity between the VST and the anterior cingulate cortex (ACC) and the insula (Wang 2016). Taken together, these findings suggest that cortico-striatal network alterations are involved in the pathophysiology of avolition and anhedonia in schizophrenia.

With respect to large-scale intrinsic networks, several studies revealed the importance of abnormal connectivity between and within distinct networks in schizophrenia including the default mode network (DMN) (Bluhm 2007; He 2013; Guo 2014; Lefort-Bensard 2018), the salience network (SN), and the central executive network (CEN) (Orliac 2013; Tu 2012; Manoliu 2013; Iwabuchi 2015; Amico 2017). Investigating the interplay between these three large scale networks and their underlying neuroanatomical regions might be instrumental to better understand impaired motivation and goal directed behaviour in schizophrenia (Menon 2011; Nekovarova 2014; Lefort-Besnard 2018). The DMN includes the vMPFC, posterior cingulate/retrosplenial cortex (pCC), inferior parietal lobule (iPL), lateral temporal cortex, dorsal medial prefrontal cortex (dmPFC), and the hippocampal formation and is involved in processing of task-independent thoughts, attention to internal emotional states, self-inspection, and future planning (Buckner 2008; Raichle 2001). The CEN is involved in goal-directed/externally oriented tasks and connects dorsolateral frontal and parietal neocortices including the dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC) and inferior parietal lobe (Seeley 2007; Manoliu 2014). Functional hubs of the SN integrating emotional, sensory and cognitive information lie in the anterior insula (AI) and the dorsal anterior cingulate cortex, amygdala, the VST, and the substantia nigra/ventral tegmental area (Seeley 2007; Menon 2010). While in schizophrenia disruptions of core regions of all three networks (DMN, CEN, SN) and aberrant between network coupling (e.g. DMN-CEN, DMN-SN, SN-CEN) have been frequently reported (Woodward 2011; Manoliu 2013; Palaniyappan 2012; Lefebvre 2016; Hu 2017; Lefort--Bensard 2017; Chen 2016; Supekar 2019) its contribution to negative symptoms has been less explored. Only few studies revealed associations between total negative symptoms with altered functional properties of SN-CEN integration (Lee 2018), disrupted salience-DMN connectivity (Hare 2019), and disrupted DMN connectivity (O'Neill 2019) and it remains an open question how functional connections between striatal sub-regions and system-wide brain networks are associated with avolition and anhedonia.

Concerning the various methods how anhedonia and avolition are assessed, there is a growing recognition that clinician-rated scores and self-rated scores might be differently related to cortico-striatal dysfunction (Mucci 2015a; Moran 2019; Kluge 2018; Dowd 2016). Of note, a recent study from Moran et al. (2019) observed that caudate activation during reward anticipation is associated with self-reported measures of motivation and pleasure scores, but not with clinician-rated motivation and pleasure deficits. These findings highlight the relevance to apply multimodal assessments of avolition and anhedonia including self-rated and clinician-rated assessments. In this context, the recently validated Self-Evaluation of Negative Symptoms (SNS) by Dollfus and colleagues (Dollfus 2016) holds promise to provide additional subjective information of self-experienced motivational and hedonic deficits.

In this explorative rs-fMRI study, we first assessed avolition and anhedonia with a self-assessment using the SNS and an interview-based clinical rating using the Brief Negative Symptoms Scale (BNSS) (Kirkpatrick 2011), and compared the relationship between the self-rated and clinician-rated avolition and anhedonia on a psychopathological level. We then examined the association of intrinsic functional cortico-striatal networks and avolition and anhedonia to identify potential shared and dissociable cortico-striatal mechanisms. Using self-rated and clinician-rated assessments of avolition and anhedonia we sought to explore whether internal (subjective-rated), and external (observer-rated) avolition and anhedonia were related to similar or different cortico-striatal connectivity patterns. Furthermore, to examine potential categorical mechanisms of striatal network alterations (Shukla 2018; Park 2017) we applied an explorative group comparison between subjects with SZ and healthy controls.

2. Materials and methods

2.1. Participants

Please note that participants' data derived from a multimodal

neuroimaging study by Stepien (2018) reporting an association between blunted ventral and dorsal striatal activity and the BNSS apathy dimension score, which consists of anhedonia, avolition, and asociality (Mucci 2015b). Subjects with SZ (n = 17) were recruited from inpatient and outpatient units of the Psychiatric University Hospital in Zurich, and from affiliated institutions. Healthy controls (HC) (n = 28) were recruited from the general community. Diagnosis of schizophrenia or schizoaffective disorder was confirmed with the structured Mini International Neuropsychiatric Interview for DSM IV (MINI) (Sheehan 1998). Individuals with any other Axis I DSM IV disorder, in particular major depression or current substance use disorder, were excluded from the study. Intellectual disability was evaluated by the attending psychiatrist while verbal intelligence was assessed using the Multiple Word Test Intelligence Quotient (MWT-B). No participant had to be excluded (all>87 IQ). To minimize the effect of potential secondary negative symptoms due to positive symptoms and medication (Kirschner 2017), subjects with scores higher 4 on any positive item (P1–P7) of the Positive and Negative Syndrome Scale (PANSS) (Kay 1987) and those with extrapyramidal side effects (i.e., a total score higher than 2 on the Modified Simpson–Angus Scale (MSAS) (Simpson 1970) were excluded. All subjects with SZ were clinically stable, received a constant dose of atypical antipsychotic with no change in medication for at least 14 days prior to testing. In addition, all inpatients were in the last phase of their hospitalization, actively took part in a multimodal treatment program, engaged in several activities outside the hospital and showed no acute psychotic symptoms or aggression. Please note that the average duration of hospitalization for patients with schizophrenia is around 40 days in Switzerland (BFS 2019), which means that nearly all inpatients would have been treated as outpatients in other healthcare systems. The study was approved by the local ethics committee of the Canton of Zurich, Switzerland. All participants signed the written informed consent in accordance with the Declaration of Helsinki. The capability of subjects with SZ to give informed consent was evaluated by the treating psychiatrist.

2.2. Clinical assessment

Self-reported avolition and anhedonia were assessed using a German translation of the 2014 version of the SNS (Dollfus et al., 2016). The German version of the SNS (V1_2015) was developed using forward and backward translation under supervision of one co-author (Stefan Kaiser) and the first author (Dr. Dollfus) from the original publication (Dollfus et al., 2016). Please note that a validation study of this German version has not been carried out yet.

The SNS (Dollfus 2016) evaluates the following five domains of negative symptoms: social withdrawal, diminished emotional range, avolition, anhedonia, and alogia. The five subscores comprise the sum of four items each and within each of the items, the patient can score either with 2 (strongly agree), 1 (somewhat agree), or 0 (strongly disagree). The total score is the sum of the 20 items, ranging from 0 (no negative symptoms) to 40 (severe negative symptoms). SNS anhedonia evaluates the patient's ability to experience consummatory and anticipatory pleasure (example item 18*: I find it hard to take pleasure even when doing things I have chosen to do.*) while SNS avolition assesses the patient's motivation to initiate or persist in goal-directed activity (example item 15: *There are many things I don't do through lack of motivation or because I don't feel like it.*).

Observer ratings of the negative symptom domains avolition and anhedonia were assessed with the BNSS (Kirkpatrick 2011). The BNSS is a semi-structured interview and consists of 13 items organized into six subscales (anhedonia, distress, asociality, avolition, blunted affect, and alogia). Each item is rated from absent to extremely severe in the following scheme: 0 (normal), 1 (questionable), 2 (mild), 3 (moderate), 4 (moderately severe), 5 (severe), 6 (extremely severe), and scores range from 0 to 78. Items forming the subscale anhedonia assess the intensity of pleasure during activities, the frequency of pleasure during activities, and the intensity of expected pleasure from future activities (example of item 2 *frequency of pleasure during activities*: Score 0 = able to enjoy activities often; no impairment in the frequency of pleasure; score 6 = no experience of pleasure during the previous week). Avolition is assessed by questions concerning the patient's behaviour and his internal experience (example of item 7 *avolition behaviour:* score 0 = no impairment: subject initiates and persists in work or school, recreational/hobbies/-pastimes, and self-care; well within normal limits. Score 6 = severe deficit: nearly total lack of initiation of activities).

To identify depressive symptoms, we used the Calgary Depression Scale for Schizophrenia (CDSS) (Addington 1993), and Beck's Depression Inventory (BDI) in HC (Beck 1961). In addition, we applied the PANSS (Kay 1987) to assess psychotic symptom dimensions using the PANSS five factor model (negative, positive, disorganized/concrete, excited and depressed) described by Wallwork and colleagues (Wallwork 2012). Medication dose was assessed using chlorpromazine equivalents (CPZ) based on the method recently described by Leucht et al. (2020) and extrapyramidal symptoms were measured via the Modified Simpson–Angus Scale (MSAS) (Simpson 1970).

2.3. MR imaging and acquisition

To evaluate spontaneous BOLD-signal fluctuations during rest, all participants underwent resting state functional magnetic resonance imaging (rs-fMRI) with the instruction to keep their eyes closed and not to fall asleep, which was ensured by interrogating all participants immediately after the scan respectively. MR-imaging was performed on a 3.0 T Achieva system (Philips Healthcare, Best, The Netherlands) using an eight channel SENSE head coil (Philips Healthcare, Best, The Netherlands). For evaluation of the fluctuating BOLD-signal during rest, rs-fMRI was performed using a gradient-echo echo planar imaging (EPI) sequence with the following parameters: Repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, flip angle (FA) = 82°, 32 slices in transverse orientation, no slice gap, voxel size = 2.75 x 2.75 × 4.00 mm^3, field of view (FoV) = 220 x 220 × 128 mm^3, total scan duration = 10:08 min. Additionally, T1-weighted anatomical data were obtained by using a 3D magnetization-prepared rapid acquisition gradient echo sequence (MP-RAGE) with the following parameters: acquisition voxel size = 1.0x1.0 × 1.0 mm^3, time between two inversion pulses = 2997 ms, inversion time = 1008 ms, inter-echo delay = 8.1 ms, flip angle = 8°, matrix = 240x240, field of view = 240 × 240 mm^2, 160 sagittal slices.

2.4. Preprocessing

Data preprocessing was performed using a custom pipeline, and comprised de-spiking using AFNI (http://afni.nimh.nih.gov/afni), slice-timing correction (Sladky 2011) using FSL5 (FMRIB Software Library, Analysis Group, FMRIB, Oxford, http://fsl.fmrib.ox.ac.uk), bias field correction using ANTs (http://stnava.github.io/ANTs), realignment (FSL5), normalization based on a custom scanner-specific EPI-template maintaining the native resolution (ANTs), and smoothing with a Gaussian kernel of 6.0 mm FWHM (FSL5). To control for differences in motion between healthy volunteers and subjects with schizophrenia, excessive head motion (linear shift >3 mm across run and on a frame-to-frame basis, rotation >1.5°) served as exclusion criteria (Sorg 2013) leading to the exclusion of one subject (SZ).

2.5. Independent component analysis (ICA)

Following a previously proposed approach (Allen et al., 2011; Manoliu 2014), preprocessed data were decomposed into 75 spatial independent components within a group-ICA framework (Calhoun 2001) based on the infomax-algorithm (Bell 1995), and implemented in the GIFT-software (http://icatb.sourceforge.net). The respective components have been selected as previously reported (Manoliu 2013) and are described in more detail in the Supplementary Methods 1 (SM1).

High-model-order ICA approaches yielded independent components (ICs), which were in accordance with known anatomical and functional segmentations (Allen 2014). fMRI data were concatenated and reduced by two-step principal component analysis, followed by independent component estimation with the infomax-algorithm. We subsequently ran 20 ICA (ICASSO) to ensure stability of the estimated components. This resulted in a set of average group components, which were then back-reconstructed into single subject space. Each back-reconstructed component consisted of a spatial z-map reflecting the component's functional connectivity pattern across space, and an associated time course reflecting the component's activity across time (Sorg 2013).

This approach yielded intrinsic striatal and cortical connectivity networks (ICNs) (Figs. 1 and 2), including three spatially distinct striatal components (putamen, VST, caudate nucleus) (Fig. 1), and one component reflecting the salience network (SN), two components reflecting the default mode network (DMN) as well as three components reflecting the central executive network (CEN) (Fig. 2). The chosen ICs, which represent the cortical intrinsic connectivity networks of interest, matched previous results of the SN, DMN and CEN (Manoliu 2014) (see also Figs. 1 and 2, and Table 1). In line with the proposed approach by Allen (2011) and Manoliu (2014) the intrinsic brain networks were calculated in the healthy controls group.

To evaluate the intrinsic functional connectivity iFC between ICs (inter-iFC) individual ICN, time courses (TCs) were detrended, despiked, and filtered using a fifth-order Butterworth low-pass filter with a high frequency cut off of 0.15Hz, and pairwise correlated by Pearson's correlation, following the approach of Jafri and colleagues (Jafri 2008) as reported in Manoliu (2013) for each participant, respectively. Please note that the main analyses concerning cortico-striatal network connectivity are based on the inter-iFCs between the three striatal components and the six cortical intrinsic networks.

2.6. Statistical analysis

Correlation between self-reported and clinician-rated avolition/anhedonia and other symptom scores.

To investigate the relationship between self-reported and clinician-rated avolition/anhedonia we calculated non-parametric Spearman correlations within and between all SNS and BNSS domains (n = 17). Differentiation of primary versus secondary negative symptoms was explored via testing for associations between SNS/BNSS avolition and anhedonia with other psychopathology scores including positive symptoms (PANSS positive factor), depressive symptoms (CDSS total score), disorganized symptoms (PANSS disorganized factor), and medication dose (CPZ).

Association of cortico-striatal network connectivity with avolition and anhedonia.

2.7. Main model

To study the relationship between cortico-striatal inter-iFCs with avolition and anhedonia (self-reported and clinician-rated), we first correlated avolition and anhedonia scores with Fisher-z-transformed inter-iFC scores using non-parametric Spearman correlation analyses in 16 remaining subjects with schizophrenia (IBM SPSS Statistics, version 22, IBM Corp., Armonk, N.Y., USA).

2.8. Correction for potential confounding variables

Partial non-parametric Spearman correlations were performed to examine whether significant correlations from the first analyses were driven by potential confounding factors. Specifically, we applied four separate partial correlations models correcting for 1) medication (CPZ equivalents), 2) depression (CDSS total score), 3) positive symptoms (PANSS positive factor, Wallwork 2012), and 4) disorganized symptoms (PANSS disorganized factor, Wallwork 2012). Each of these four partial correlation models included age and sex as additional covariates.

2.9. Bootstrap resampling

To further assess the stability and reliability of the significant correlation coefficients derived from our main model (simple non-parametric correlation), 95% bootstrap confidence intervals were assessed for each correlation using 10,000 bootstrap samples (Efron 1986, 1993) (bootci function matlab R2020a). Each time, the rows of the data matrices (i.e. x = self-reported avolition and anhedonia; y = cortico-striatal inter-iFC) were randomly resampled with replacement and new correlation coefficients were calculated using the resampled data

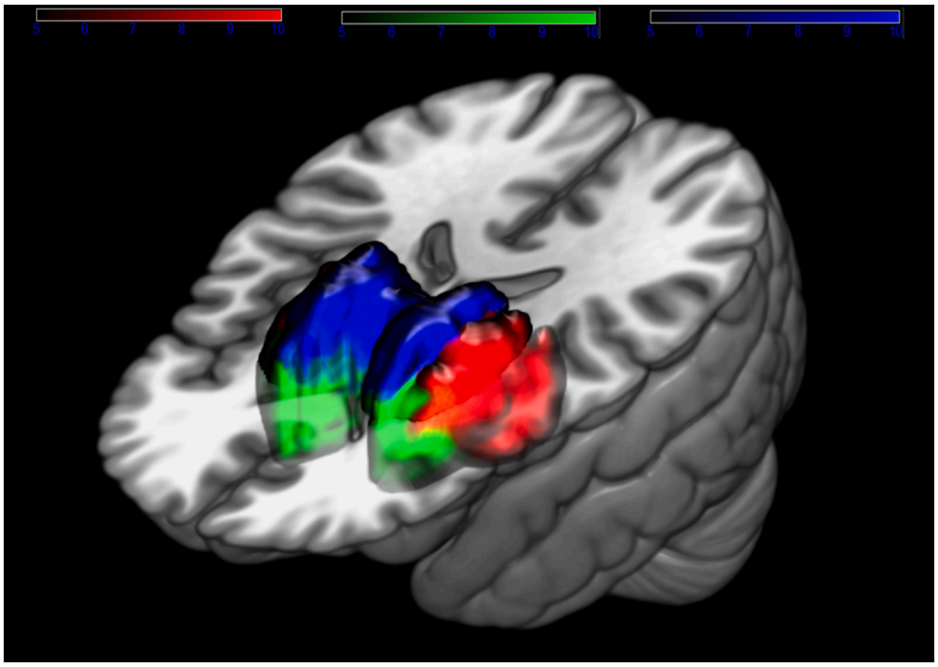

Fig. 1. Striatal intrinsic brain networks. Independent component analysis across all subjects yielded 3 spatially distinct striatal connectivity networks, including the putamen (red), ventral striatum (green) and caudate nucleus (blue) (FWE-corrected, cluster-threshold >20 voxel; T-values are color-coded ranging from 5 (black) to 10 (corresponding colour, see also Table 2 for detailed presentation of coordinates).
(see separate file "Fig. 1" for high resolution image).. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

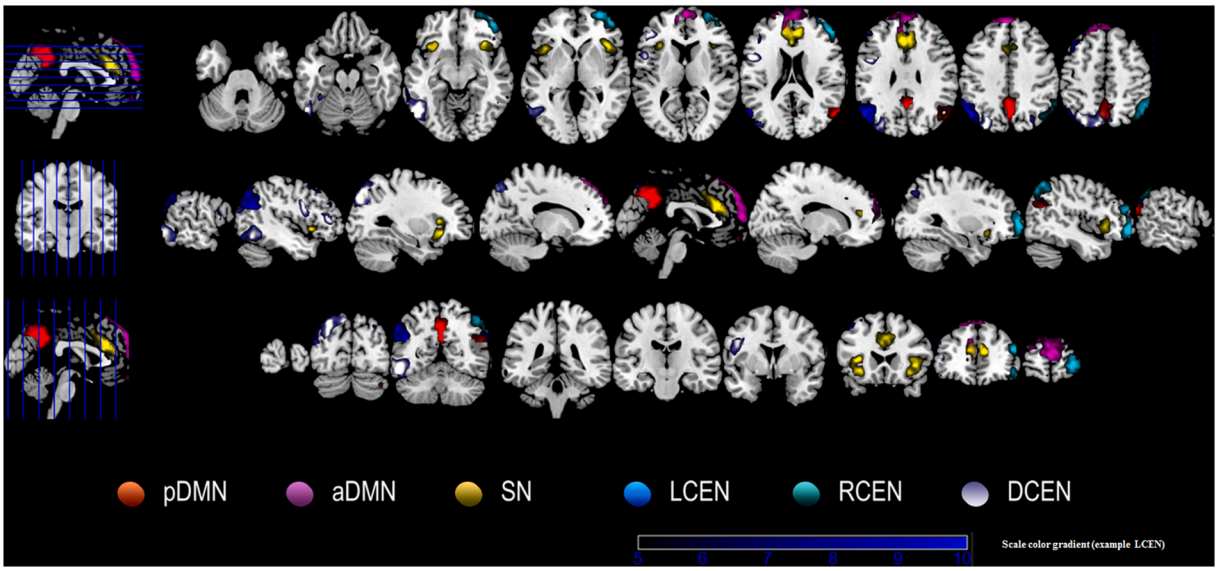

Fig. 2. Cortical intrinsic brain networks. Independent component analysis across all subjects yielded 6 spatially distinct cortical connectivity networks. Upper row: horizontal plane (left to right: inferior to superior); middle row: Saggital plane (left to right); lower row: Coronal plane (left to right: posterior to anterior). Abbreviations: a/pDMN, anterior/posterior Default-Mode-Network (red/magenta); SN, Salience Network (yellow); L/R/DCEN, left/right/dorsal Central Executive Network (blue, turquoise, grey-blue). All spatial maps were FWE-corrected (cluster-threshold >20 voxel); T-values are color-coded ranging from 5 (black) to 10 (corresponding color, see also Table 2 for detailed presentation of coordinates).
(see separate file "Fig. 2" for high resolution image).. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

matrices. 95% bootstrap confidence intervals were calculated based on the correlation coefficients derived from all 10,000 bootstrap samples using the bias corrected and accelerated percentile method (BCA, default method of bootci function in matlab R2020a). Finally, simple non-parametric Spearman correlations from the main model were corrected for multiple comparisons across all 21 striatal inter-iFCs using a false discovery rate (FDR) of $q = 0.05$ (Benjamini and Hachberg, 1995; Storey 2003).

2.10. Explorative group comparison between SZ and HC

To perform explorative group comparison of cortico-striatal network connectivity (inter-iFC) between SZ and HC, Fisher-z-transformed inter-iFC scores were entered into two-sample t-tests with age and sex as covariates of no interest (FDR correction, $q = 0.05$, for multiple comparisons). In addition, potential group differences of iFC within selected ICs (intra-iFC) were examined using SPM8 (Wellcome Department of Cognitive Neurology). Two-sample t-tests on participants' reconstructed spatial maps including age, and sex as covariates of no interest ($p < 0.05$, family-wise-error (FWE)-corrected for multiple comparisons).

3. Results

3.1. Sample characteristics

Demographic and clinical data are summarized in Table 2. There were no significant group differences with regard to age, but a significant difference in years of education ($p < 0.00001$), and sex ($p = 0.037$). The duration of untreated psychosis was 619.7 days (standard deviation (SD) = 833.1 days), and the dosage of medication was 490.5 mg per day chlorpromazine equivalents (SD = 386.3 mg). Subjects with SZ showed low to mild PANSS positive scores (7.2, SD = 2.4), low PANSS disorganized (5.9, SD = 2.1) and PANSS excited scores (4.8, SD = 1.2). Specifically, fourteen subjects showed mild or less symptom severity (≤3) on all positive items, while only three subjects showed slightly higher scores in one positive item (score of 4). In addition, severity of interview-rated depression (CDSS) was below the proposed cut-offs for major depression (CDSS total>6) and self-reported depression indicated no to minimal depression (BDI 0–13). These low levels of positive, disorganized and depressive symptoms are in line with previous neuroimaging studies focusing on primary negative symptoms (Amodio 2018; Giordano 2018).

3.2. Psychopathological data

Characteristics of self-reported (SNS) and clinician-rated (BNSS) avolition and anhedonia.

To examine the relationship between self-reported and clinician-rated avolition/anhedonia, we correlated SNS domain scores with the corresponding BNSS domain scores. Neither avolition nor anhedonia correlated significantly between the two assessment tools (SNS/BNSS avolition, $r = 0.32$, $p = 0.21$; SNS/BNSS anhedonia, $r = 0.21$, $p = 0.42$). These effects sizes were similar to the study from Dollfus et al. (2016) comparing global scores from the Scale for the Assessment of Negative Symptoms (SANS) with SNS avolition and anhedonia scores (SANS avolition-apathy: $r = 0.39$, $p < 0.01$; SANS anhedonia-asociality: $r = 0.40$, $p < 0.01$). In a next step, we assessed the association between avolition and anhedonia within each assessment tool. We found a highly significant correlation between BNSS avolition and BNSS anhedonia ($r = 0.81$, $p < 0.01$) while SNS avolition and SNS anhedonia were also positively correlated, but to a lesser extent ($r = 0.41$, $p = 0.11$). Compared to all other correlations within the SNS domains (all $rs < 0.26$), the association between SNS avolition and anhedonia was the strongest ($r = 0.41$). In contrast, domains of interview-based rated BNSS showed significant correlations suggesting a higher dependency of interview-based clinical ratings compared to the self-rated negative symptom domains (see ST1).

Nature of negative symptoms (primary or secondary negative symptoms).

In order to discriminate between primary and secondary negative symptoms, we investigated associations between SNS/BNSS avolition and anhedonia with other psychopathology scores and medication dose. SNS and BNSS anhedonia/avolition were not significantly correlated with positive symptoms, depressive symptoms and medication dose

Table 1
Intrinsic brain networks in healthy controls.

Anatomical Region	L/R/Bi	Cluster	Z-score	p-value[a]	MNI (x)	MNI (y)	MNI (z)
(A) PU							
Putamen	L	2815	>8.00	<0.001	−24	2	4
		"	>8.00	<0.001	−27	−6	8
		"	7.16	<0.001	−26	−1	−7
Putamen	R	2670	>8.00	<0.001	26	6	5
		"	7.8	<0.001	32	−16	6
		"	7.39	<0.001	24	−2	10
(B) VST							
Ventral Striatum	L	2002	>8.00	<0.001	−8	12	−7
		"	>8.00	<0.001	−21	5	−7
		"	7.61	<0.001	−24	8	4
Ventral Striatum	R	2172	>8.00	<0.001	24	11	0
		"	>8.00	<0.001	21	5	−8
		"	7.74	<0.001	18	16	−7
(C) NC							
Caudate Nucleus	R	1728	>8.00	<0.001	10	0	14
		"	>8.00	<0.001	8	4	5
Caudate Nucleus	L	1523	>8.00	<0.001	−10	6	12
		"	>8.00	<0.001	9	2	1
(D) SN							
Anterior Cingulate Cortex	B	3116	>8.00	<0.001	−4	29	28
		"	>8.00	<0.001	−8	36	26
Anterior Insula	R	"	>8.00	<0.001	8	34	26
		1073	>8.00	<0.001	−45	14	−2
		"	7.58	<0.001	−45	14	−2
		"	7.53	<0.001	−32	26	−7
Anterior Insula	R	1153	7.63	<0.001	39	23	−1
			7.21	<0.001	34	24	10
(E) pDMN							
Precuneus/PCC	Bi	4525	>8.00	<0.001	2	−50	36
		"	>8.00	<0.001	3	−60	35
		"	>8.00	<0.001	2	−55	28
Superior parietal gyrus	R	3271	7.25	<0.001	52	−67	22
		"	6.9	<0.001	52	−55	24
		"	6.22	<0.001	44	−62	24
Superior parietal gyrus	L	126	4.51	<0.001	56	−16	−24
		319	4.47	<0.001	−44	−66	29
		"	4.24	<0.001	−51	−72	32
(F) aDMN							
Medial prefrontal cortex	R	5195	7.56	<0.001	4	62	12
Medial prefrontal cortex	L	"	7.35	<0.001	−8	58	11
		53	6.15	<0.001	−4	62	−14
		10	6	<0.001	−28	38	47
		41	5.87	<0.001	34	20	−18
(G) LCEN							
Inferior parietal lobule	L	2571	>8.00	<0.001	−51	−67	41
		"	>8.00	<0.001	−54	−64	32
		"	7.7	<0.001	−54	−6	24
Superior frontal gyrus	L	308	6.31	<0.001	−42	12	54
		"	6.09	<0.001	−44	26	47
Inferior parietal lobule	R	173	5.74	<0.001	56	−58	26
		"	5.27	<0.001	52	−62	41
(H) RCEN							
Inferior parietal lobule	R	2793	>8.00	<0.001	46	48	−6
		"	7.77	<0.001	30	60	4
		"	7.56	<0.001	51	40	18
Superior frontal gyrus	R	1453	6.95	<0.001	44	−61	53
		"	6.82	<0.001	51	−55	52
		"	6.55	<0.001	57	−62	38
Frontal lateral gyrus	R	110	6.35	<0.001	42	17	3
		"	6.11	<0.001	39	12	59
(I) DCEN							
Supramarginal gyrus	L	3028	>8.00	<0.001	−28	−78	47
		"	>8.00	<0.001	−32	−82	38
		"	7.54	<0.001	−9	−79	50
Inferior temporal gyrus	L	2303	>8.00	<0.001	−54	−58	−13
		"	>8.00	<0.001	−56	−66	−7
		"	5.84	<0.001	−60	−49	−10
Inferior frontal gyrus	L	881	>8.00	<0.001	−46	5	28
		"	>8.00	<0.001	−52	6	22
Supramarginal gyrus	R	459	7.49	<0.001	48	36	11

[a] One-sample-t-test, significant for $p < 0.05$, FWE-corrected for multiple comparisons, cluster-threshold >20 voxel (see Figs. 1 and 2). Abbreviations: MNI, Montreal Neurological institute; L, left hemisphere; R, right hemisphere; Bi, bilateral; PU, Putamen; VST, Ventral striatum; NC, caudate nucleus; a/pDMN, anterior/posterior Default-Mode-Network; SN, Salience Network; L/R/DCEN, left/right/dorsal Central Executive Network.

Table 2
Clinical and demographic characteristics.

Characteristics	SZ (n = 17)	HC (n = 28)	Statistical test	p value
Age	32.5 (8.9)	27.5 (5.7)	U = 231.5	0.177
Sex	2w,15m	14w,14m	U = 257.0	0.037
Education, yr.	11.8 (1.9)	15.1 (2.2)	t = 5.0	<0.00001
DUP, days	619.7 (833.1)			
Chlorpromazine equivalents, mg/d	490.5 (386.3)			
Negative Symptoms				
BNSS scores				
Avolition	4.8 (2.7)	0.75 (1.4)	t = −6,7	<0.00001
Anhedonia	6.9 (4.5)	0.5 (0.8)	t = −7.5	<0.00001
SNS scores				
Avolition	3.6 (2.1)			
Anhedonia	1.5 (1.8)			
PANSS score				
Positive	7.2 (2.4)			
Negative	15.5 (7.1)			
Disorganized	5.9 (2.1)			
Excited	4.8 (1.2)			
Depressed	6.1 (2.0)			
Total	54.8 (11.4)			
Depression				
CDSS	2.6 (2.2)			
BDI	10.7 (10.2)	3.2 (3.6)	−3.2	0.003

Notes: Data are presented as means and standard deviations. BDI= Beck Depression Inventory; BNSS= Brief Negative Symptom Scale; CDSS= Calgary Depression Scale for Schizophrenia; DUP = Duration of untreated psychosis; PANSS= Positive and Negative Syndrome Scale; PANSS positive, negative, disorganized, excited and depressed factor based on Wallwork et al. (Wallwork 2012).

(CPZ) (all rs < 0.47, all ps > 0.05); see Supplementary Table 2 (ST2)). With regards to the PANSS disorganized concrete factor, BNSS anhedonia showed a significant correlation (r = 0.535, p = 0.03), while BNSS avolition (r = 0.461. p > 0.05) and SNS avolition and SNS anhedonia showed non-significant positive correlations (SNS avolition: r = 0.477,

SNS anhedonia: r = 0.235 both p > 0.05). With respect to BNSS avolition and SNS avolition, the correlation coefficients were only marginal different from the correlation of BNSS anhedonia and the non-significant results are likely due to the small sample size of the study. Despite the correlations with low levels of disorganized symptoms, these results indicate that SNS and BNSS avolition/anhedonia were not related to potential secondary sources for negative symptoms (Kirschner 2017).

3.3. Cortico-striatal networks and avolition/anhedonia

Associations with self-reported but not clinician-rated avolition/anhedonia.

To study the association between functional cortico-striatal networks and both symptom domains, we first used simple non-parametric Spearman correlation to investigate the association between inter-iFC scores with self-reported avolition and anhedonia (SNS), and clinician-rated avolition and anhedonia (BNSS). Self-reported avolition (SNS) showed a significant positive correlation with inter-iFC scores between the caudate (NC) and the pDMN (r = 0.664, p = 0.005) and between NC and right CEN (RCEN) (r = 0.591, p = 0.016) (Table 3). Correlation analysis of self-reported anhedonia (SNS) revealed similar results. In particular, we found significant associations between anhedonia and inter-iFC scores of NC-pDMN (r = 0.641, p = 0.007), NC-RCEN (r = 0.603, p = 0.013), NC to left CEN (NC-LCEN) (r = 0.636, p = 0.008), and VST to LCEN (r = 0.504, p = 0.047) (Table 3). The other SNS domains (alogia, flat affect, social) showed no significant correlation with the NC-pDMN, NC-RCEN, NC-LCEN (all rs < 0.29, all ps > 0.275) suggesting a specific mechanism related to avolition and anhedonia (see Supplementary Table 3a (ST3a)).

In contrast to self-reported avolition/anhedonia, no significant correlations were observed with clinician-rated avolition and anhedonia (all ps > 0.05, Table 3). For detailed cortico-striatal inter network iFC correlations with SNS and BNSS avolition/anhedonia see Supplementary Table 3b (ST3b)). Using Steiger's test (Steiger 1980), we found that the correlation of self-reported avolition or anhedonia and NC-pDMN was significantly different compared to the correlation between clinician-rated avolition or anhedonia and NC-pDMN (avolition: z-score = 2.523, p = 0.006, anhedonia: z-score = 1.926, p = 0.027).

3.4. Associations with anticipatory and consummatory anhedonia

In a second step, we examined whether significant correlations of anhedonia were driven by anticipatory or consummatory anhedonia deficits. Repeating separate correlation analyses for consummatory and anticipatory SNS/BNSS anhedonia we found that both self-rated anticipatory and consummatory anhedonia showed significant positive correlations with NC-pDMN, NC-LCEN and NC-RCEN, yet only anticipatory SNS anhedonia was correlated to a significant level with VST-LCEN inter-iFC. Similar to the main analysis, none of the inter-iFCs was significantly correlated with clinician-rated (BNSS) consummatory or anticipatory anhedonia (all rs < 0.5, all ps > 0.05; see Supplementary Table 4 (ST4)). In sum, associations between cortico-striatal hyperconnectivity and anhedonia were not specific for either anticipatory or consummatory domains suggesting a more general neural mechanism.

Stability and reliability testing of cortico-striatal network connectivity with self-reported avolition and anhedonia.

Table 3
Simple non-parametric Spearman correlations between inter-iFC of striatal networks and severity of negative symptoms in patients with schizophrenia.

	SNS		BNSS	
	avolition	anhedonia	Avolition	anhedonia
Inter-iFC	r-score (p-value)	r-score (p-value)	r-score (p-value)	r-score (p-value)
VST-LCEN	0.193 (0.474)	0.504 (0.047)	0.144 (0.594)	0.269 (0.314)
NC-pDMN	0.664* (0.005)	0.641* (0.007)	−0.030 (0.913)	0.075 (0.782)
NC-LCEN	0.276 (0.301)	0.636* (0.008)	0.146 (0.590)	0.208 (0.439)
NC-RCEN	0.591* (0.016)	0.603 (0.013)	0.137 (0.613)	0.183 (0.497)

Simple non-parametric Spearman correlations. Bold font indicates p < 0.05. *remained significant after correction for multiple comparison using FDR (q = 0.05). Abbreviations: SNS, Self-evaluation of negative symptoms; BNSS, Brief Negative Symptom Scale; inter-iFC = inter-network intrinsic functional connectivity; VST = ventral striatum, NC = caudate; LCEN = left Central Executive Network, pDMN = posterior Default-Mode-Network, RCEN = right Central Executive Network.

3.5. Partial correlation models including confounding variables

To examine whether the significant associations between cortico-striatal inter-iFC and self-reported avolition and anhedonia were driven by potential confounding variables we used four separate non-parametric partial correlations models correcting for medication, depression, positive and disorganized symptoms (each of the models also included age and sex as covariates of no interest). Effect sizes (correlation coefficient) of the two correlations between self-rated avolition with cortico-striatal iFC (NC-pDMN, NC-RCEN) as well as the three correlations between self-rated (SNS) anhedonia (NC-pDMN, NC-LCEN, NC-RCEN) remained almost the same (all r ≥ 0.51) and were all significant (exception, correlation of avolition with NC-RCEN corrected for PANNS disorganized factor, r = 0.510, p = 0.075). All non-parametric partial correlation models are displayed in Table 4.

3.6. Bootstrap resampling

In a last step we assessed the stability and reliability of the significant association derived from the main model (simple non-parametric correlation) calculating 95% confidence intervals using 10,000 bootstrap samples (Efron 1986, 1993). Bootstrap resampling with replacement yielded significant results for the association between SNS avolition with NC-pDMN inter-iFC (r = 0.664, p = 0.005, 95% CI: [0.30, 0.88]) and SNS avolition with NC-RCEN inter-iFC (r = 0.591, p = 0.016, 95% CI: [0.08, 0.83]). Concerning SNS anhedonia, significant correlations were observed with NC-pDMN inter-iFC (r = 0.641, p = 0.007, 95% CI: [0.12, 0.82]), NC-LCEN inter-iFC (r = 0.636, p = 0.008, 95% CI: [0.17, 0.87]) but not between SNS anhedonia and NC-RCEN inter-iFC (r = 0.603, p = 0.013, 95% CI: [−0.113, 0.844]) (see Fig. 3a and b). Taken together, four of the initial significant associations between SNS avolition/anhedonia and cortico-striatal inter-iFC remained significant after accuracy testing using 10,000 bootstrap samples with replacement. For detailed bootstrap analysis results see Supplement Table 5 (ST5). Finally, all four associations between SNS avolition and NC-pDMN/NC-RCEN inter-iFC (see Fig. 4a,c) as well as SNS anhedonia and NC-pDMN/NC-LCEN (see Fig. 4b,d) remained significant after correction for multiple comparison using FDR (q = 0.05).

Explorative group comparison of striatal inter-iFC, striatal intra-iFC, and cortical network inter-iFC.

Regarding potential group differences of striatal inter-iFC, subjects with SZ showed decreased inter-iFC between PU and NC (p = 0.027), VST and pDMN (p = 0.039), VST and aDMN (p = 0.047), VST and DCEN (p = 0.025) as well as NC and SN (p = 0.008) compared to HC. However, after correction for multiple comparisons, no inter-iFC reached a level of significance (Supplementary Table 6 (ST6)). Explorative analysis of intra-iFC within all three striatal networks did not reveal any significant group differences between HC and SZ. In contrast, SZ showed increased intra-iFC of the pDMN (precuneus) and RCEN (frontal lateral gyrus) compared to HC (cluster-level FWE corrected for multiple comparisons, cluster-threshold >20 voxel; see Supplementary Table 7 (ST7)). Intrinsic functional connectivity between intrinsic cortical networks (inter-iFC) is presented in Supplementary Table 8 (ST8) and matched almost perfectly

Table 4
Partial non-parametric Spearman correlations between inter-iFC of striatal networks and severity of SNS avolition and anhedonia in subjects with schizophrenia.

a) Partial non-parametric correlation of NC-pDMN with SNS avolition and anhedonia		
Covariates	Spearman rho r-score (p-value)	
	Avolition/NC-pDMN	Anhedonia/NC-pDMN
CPZ	0.677 (0.011)	0.640 (0.019)
Depression (CDSS)	0.696 (0.008)	0.601 (0.030)
Positive (PANSS)	0.673 (0.012)	0.655 (0.015)
Disorganized (PANSS)	0.593 (0.033)	0.602 (0.029)
No covariates*	0.664 (0.005)	0.641 (0.007)
b) Partial non-parametric correlation of NC-RCEN with SNS avolition and anhedonia		
	Avolition/NC-RCEN	Anhedonia/NC-RCEN
CPZ	0.667 (0.013)	0.653 (0.015)
Depression (CDSS)	0.650 (0.016)	0.623 (0.023)
Positive (PANSS)	0.649 (0.016)	0.720 (0.005)
Disorganized (PANSS)	0.510 (0.075)	0.657 (0.015)
No covariates*	0.591 (0.016)	0.603 (0.013)
c) Partial non-parametric correlation of NC-LCEN with SNS avolition and anhedonia		
	Avolition/NC-LCEN	Anhedonia/NC-LCEN
CPZ	NaN	0.599 (0.031)
Depression (CDSS)	NaN	0.612 (0.026)
Positive (PANSS)	NaN	0.591 (0.034)
Disorganized (PANSS)	NaN	0.605 (0.029)
No covariates*	0.276 (0.301)	0.636 (0.008)
d) Partial non-parametric correlation of VST-LCEN with SNS avolition and anhedonia		
	Avolition/NC-LCEN	Anhedonia/NC-LCEN
CPZ	NaN	0.435 (0.137)
Depression (CDSS)	NaN	0.333 (0.266)
Positive (PANSS)	NaN	0.428 (0.145)
Disorganized (PANSS)	NaN	0.503 (0.080)
No covariates*	0.193 (0.474)	0.504 (0.047)

Note. All non-parametric partial correlation models are corrected for age and sex and one of the four additional covariates (CPZ, Depression, Positive, Disorganized). * No covariates show correlations coeffecients of simple non-parametric correlation for comparison. Bold font indicates $p < 0.05$; NaN, partial correlations were not applied when correlation coefficient of initial simple correlation model was not significant. Abbreviations: SNS, Self-evaluation of negative symptoms; CDSS, Calgary Depression Scale for Schizophrenia; PANSS, positive and negative syndrome scale for schizophrenia based on Wallwork et al. (Wallwork 2012); NC, caudate; pDMN, posterior Default-Mode-Network: RCEN, right Central Executive Network: LCEN, left Central Executive Network.

with the results of Allen and colleagues (Allen 2011).

4. Discussion

4.1. Summary

This neuroimaging study employed rs-fMRI and independent component analysis (ICA) as a data-driven approach in a small sample of subjects with schizophrenia (SZ), and in healthy controls (HC). To our knowledge, this is the first study investigating correlations of self-rated and clinician-rated avolition and anhedonia with functional coupling between striatal sub-regions and large-scale intrinsic networks in schizophrenia. We found an increased inter-iFC between the caudate (NC) and lateral prefrontal cortex (NC-RCEN, NC-LCEN), and between NC and posterior parietal regions (NC-pDMN) for self-rated avolition and anhedonia. In contrast, clinician-rated avolition and anhedonia were not associated with cortico-striatal connectivity. Finally, explorative group comparison revealed trend-wise reduced connectivity between the caudate and SN, and reduced connectivity between the VST and pDMN, the VST and aDMN, and the VST and DCEN.

4.2. Increased cortico-striatal connectivity in schizophrenia

The present study revealed an association between avolition/anhedonia and increased functional cortico-striatal connectivity between the caudate (NC) and lateral prefrontal cortex (NC-RCEN, NC-LCEN), and between the caudate and posterior parietal regions (NC-pDMN). Abnormal cortico-striatal connectivity has been previously shown in studies using categorical approaches comparing subjects with SZ and HC. Specifically, increased functional connectivity between the dorsal striatum and parts of the DMN (the right inferior temporal gyrus, Fornito 2013), increased intrinsic caudate-prefrontal functional connectivity (Duan et al., 2015), increased inter-iFC between the caudate and the prefrontal cortex (Duan 2015), increased thalamo-cortical connectivity (Anticevic et al., 2013; Martino 2018), and increased striatal resting-state activity (Sorg 2013) has been reported in subjects with SZ. With respect to negative symptoms, few studies found associations between total scores and increased NC-DMN connectivity (right inferior temporal gyrus, Fornito 2013), and increased intrinsic ventral striatum activity (Sorg 2013). Our findings contribute and extend these observations showing that increased dorsal striatal connectivity with large-scale resting-state networks is associated with avolition and anhedonia. Interestingly, Wang et al. (2016) found a similar association of hyperconnectivity between the dorsal striatum and the prefrontal cortex and anhedonia in healthy individuals with schizotypal personality traits. Together, these findings support the idea that increased inter-iFC of cortico-striatal networks might reflect a dimensional mechanism of motivational and hedonic deficits in humans.

Of note, the positive association of avolition with NC-RCEN was not significant after correcting for disorganized symptoms. One explanation for this observation could be the positive yet not significant correlation between SNS avolition and PANSS disorganized concrete factor ($r = 0.477$, ST2). This observation is partly consistent with previous reports showing a relationship between avolition and disorganized symptoms in patients with schizophrenia (Galderisi 2014; Strauss 2013a) and clinical high risk individuals (Gupta 2020). With respect to our functional connectivity findings, the observed influence of disorganization on the correlation between SNS avolition with NC-RCEN connectivity suggests a more non-specific role of NC-RCEN dysconnectivity. It would be interesting to explore in future studies whether NC-RCEN dysconnectivity reflects a shared neural mechanism of the observed association between disorganization and avolition.

In contrast to the association of avolition/anhedonia with NC-pDMN and NC-CEN hyperconnectivity, inter-iFCs between the VST and other cortical networks were not correlated with avolition/anhedonia. This lack of association might be explained by a dorsal-to-ventral gradient of striatal hyperconnectivity-to-hypoconnectivity with posterior cortical regions, which has been proposed by Fornito and colleagues (Fornito 2013). In addition, our group comparisons provide some support for this explanation since we revealed trend-wise reduced VST-pDMN and VST-DCEN connectivity. Of note, Fornito and colleagues also reported a dorsal-to-ventral, hypoconnectivity-to-hyperconnectivity gradient for prefrontal-striatal connections (Fornito 2013), which might explain our findings of reduced NC-SN connectivity. Finally, our exploratory group comparison revealed increased intra-iFC of the pDMN and the RCEN which could be interpreted as an additional reason for aberrant cortico-striatal coupling in SZ displayed by the abnormal connectivity between and within the three large-scale networks (SN, DMN, CEN), and their functional connection with striatal sub-regions and striatal dysfunction.

In this regard, increased striatal coupling with the DMN and CEN at rest might reduce flexible task-relevant adaptation of the striatum. Specifically, this could impair adequate striatal response during task-switching, reward anticipation and reinforcement learning. Ultimately, these imbalances between cortico-striatal hyperconnectivity at rest and blunted task-related signals could contribute to reduced goal-directed behaviour and hedonic deficits in subjects with high levels of

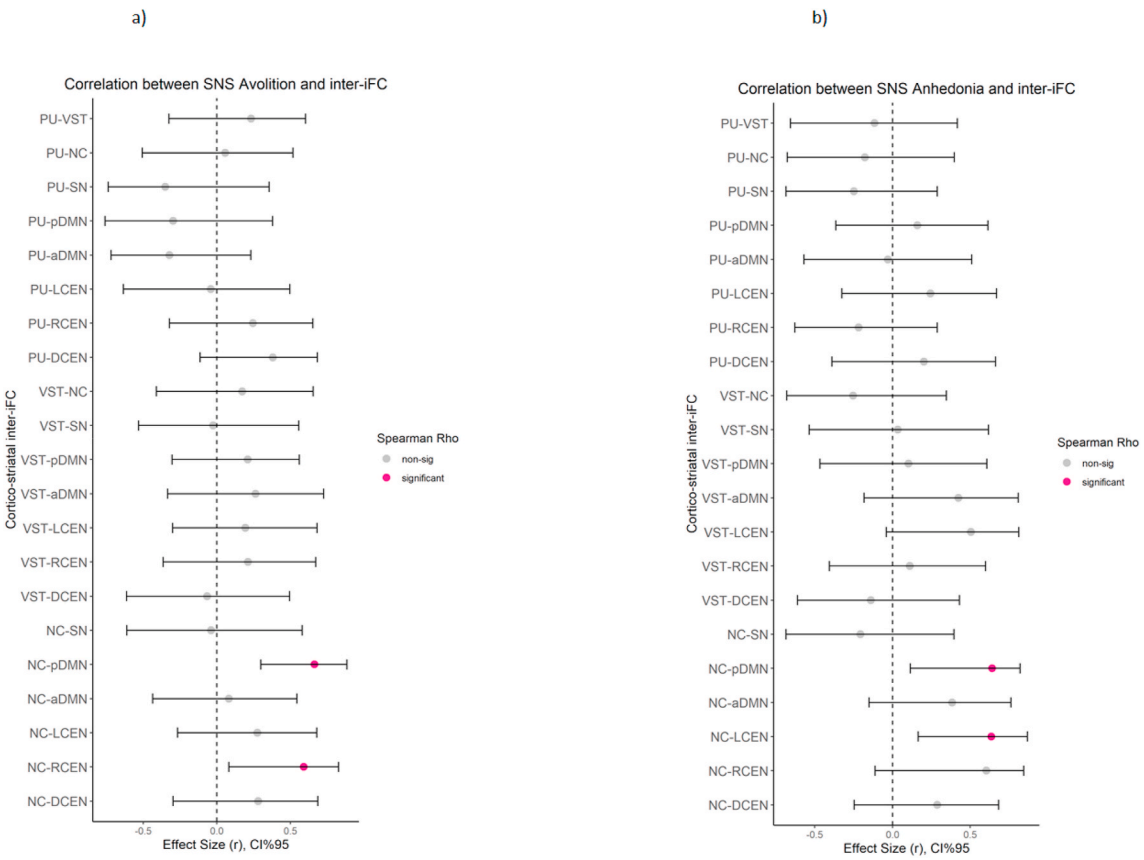

Fig. 3. 95% confidence intervals of correlation between self-reported avolition and anhedonia with striatal inter-iFC.

avolition and anhedonia.

4.3. Cortico-striatal correlates of self-reported and clinician-rated avolition/anhedonia

One of the major results of this study concerns the different relationships of cortico-striatal connectivity with self-reported and clinician-rated avolition and anhedonia. Different associations of striatal activation with self-reported, and clinician-rated negative symptoms were previously observed in task-related fMRI studies (Mucci 2015a; Dowd 2016; Kluge 2018; Moran 2019). In this regard, our findings fit well with the recent work from Moran and colleagues (Moran 2019) showing a significant association of caudate activation during reward anticipation, and self-reported measures of motivation and pleasure scores (derived from ecological momentary assessment), but not clinician-rated motivation and pleasure deficits (Clinical Assessment Interview for Negative Symptoms (CAINS), Kring 2013b).

These findings raise the question to what extent self-reported, and clinician-rated avolition/anhedonia assessments measure overlapping or different aspects of motivational and hedonic deficits. In the present work and previous studies, self-reported and clinician-rated negative symptoms showed only a weak-to-moderate correlations (Dollfus 2016; Kluge 2018; Moran 2019) suggesting that these measures were partly independent. One possible explanation could be that clinical interviews and self-reports measure different temporal states of negative symptoms. Clinician-rated scores of avolition/anhedonia refer to the memory recall of the last weeks and might capture a broader temporal state of avolition/anhedonia. In contrast, self-report assessments might be more likely to capture the in-the-moment state of avolition/anhedonia. In addition, self-evaluation measures provide direct information of subjective perceptions, and experiences of avolition and anhedonia (Dollfus 2016), which might be partly different to objective evaluation with clinical interviews such as the BNSS or CAINS. Hence, it is likely that self-reports and clinical interviews measure, to some degree, independent aspects of negative symptoms, which might relate to different functional neural mechanisms. Together with these recent findings (Mucci 2015a; Dowd 2016; Kluge 2018; Moran 2019), the present results motivate future work with multimodal assessments of motivational and hedonic deficits including self-reported questionnaires, ecological momentary assessment, clinician-rated and behavioural measures (e.g. actigraphy) to further elucidate the neural mechanisms of this complex clinical construct.

Finally, the observation that both self-reported avolition and anhedonia relate to the same aberrant striatal coupling with intrinsic networks (pDMN, CEN) suggests that both constructs are difficult to separate on a neural level. This is in line with previous studies combining clinical scores of avolition and anhedonia in one single score (Kirschner 2016; Dowd 2016; Waltz 2018; Moran 2019), but contradicts two studies separating avolition and anhedonia (Morris 2015; Mucci 2015a). These partly divergent findings might be due to the moderate correlation between self-reported avolition and anhedonia scores in the present work, compared to the clear separation of avolition and anhedonia on the psychopathological level in the study from Mucci and colleagues' (Mucci 2015a). Thus, the present study examined neural mechanisms of partly overlapping clinical domains, while Mucci et al. disentangled avolition and anhedonia on a clinical and neural level (Mucci 2015a).

In this regard, it remains an open question whether the available clinician-rated and self-rated assessments allow a differentiation of neural mechanisms specifically related to avolition scores and/or anhedonia scores, which has recently been reported in large-scale psychometric studies (Ahmed 2019; Strauss 2013a, 2018).

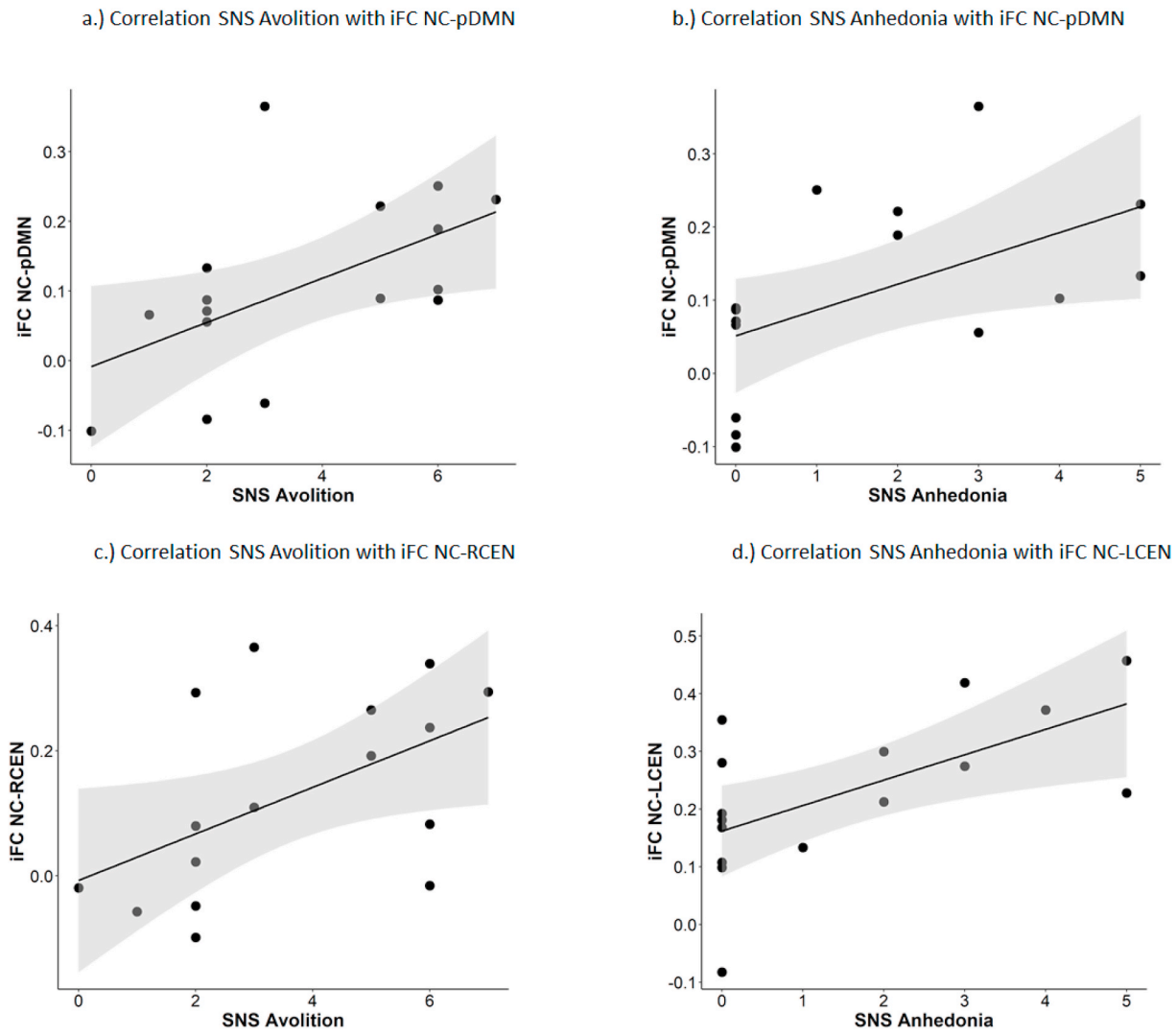

Fig. 4. Associations of self-reported avolition and anhedonia with aberrant striatal-pDMN and striatal-CEN coupling.

4.4. Limitations and future directions

There are limitations to this study. The sample size of this explorative study was small and therefore the detected significantly altered cortico-striatal inter-iFC, and its correlation with avolition and anhedonia should be interpreted with caution. By focusing on a specific research question in a small number of regions and distinct symptom domains, the chance to yield significant results can be increased (Friston 2012). In contrast, explorative group comparisons did not survive multiple comparisons, which might be partly due to limited power to detect smaller effects. Furthermore, studies with small sample sizes have an increased statistical risk for type II errors (false negative), which might have limited the ability to detect other "true" effects in the present study (Friston 2012).

With respect to the clinical characteristics, longitudinal aspects of negative symptoms were not assessed and we cannot completely exclude a possible transient nature of the symptomatology in subjects with SZ. At the time of testing all subjects with SZ were not in an acute exacerbation of psychosis and showed low levels of positive, disorganized and depressive symptoms. However, the duration of 14 days with no medication change was rather short and a longer period would have been valuable to ensure clinical stability. Furthermore, while subjects with extrapyramidal symptoms were excluded using a conservative cut-off of 2 on the MSAS (Simpson 1970), data were not available for further post-hoc analysis to correct for extrapyramidal symptoms within the normal range (total score: 0–3).

Finally, although we included self-reported and clinician-rated assessment, we had no measure of daily activity/functioning or behavioural measures for avolition/anhedonia. Future studies combining multimodal assessments and multiple imaging modalities (e.g. task-related fMRI, rs-fMRI and PET) are warranted to advance an integrative neuroscientific understanding of avolition and anhedonia.

5. Conclusion

Hyperconnectivity between the caudate-pDMN and the caudate-CEN was associated with self-reported avolition and anhedonia scores, while correlations of clinician-rated avolition and anhedonia scores did not reveal significant associations with cortico-striatal networks. The present study suggests that self-reports and interview-based clinical ratings might capture different aspects of motivational and hedonic deficits in schizophrenia and therefore relate to different cortico-striatal functional abnormalities. Taken together, these results extend our knowledge of the relationship between specific functional cortico-striatal network organizations, and clinical manifestation of motivational and hedonic deficits in schizophrenia.

Author statement

S. Kaiser and M. Kirschner designed the study. M. Kirschner conducted the study. J. Brakowski and A. Manoliu conducted the analyses and J. Brakowski wrote the first draft of the manuscript. A. Manoliu, P. Homan, Oliver G. Bosch, M. Herdener, E. Seifritz, S. Kaiser and M. Kirschner revised the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest/role of funding

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Declaration of competing interest

All authors declare no biomedical financial interests or any other potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.10.047.

Bootstrap resampling with 95% confidence intervals (CI). Abbreviations: inter-iFC, inter-network intrinsic functional connectivity; PU, Putamen; VST, Ventral striatum; NC, caudate nucleus; a/pDMN, anterior/posterior Default-Mode-Network; SN, Salience Network; L/R/DCEN, left/right/dorsal Central Executive Network; SNS, Self-evaluation of negative symptoms; non-sig, non-significant; significant, significant after correction for multiple comparison using FDR ($q = 0.05$); Spearman Rho, simple non-parametric Spearman correlation.

Non-parametric Spearman correlations between self-reported avolition and anhedonia and increased intrinsic functional Connectivity of NC-pDMN (a,b) and NC-CEN (c,d). A.) SNS avolition and NC-pDMN inter-iFC ($r = 0.664$, $p = 0.005$, 95% CI: [0.30, 0.88]), b.) SNS anhedonia and NC-pDMN inter-iFC ($r = 0.641$, $p = 0.007$, 95% CI: [0.12, 0.82]), c.) SNS avolition with NC-RCEN inter-iFC ($r = 0.591$, $p = 0.016$, 95% CI: [0.08, 0.83]), and d.) SNS anhedonia with NC-LCEN inter-iFC ($r = 0.636$, $p = 0.008$, 95% CI: [0.17, 0.87]). All correlations survived multiple testing using FDR ($q = 0.05$).

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