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Intrinsic mesocorticolimbic connectivity is negatively associated with social amotivation in people with schizophrenia

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A B S T R A C T

Background: Social amotivation is a core element of the negative symptoms of schizophrenia. However, it is still largely unknown which neural substrates underpin social amotivation in people with schizophrenia, though deficiencies in the mesocorticolimbic dopamine system have been proposed.

Methods: We examined the association between social amotivation and substantia nigra/ventral tegmental area-seeded intrinsic connectivity in 84 people with schizophrenia using resting state functional magnetic resonance imaging.

Results: Spontaneous fluctuations of midbrain dopaminergic regions were positively associated with striatal and prefrontal fluctuations in people with schizophrenia. Most importantly, social amotivation was negatively associated with functional connectivity between the midbrain's substantia nigra/ventral tegmental area and medial-lateral prefrontal cortex, the temporoparietal junction, and dorsal and ventral striatum. These associations were observed independently of depressive and positive symptoms.

Conclusions: Our findings suggest that social amotivation in people with schizophrenia is associated with altered intrinsic connectivity of mesocorticolimbic pathways linked to cognitive control and reward processing. Dysconnectivity of dopaminergic neuronal ensembles that are fundamental to approach behavior and motivation may help explain the lack of initiative social behavior in people with social amotivation.

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1. Introduction

Social amotivation is one of the most prominent features of schizophrenia (Foussias and Remington, 2010). Social amotivation could be seen as a core component of apathy and negative symptoms, which both have been associated in schizophrenia with widespread deficits in reward processing (Park et al., 2015; Simon et al., 2010), executive control (Benedetti et al., 2009; Faerden et al., 2009) and social cognition (Couture et al., 2006; Green et al., 2015; Sergi et al., 2007). However, the neural mechanisms underlying social amotivation in schizophrenia remain largely unknown.

It has been proposed that amotivation may be related to dysfunction of the mesocorticolimbic dopamine system, which is composed of dopaminergic neurons in the midbrain substantia nigra (SN) and ventral tegmental area (VTA) and their projections to striatal and prefrontal regions (Levy and Dubois, 2006; Rolls et al., 2008). Ascending midbrain dopamine projections are pivotal to reward learning and motivational processing (Duzzel et al., 2008). A large body of evidence has also pointed to involvement of an aberrant mesocorticolimbic dopamine pathway in motivational and voluntary impairments in schizophrenia (for a review, see Strauss et al., 2014). Preliminary findings have also suggested attenuated reward signals in people with schizophrenia to be related to negative symptoms, e.g., anhedonia and social amotivation (Fulford et al., 2018; Gradin et al., 2013). However, whether social amotivation in schizophrenia is associated with intrinsic connectivity variations of the mesocorticolimbic dopaminergic circuits has not been investigated yet.

To this end, we examined the association between social amotivation and connectivity of the dopaminergic brain reward system in people...
with schizophrenia/schizoaffective disorders using resting state functional magnetic resonance imaging (fMRI).

2. Materials and methods

2.1. Participants

Data from eighty-four participants with a diagnosis of schizophrenia or schizoaffective disorder who participated in one of five neuroimaging studies at our department (Dlabac-de Lange et al., 2015; Liemburg et al., 2015; Liemburg et al., 2012; Pijnenborg et al., 2011; Vercammen et al., 2011) were included for the analyses of the current study (see Table 1 for details about the participants). In these studies, participants from both inpatient and outpatient care units were included if they were 18 years or older and were considered able to give informed consent. Exclusion was based on MRI incompatibility (e.g., due to metal implants, claustrophobia, suspected pregnancy). Specific to the current analysis, participants were included if they were diagnosed with schizophrenia or schizoaffective disorder, had undergone resting state scanning, and had Positive and Negative Syndrome Scale (PANSS) data available (including reliable scoring of items that rely entirely on informant report, i.e., item N4 Passive/apathetic social withdrawal and G16 Active social avoidance). Participants were excluded if their resting state data was not of sufficient quality due to clearly visible artifacts, abortion of the scan, or non-compliance with scanning instructions (i.e., refusing to close the eyes). All studies have been approved by the local ethical committee of the University Medical Center of Groningen, and all of the participants gave oral and written informed consent after the study procedure had been fully explained. All procedures were performed according to the Declaration of Helsinki.

Participants were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Diagnosis was confirmed with either the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1; Giel and Nienhuis, 1996) or the Mini-International Neuropsychiatric Interview-Plus (MINI-Plus) diagnostic interview (Sheehan et al., 1998). The level of social amotivation was assessed by calculating a social amotivation factor (including items N2 Emotional withdrawal, N4 Passive/apathetic social withdrawal, and G16 Active social avoidance) (Liemburg et al., 2013; Steikema et al., 2016) based on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). This factor has been shown to correlate highly with the Apathy Evaluation Scale (AES) (Faerden et al., 2008; Fervaha et al., 2014; Liemburg et al., 2013), a scale often used to assess apathy or social amotivation. To control for the potential effect of depression, the severity of depression was assessed by calculating a depressive symptom factor (G1 including somatic concern, G2 anxiety, G3 guilt feeling and G6 depression) (El Yazaji et al., 2002). The assessment of the PANSS was conducted within one week from scanning.

2.2. Image acquisition

MRI data were acquired with a 3T Philips Intera MR-system (Best, the Netherlands) equipped with an eight-channel SENSE head coil. Head movement was restricted by foam pads fixing the head. Scanner sounds were reduced using earplugs and headphones. The resting state fMRI data were acquired by measuring the blood oxygen level-dependent (BOLD) signal using gradient-echo echo-planar imaging (EPI) with the following sequence parameters settings: FOV = 220 mm × 220 mm, data matrix = 64 × 64, slice thickness = 3 mm, interleaved transversal slices. Owing to the fact that we combined data from different studies at our center, other acquisition parameters differed slightly per study: 1) TR = 2000 ms, TE = 30 ms, flip angle = 70°, 37 slices with 0.3 mm gap, 300 volumes, n = 22; 2) TR = 2300 ms, TE = 28 ms, flip angle = 85°, 43 slices with no gap and 200 volumes, n = 29 (including one participant with 39 slices); 3) TR = 3000 ms, TE = 28 ms, flip angle = 85°, 43 slices with no gap and 250 volumes, n = 33. All participants were instructed to keep their eyes closed without falling asleep during scanning.

Furthermore, a 3D high-resolution structural image was acquired for each subject using a gradient-echo T1-weighted sequence with the following sequence parameters corresponding to above EPI sets: 1) TR/TE = 9 ms/3.5 ms, flip angle = 8°, FOV = 232 mm × 256 mm, data matrix = 256 × 256 and 170 transversal slices; 2) TE = 3.6 ms, and other parameters same with those of 1); 3) TR/TE = 25 ms/4.6 ms, flip angle = 30°, FOV = 256 mm × 204 mm, 160 slices, and other parameters same with those of 1).

2.3. Preprocessing

MRI data was preprocessed using SPM12b (version 5970; http://www.fil.ion.ucl.ac.uk/spm/), implemented in Matlab (version 8.1; The Mathworks Inc., USA). The functional images were corrected for slice timing and realigned to correct for head movement. The T1-weighted images were then coregistered to the mean EPI image. The functional images were subsequently normalized to the MNI template and resampled to a voxel size of 3 × 3 × 3 mm3, and spatially smoothed with an 8 mm full width at half maximum Gaussian isotropic kernel. Finally, using the DPARSF toolbox (version 2.3; http://www.rfmri.org/DPARSF), the waveform of each voxel was detrended (to remove the systematic drift or trend) and passed through a band-pass filter (0.01–0.08 Hz) to reduce the effects of low frequency drift and high-frequency physiological noise. Given that global signal regression could potentially change functional connectivity distributions and result in increased negative correlations and thus introduce spurious correlations (Saad et al., 2012), we refrained from using global signal regression. Instead, we used a principal component-based noise reduction method (CompCor) to correct for physiological noise by regressing out the first 5 principal components consisting of white matter (WM) signal and cerebrospinal fluid (CSF) signal (Behzadi et al., 2007). Furthermore, six motion parameters and framewise head displacement were used as nuisance variables to account for the influence of head motion on the resting state functional connectivity (RSFC). To characterize potential effects of confounding factors (including head movements and physiological noise) on our main results, Pearson correlations between social amotivation and mean values of head motion parameters (including both framewise head displacement (Power et al., 2012) and root-mean-square of the translation parameters (Van Dijk et al., 2012)) and the first 5 principal components of physiological noise were calculated.

2.4. Functional connectivity analysis

2.4.1. Seed definition

The bilateral SN/VTA seed regions were defined as two 5-mm-radius spheres centered on MNI coordinates (left SN/VTA, x = −8, y = −20, z = −22; right SN/VTA, x = 6, y = −18, z = −22), based on a previous study (Passamonti et al., 2015), in which these regions responded to both olfactory and visually delivered reward stimuli in healthy individuals.

2.4.2. Statistics

Using DPARSF, the mean time-course of the SN/VTA was extracted from each SN/VTA seed and the voxel-wise linear correlation between the mean time course of the SN/VTA seed and the time course of each voxel in the whole brain was calculated. Using SPM12, the correlation map of each subject was Z transformed (Fisher’s Z) and entered into a second-level general linear model (GLM) to identify the SN/VTA-seeded networks of people with schizophrenia. To test the relationships between social amotivation and the SN/VTA-seeded reward networks, a whole-brain-wise multiple linear regression was performed with brain connectivity as the dependent variable and social amotivation scores as the predictor. Age, sum scores of the positive subscale of the PANSS, and
sum scores of the depression factor of the PANSS were included as nuisance variables. The different sets of scanning parameters (nominal variable) were entered as dummy regressors to control for their potential influence. One-way ANOVA was conducted to further test the difference in RSFC among different sets of scan parameters.

To test for the robustness of the results with respect to medication use, we performed an additional second-level GLM analysis selectively including a relatively homogeneous sample treated with atypical antipsychotics only (N = 66). Because of the very different sample size of participants treated with typical and atypical antipsychotics, we could not directly compare the RSFC in these two groups. Furthermore, haloperidol dose equivalent or D2-receptor occupancy could not be calculated, because details about antipsychotic medication dosage were not available for all participants.

We used a threshold-free cluster enhancement (TFCE) algorithm (Smith and Nichols, 2009) to integrate extent and magnitude of brain connectivity using the following parameters: H = 2 and E = 0.5 (see following website for full explanation). To this end, we used the TFCE toolbox implemented in SPM (http://dbm.neuro.uni-jena.de/tfce/). Statistics were performed using nonparametric permutation testing (with 5000 permutations). A significance threshold was set at p < 0.05 family-wise error (FWE) corrected (Takeuchi et al., 2016).

3. Results

Demographic and clinical information on the participants can be found in Table 1. Social amotivation scores ranged from 3 to 16 (6.39 ± 2.66, M ± SD; Fig. 1). Using the SN/VTA as seed regions (Fig. 2), the functional connectivity analysis showed that the BOLD-signal in the dopaminergic midbrain was positively associated with fluctuations in a broad set of brain regions, mainly including the dorsal and ventral striatum, areas corresponding to the frontoparietal network and prefrontal and parietal regions often implicated in the default mode network (Fig. S1; Table S1). No area was found that was negatively correlated with the SN/VTA. No significant difference in RSFC was found among different sets of scan parameters (p > 0.3; Fig. S2).

The multiple regression analyses revealed that social amotivation was negatively associated with RSFC between the left SN/VTA and the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), orbital frontal cortex (OFC), dorsal anterior cingulate cortex (dACC), bilateral temporoparietal junction (TPJ) and putamen (Fig. 2A and B; Table 2). Social amotivation was also negatively associated with right SN/VTA-seeded RSFC with the bilateral dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vPFC), mPFC, PCC, OFC, dACC, TPJ, caudate and left pallidum (Fig. 2C and D; Table 2). These results were also present in the robustness analysis limited to people treated with atypical antipsychotics only (Tables S2 and S3). No correlation was found between positive or depressive symptoms and SN/VTA-seeded RSFC. No significant correlation was observed between social amotivation and head motion measures or between social amotivation and physiology noise parameters (p > 0.69). To compare brain networks of the midbrain dopaminergic regions found in our study with previously reported reward brain regions, we generated a meta-analytic reward processing map using the Neurosynth platform (http://neurosynth.org). This map was based on 922 studies identified in a search using the term “reward”. Overlay between the meta-analytic reward processing map and social amotivation-related connectivity of the SN/VTA is shown in Fig. S3. Results of additional analyses to control for potential influences of sex, handedness and the expressive deficits factor are shown in Figs. S4–6, respectively.

4. Discussion

We examined the neural substrates of social amotivation as reflected by spontaneous BOLD-signal fluctuations in mesocorticolimbic networks (defined by SN/VTA connectivity) in 84 people with schizophrenia. The large and presumably adequately powered sample in the current study provide a unique opportunity to examine the social amotivation in people with schizophrenia. In line with the positive correlations within mesocorticolimbic networks observed in healthy individuals during rest (Passamonti et al., 2015), our results showed intrinsic positive functional couplings of midbrain dopaminergic regions with striatal and prefrontal areas in people with schizophrenia. Although our results showed a pattern of right hemisphere dominance of the SN/VTA connectivity, we did not statistically compare differences of the connectivity patterns between left and right VTA, because we did not have any hypothesis on the lateralization. Future studies are needed to address this question. Notably, we observed that connectivity of these mesocorticolimbic pathways was negatively related to social amotivation, indicating that individuals characterized by higher levels of social amotivation showed lower functional connectivity between these brain regions. Crucially, this relationship was independent of concurrent depressive and positive symptoms, which have been associated with alterations of the reward system (Fletcher and Frith, 2009; Hamilton et al., 2011). These results suggest that social amotivation in schizophrenia is related to disruptions in the functional circuitry of the reward system. More speculatively, social amotivation could be more strongly related to dopaminergic fluctuations than positive and depressive symptoms in the present study.

Striatal dopamine dysregulation in schizophrenia has been found in numerous reward-related neuroimaging studies (Radua et al., 2015) and has been hypothesized to play an important role in the genesis of psychotic symptoms (Howes and Kapur, 2009). Despite that reward processing was not investigated in the present study, there is a large body of neuroimaging studies that has shown the role of the SN/VTA in dopamine-related reward processing (for a review, see Duzel et al., 2009). Passamonti et al. (2015), who used the same method for voxel-based SN/VTA connectivity as we applied in this study, demonstrated that these areas were directly associated with reward from both olfactory and visually delivered pleasant stimuli in healthy individuals. Interestingly, they have found that connectivity of these mesocortical networks was positively correlated with the personality trait “openness to experience”, while social amotivation can be characterized as a loss of social interest and a reduction of voluntary social behavior, which could be to some degree regarded as the inverse of openness to experiences. Indeed, being open to new experiences is an item of the widely used AES (Marin et al., 1991). Different from previous studies who investigated reward processing in schizophrenia with a specific reward task manipulation (Gold et al., 2008; Strauss et al., 2014), our findings demonstrate that dysconnectivity of the midbrain dopaminergic system

| Patient characteristics and clinical measures. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Age (Years, mean ± SD)** | **Sex (Male/female)** | **Handednessa** | **Medication typeb** | **PANSSc scores (mean ± SD)** |
| 34.88 ± 10.98 | 59/25 | 7/74 | 66/5/9 | 60.55 ± 13.26 |
| **Total** | **General** | **Positive** | **Negative** | **Depressive** |
| 30.69 ± 7.31 | 14.69 ± 4.54 | 15.16 ± 4.57 | 8.99 ± 3.62 |

a For three participants, information on handedness was not available.

b For four participants, medication records were not available. Free - free of antipsychotic medication.

c PANSS, Positive and Negative Syndrome Scale.
Fig. 1. Frequency distribution of levels of social amotivation in people with schizophrenia. (A) The frequency as a function of social amotivation severity. The red curve is the curve best fitting with a normal distribution. The black vertical line represents the mean social amotivation severity. (B) The cumulative frequency as a function of social amotivation severity. The x-axis represents social amotivation levels measured by the PANSS social amotivation factor. The y-axis represents the cumulative frequency on the left and the cumulative proportion on the right side. The colored histogram depicts actual frequency in each bin. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. Associations between social amotivation and resting state functional connectivity of the substantia nigra (SN)/ventral tegmental area (VTA) in schizophrenia. (A) Areas showing negative associations between social amotivation and RSFC of the left SN/VTA. Color bars show the TFCE-values. (B) Scatter plot of the local maxima associations shown in A. (C) Negative associations between social amotivation and functional connectivity of the right SN/VTA. Color bars show the TFCE values. (D) Scatter plot from the local maxima (peak voxel of the cluster) connectivity shown in C. Dashed lines indicate 95% confidence intervals, and solid line indicates the best linear fit. Abbreviations: dlPFC, dorsal lateral prefrontal cortex; vmPFC, ventral medial prefrontal cortex; PCC, posterior cingulate cortex; VS, ventral striatum; TPJ, temporoparietal junction.
related to social amotivation is intrinsic and occurs independently of task performance.

Weaker connectivity between dopaminergic midbrain areas and the prefrontal cortex in people with schizophrenia with higher degree of social amotivation may indicate an attenuated dopaminergic input to prefrontal control areas (Rolls et al., 2008). The prefrontal cortex plays a fundamental role in cognitive control and in translation of motivation into action, thereby initiating goal-directed behavior (Koueïneïr et al., 2009). Dysregulated dopaminergic inputs have been suggested as the key to pathophysiological changes in prefrontal activation in schizophrenia (Lesh et al., 2011). Previous findings have shown that striatofrontal dysfunction is associated with social amotivation (Levy and Dubois, 2006), disturbed goal representation and motivational drive (Barch and Dowd, 2010), and severity of negative symptoms in people with schizophrenia (Reckless et al., 2015). Our results are consistent with these findings.

We also found that social amotivation was negatively associated with connectivity of the dopaminergic midbrain areas with the TPJ and mPFC. Hypoactivation of these areas has been pointed out to contribute to social anhedonia in schizophrenia (Doddell-Feder et al., 2014). Social amotivation is the main factor composing the measurement of social amotivation used in this study, therefore our findings may also contribute to neuroimaging evidence relevant for the neural basis of social dysfunction in schizophrenia. Dopaminergic mesocortical networks have also been shown to mediate associative learning (Murray et al., 2008) and indeed the processing of social reward that enhances social interaction (Stephan et al., 2009). Our results may be implicated in difficulties regarding reward-based learning from social experiences, which may ultimately increase social withdrawal and apathetic behavior in schizophrenia.

Moreover, our results support the dysconnection hypothesis of schizophrenia, which emphasizes that a disruption in connectivity between brain regions may underlie the disintegration among thoughts, emotions, and behaviors in schizophrenia (Friston, 2002). The association between increasing levels of social amotivation and reduced functional connectivity of mesocorticolimbic dopamine circuits suggests a pathological lack of functional integration/interaction of multiple brain processes, which may be caused by impaired anatomical connectivity and/or synaptic plasticity (Stephan et al., 2009). Given the role of dopamine in modulation of the default mode network (Cole et al., 2013a; Cole et al., 2013b; Delaveau et al., 2010), decreased connectivity between the SN/VTA and the default mode network along with increased social amotivation in our study may contribute to disturbances of thought in schizophrenia. Although the dysconnection hypothesis has been implied for schizophrenia as a diagnostic group and specifically for positive symptomatology (for a review, see Pettersson-Yeo et al., 2011), our results show that functional disintegration of reward and cognitive-control brain systems may be of importance for negative symptomatology as well. This dysfunctional integration among components of the dopaminergic systems may be related to both subcortical hyperdopaminergia and prefrontal hypodopaminergia in people with schizophrenia (Howes and Kapur, 2009), but the exact nature and implications of the abnormalities await further clarification.

5. Limitations

Potential limitations of our study should be considered. The measurement of social amotivation in the current study was assessed based on a social amotivation factor from the PANSS (Liemburg et al., 2013), while recent studies have shown that negative symptoms could be comprised of five constructs (Ahmed et al., 2018; Marder and Muscatelli, 2017; Ahmad et al., 2018; Marder and Galderisi, 2017; Strauss et al., 2018). It would be very interesting if future study could compare the common and specific aspects across these different models as well as the underlying neural mechanisms. Without any molecular imaging, interpretation regarding the dopaminergic system based on our findings should be made with caution. For example, a recent review proposes that the negative symptoms are associated with decreased phasic dopamine responses to events, whereas positive symptoms links to increased spontaneous phasic dopamine release (Maia and Frank, 2017). Because the reward system and pathophysiological mechanisms in people with schizophrenia are modulated

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Note: L, Left; R, right; BA, Brodmann’s area. For each cluster, the cluster size was reported in the line of the local maxima.
by multiple neurotransmitter systems (Stephan et al., 2009), future studies specifically investigating the neurotransmitter systems would be necessary. Although participants in this study received different antipsychotic treatments (typical, atypical and free of antipsychotics), the pattern of results remained in the robustness analysis, which only included people with atypical antipsychotics. This suggests that the current results may be irrespective of type of medication. Importantly, a recent study suggested that effects of antipsychotics are only marginal on motivational impairment (Fervaha et al., 2015). However, because blockade of dopamine D2 receptors is a common mechanism of antipsychotics, these pharmacological agents also affect the mesocorticolimbic pathways. Another potential confounding effect might be history of substance abuse or dependence, including smoking. These potential modulatory effects give rise to an important issue for future study. Given the direction of the connectivity in the current study was unclear, future study with dynamic causal modelling is needed to explore the reward modulation on these connections and the input to the pathway.

6. Conclusions

In summary, we report neuroimaging evidence that diminished intrinsic connections within mesocorticolimbic circuits might underlie the lack of initiative and motivation in schizophrenia. Hypo-connectivity of the dopaminergic midbrain with the brain systems involved in reward, social and executive control may be related to social amotivation in people with schizophrenia, especially for patients on atypical medication. These findings may inspire further development of treatment approaches that enhance reward sensitivity and behavioral activation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.01.023.

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