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Schizotypal Traits are Linked to Dopamine-Induced Striato-Cortical Decoupling: A Randomized Double-Blind Placebo-Controlled Study

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The dopamine hypothesis of schizophrenia implies that alterations in the dopamine system cause functional abnormalities in the brain that may converge to aberrant salience attribution and eventually lead to psychosis. Indeed, widespread brain disconnectivity across the psychotic spectrum has been revealed by resting-state functional magnetic resonance imaging (rs-fMRI). However, the dopaminergic involvement in intrinsic functional connectivity (iFC) and its putative relationship to the development of psychotic spectrum disorders remains partly unclear—in particular at the low-end of the psychosis continuum. Therefore, we investigated dopamine-induced changes in striatal iFC and their modulation by psychometrically assessed schizotypy. Our randomized, double-blind placebo-controlled study design included 54 healthy, right-handed male participants. Each participant was assessed with the Schizotypal Personality Questionnaire (SPQ) and underwent 10 minutes of rs-fMRI scanning. Participants then received either a placebo or 200 mg of L-DOPA, a dopamine precursor. We analyzed iFC of 6 striatal seeds that are known to evoke modulation of dopamine-related networks. The main effect of L-DOPA was a significant functional decoupling from the right ventral caudate to both occipital fusiform gyri. This dopamine-induced decoupling emerged primarily in participants with low SPQ scores, while participants with high positive SPQ scores showed decoupling indifferently of the L-DOPA challenge. Taken together, these findings demonstrate that schizotypal traits may be the result of dopamine-induced striato-occipital decoupling.

Key words dopamine/resting-state fMRI/connectivity/striatum/schizotypy/psychosis/psychotic-like experiences/

Introduction

Psychosis appears to occur along a continuum, with one end featuring healthy individuals with sporadic and subtle psychotic-like experiences.[1,2] At the other end are persons with diagnosed psychotic illnesses such as schizophrenia. A useful concept at the attenuated end of the psychosis continuum is schizotypy.[3,4] Schizotypy reflects the heterogeneous spectrum of the psychotic phenotype within its 3 subgroups[5,6]: positive (ie, cognitive-perceptual), negative (ie, interpersonal), and disorganized symptoms, suggesting corresponding mechanisms in their pathogenesis.[7,8]

The hypothesis that dysfunction of dopaminergic mechanisms are central to the etiology of psychotic disorders has been one of the most enduring theories in psychiatry.[9] The dopaminergically sensitive striatum receives top-down inputs from cortical areas as part of the basal ganglia-thalamocortical loops.[10–12] It forms a key station for modulating and encoding motivational value and salience to these inputs.[13,14] In schizophrenia, it has been suggested that different environmental and genetic risk factors interact to join through one final common pathway through an increase in synaptic dopamine availability and enhanced presynaptic dopamine synthesis.[9,15] This dysregulated dopaminergic transmission may thus be a possible mediator for disturbances associated with altered processing of reward, salience and learning across the psychotic spectrum.[7,16–18]

Recent resting-state functional magnetic resonance imaging (rs-fMRI) studies have revealed broad intrinsic functional connectivity (iFC) abnormalities along the whole spectrum of psychotic disorders.[19–21] The disconnection hypothesis suggested that the core pathology of

schizophrenia is an impaired control of synaptic plasticity that manifests as abnormal iFC.[22,23] In schizophrenia, cortico-striatal iFC is thought to be disrupted during an acute episode, but improves with antipsychotic treatment.[24] In contrast, iFC appears to increase generally in subthreshold psychosis, which correlates directly to the level of (subthreshold) positive symptoms.[20,25] While some studies have addressed the disturbance of iFC in participants with psychotic-like experiences,[19] only a few have investigated persons with schizotypy. There is evidence for weaker iFC between the left insula and the putamen, but stronger connectivity between the cerebellum and the medial frontal gyrus in individuals with elevated scores on a schizotypy scale.[26] Other resting-state research indicated a positive correlation between schizotypal personality measures and a visual network, but negative correlations with an auditory network. Further, no disturbance of the default mode network related to schizotypal trait expression was found.[27] That outcome contrasted with the aberrant coupling of the default mode network reported in persons with schizophrenia[28–30] as well as in participants at risk for psychosis.[20]

Importantly, a strong association has been suggested between dopamine and striatal iFC. Cortico-striatal connectivity, predominately from the ventral caudate, was shown to be disrupted in schizophrenia, and was correlated not only with elevated positive symptoms but also with a reduced baseline density of D2 receptors across extra-striatal regions.[31] Furthermore, previous studies have shown that dopamine manipulations can modulate both task-based[32,33] and resting-state iFC.[34,35] While dopamine-dependent changes in iFC have been examined primarily in cases of Parkinson's disease,[36] few studies have directly tested the dopaminergic influence on striatal connectivity in healthy individuals.

Kelly et al[37] found that the administration of L-DOPA, a dopamine precursor, modulates cortico-striatal iFC in healthy individuals. However, dopaminergic influence on iFC has not yet been evaluated in participants with psychometric schizotypy. Thus, we aimed to advance the understanding of the dopaminergic involvement in iFC and its putative relationship to the development of psychotic disorders, by investigating the link between L-DOPA and its modulation of striatal iFC in subthreshold psychosis, ie, in schizotypy. Consequently, we assessed Schizotypal Personality Questionnaire (SPQ) in 54, healthy, right-handed men. Adopting a randomized, double-blind placebo-controlled design using L-DOPA and a placebo, we analyzed the resting-state iFC of 6 striatal seeds that are known to evoke the modulation of dopamine-related networks.[37]

We hypothesize that, within the L-DOPA treatment group, the striatal iFC would be disrupted due to increased availability of dopamine. We further hypothesize that individuals with high schizotypal scores would show a disruption of striatal connectivity, as has been reported with schizophrenia.[24] In addition, we hypothesized that the L-DOPA-dependent change in striatal iFC would interact with the severity of positive symptoms, as has been found in previous studies in nonclinical psychosis.[25] We anticipated this symptom-dependent change, especially in the ventral striatal regions, because they are thought to modulate cortico-striatal loops associated with cognition and emotion.[17,38]

Methods

Participants

Participants were recruited in the region of Zurich, Switzerland, within the frame of a larger study investigating psychotic-like symptoms in a sample of healthy adults.[39] Sixty-five right-handed men (20 to 40 y old; Caucasian origin) were selected from the mentioned study population. Exclusion criteria encompassed current drug intake with psychotropic effect, a history of psychotic spectrum disorders (ie, psychosis or schizophrenia) for self or first-degree family members, acute or chronic disease of the nervous system, traumatic brain injury with lasting damage, and strong cigarette-craving (≤4 h without a cigarette). The Mini-International Neuropsychiatric Interview[40] was administered to exclude individuals with any current or prior history of psychiatric illness or substance abuse.

Our experiments were performed in accordance with principles specified in the "Declaration of Helsinki," the guidelines of Good Clinical Practice, and were approved by the local ethics committee of Zurich (KEK-ZH-No. 2011-0423). Participation required 2 sessions (3 h each), and individuals received 200 Swiss francs after completion of the second visit. Randomization with an Interactive Web Response System (IWRS), blinding, as well as the preparation of both the interventions and packaging in sequentially numbered containers, was done by the "Kantonsapotheke Zürich" (the state-run pharmacy of Zurich).

The 65 participants were split into 2 randomized groups—L-DOPA group, with 33 participants; and placebo group, 32 participants. After rs-fMRI scanning, 11 of the original 65 participants had to be excluded from further analysis: 5 due to anomalies in their psychometric questionnaires and 6 because of erroneous rs-fMRI sequence setup. The remaining 54 participants stayed in their allocated group, according to protocol. The 2 groups did not differ significantly in terms of age and intelligence (table 1).[41]

Participants were instructed not to take drugs or drink alcohol 24 hours before the experiment, not to smoke for 1 hour and not to eat for 3 hours. A block of assessment tasks and questionnaires were administered prior to receiving either 200 mg L-DOPA and 50 mg Benserazide in a dual-release formulation (Madopar DR, Roche Pharma AG), with peak absorption within 1 hour

Table 1. Demographic Characteristics and Symptoms Ratings of the L-DOPA Group and the Placebo Group

	Madopar	Placebo	Statistical Evaluation
N	28	26	
Age (y)	28.4 ± 4.9	27.0 ± 4.4	$T = 1.12$, $P = .269$
Estimated intelligence (IQ)	111.5 ± 13.7	114.6 ± 10.9	$T = -0.91$, $P = .367$
Education (y)	14.0 ± 2.1	14.3 ± 2.3	$T = -0.49$, $P = .630$
SPQ total	19.0 ± 10.3	16.8 ± 10.8	$T = 0.79$, $P = .434$
SPQ positive	8.6 ± 6.0	8.2 ± 6.6	$T = 0.22$, $P = .826$
SPQ negative	5.8 ± 4.1	4.7 ± 3.9	$T = 1.07$, $P = .290$
SPQ disorganized	4.6 ± 3.6	3.9 ± 3.4	$T = 0.76$, $P = .453$

Note: Statistical evaluations utilized *t*-tests; (1) Premorbid intelligence was determined by extrapolating IQ values via Mehrfachwahl-Wortschatz-Intelligence Test (MWT-B). (2) Schizotypal Personality Questionnaire (SPQ); positive, negative, and disorganized subscores.

and a stable level thereafter for approximately 1 hour.[42] Participants received a standardized sandwich 20 minutes after capsule ingestion,[43] followed by another behavioral test battery. MRI scanning started after 100 minutes, commencing when the drug was at its estimated maximal serum concentration. All scans were administered in the afternoon, between 2 PM and 4 PM. The psychological, somatic, and motor (adverse) effects of the drugs were assessed through subjective ratings after the testing session ended. None of the participants reported more than small noticeable side effects.

To check the efficacy of the blinding, we then asked them to guess which substance they had received and found that 18 participants were correct (10 Madopar/8 placebo group) while 29 were incorrect (14 Madopar/15 placebo group). Seven participants gave no answer. Chi-square analysis revealed that this difference was not significant ($\chi^2 = 2.61$, $P > .1$).

Measurement of Psychotic-Like Traits

Psychotic-like traits were assessed using the SPQ,[44] which entails 74 questions and measures a diverse set of schizotypal traits within 3 subscores (ie, 33 positive, 25 negative, and 16 disorganized items) on 9 subscales.[5,45] Because our sample pool consisted of participants not psychiatrically diagnosed, the distribution of total scores and subordinate scores skewed slightly to the left (supplementary figure 1). Diagnosis of multicollinearity asserted that the total SPQ score did not correlate to the subscores (SPQ positive: Tolerance [VIF] = 0.543 [1.842]; SPQ negative: Tolerance [VIF] = 0.942 [1.061]; SPQ disorganized: Tolerance [VIF] = 0.520 [1.922]).

Image Data Acquisition

The rs-fMRI data were acquired at the Zurich University Hospital of Psychiatry, Switzerland, using a Philips Achieva TX 3-T whole-body MR unit with an 8-channel head coil. Functional scans (10-minute runs) involved a sensitivity-encoded single-shot echoplanar (factor 1) T2*-weighted echoplanar imaging (EPI) sequence (repetition time [TR] = 2000 ms; echo time [TE] = 35 ms; field of view [FOV] = 128 × 220 mm^2; 32 slices with a spatial resolution of 2.5 × 2.5 × 4 mm^3; flip angle $\theta = 82°$; and sensitivity-encoded acceleration factor $R = 2$). Using a mid-sagittal scout image, we placed the contiguous axial slices along the anterior-posterior commissural plane, which covered the entire brain. The slices were acquired in interleaved order. We also obtained 3-dimensional T1-weighted anatomical images (160 slices; $\theta = 8°$; spatial resolution, 1 × 1 × 1 mm^3 [reconstructed 0.94 × 0.94 × 1 mm^3]; FOV = 160 × 240 mm^2). The EPI sequences were conducted in the dark and participants were asked to keep their eyes closed during the session, lie as quietly as possible, and avoid falling asleep. All participants denied falling asleep during the scan.

Resting-State Data Analysis

After the first 10 frames were removed to allow for signal equilibration, the data were pre-processed using the CONN-fMRI functional connectivity toolbox v16 (http://www.nitrc.org/projects/conn; accessed October 3, 2016).[46] The steps included realignment, slice-timing correction, co-registration to structural T1 scan, spatial normalization to Montreal Neurological Institute (MNI) coordinates space, and spatial smoothing (6-mm Gaussian kernel). The structural scans were segmented per the unified segmentation approach that utilized Statistical Parametric Mapping (SPM8 Package) default values. None of the participants had to be excluded due to excessive head motion (linear shift <2.5 mm across and, on a frame-to-frame basis, rotation <2.5°). Frames with movement >0.5 mm or a global signal *z* score change >3 were identified with artifact detection, scrubbed, and excluded from analyses.[47] Residual data were bandpass-filtered (0.009–0.080 Hz). Further exclusion criteria were if >50% of the frames were contaminated by movement, or if the mean framewise displacement exceeded 2 mm. No scans met these criteria. Spurious sources of noise, such as heart rate and respiration signals, were first estimated by the anatomical component base noise reduction (aCompCor) strategy, and then included with the

head movement parameters as nuisance regressors in a general linear model (GLM). The aCompCor algorithm does not rely on global signal regression, which can artificially introduce negative correlations.[48]

A seed-to-voxel correlation map for each subject was computed using a weighted GLM for bivariate-weighted correlations. To investigate differences in iFC from the striatal seeds between the L-DOPA group and the placebo group, we processed the data via 1-way ANCOVA, which controlled for covariation of total SPQ scores. Thereby, the ANCOVA would be slightly more sensitive particularly in cases where the variability associated with score differences may be large compared to the between-group differences. For further assessment of associations between L-DOPA-induced connectivity and schizotypal traits, those analyses included only regions that showed significant differences in iFC between treatment groups (height threshold: P-uncorrected < .001, cluster threshold: P-FWE corrected < .05, 2-sided statistics). Because we analyzed 6 seeds bilaterally, we additionally report the Bonferroni-corrected significance level at $P < .004$. The associations among the 3 types of SPQ subscores (positive, negative, and disorganized) were identified by extracting the connectivity values of another 1-way ANCOVA for those subscores in the masked clusters. Because the resulting effect sizes (ie, statistically significant differences in Fisher-transformed correlation values between the L-DOPA and placebo groups) showed only relative changes (eg, higher connectivity could imply either stronger correlation or weaker anticorrelation) in iFC associated with SPQ subscores, the actual connectivity values for each subject within the supra-threshold cluster were imported into a post hoc linear regression analysis. This enabled us to use a regression model to display absolute L-DOPA-induced alterations in iFC related to the SPQ sub-scores. Then, in a pairwise approach the significance of difference between each of the 3 pairs of correlation coefficients was calculated in VassarStats (http://vassarstats.net/rdiff.html, accessed December 17, 2017). The coordinates are presented in MNI space.

Seed Selection

As reported previously,[49] 12 striatal seeds coherent with anatomical and functional subdivisions were defined by coordinates in the MNI space, and were used to investigate the effect of L-DOPA on functional connectivity in the striatal networks.[37] Each region of interest was created by defining spheres (volume = 257 × 1 mm^3 voxels, radius = 4 mm) around the coordinates using the MARSBAR toolbox (http://marsbar.sourceforge.net; accessed October 3, 2016). These were located in the (1) inferior ventral striatum (±9, 9, −8; VSi, corresponding to the nucleus accumbens), (2) superior ventral striatum (±10, 15, 0; VSs, corresponding to the ventral caudate), (3) dorsal caudate (±13, 15, 9; DC), (4) dorsal caudal putamen (±28, 1, 3; dcP), (5) dorsal rostral putamen (±25, 8, 6; drP), and (6) ventral rostral putamen (±20, 12, −3; vrP).

Results

Effect of L-DOPA Treatment on Striatal iFC

The 1-way ANCOVA, controlled for covariation of the total SPQ score, was used to identify regions with group differences in iFC from the striatal seeds. The results of this analysis indicated that only the right VSs (corresponding to the ventral caudate) displayed a significant difference between the L-DOPA and the placebo group: L-DOPA treatment resulted in an increase in iFC relative to placebo between the right VSs and 2 clusters corresponding to the left occipital fusiform gyrus (−18, −80, −6; cluster size = 257 voxels; cluster-size P-FWE = .001) and to the right occipital fusiform gyrus (26, −62, −16; cluster size = 135 voxels; cluster-size P-FWE = .032) (figure 1). The increase of iFC to the right occipital fusiform gyrus does not reach significance on a Bonferroni-corrected level of $P < .004$, but as we consider this result as potentially being important for future studies the further analyses are available as supplementary material.

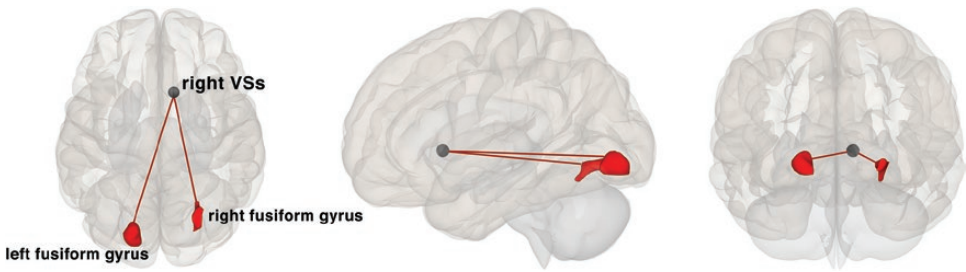

Fig. 1. Differences in seed to voxel intrinsic functional connectivity (iFC) between L-DOPA and placebo groups. One-way ANCOVA controlled for Schizotypal Personality Questionnaire (SPQ) covariate revealed significant changes in iFC between the right VSs (ventral caudate seed) and 2 bilateral supra-threshold clusters corresponding to the left occipital fusiform gyrus (cluster size = 257 voxels; cluster-size P-FWE = .001) and the right occipital fusiform gyrus (cluster size = 135 voxels; cluster-size P-FWE = .032). Left to right: axial, sagittal, and coronal views.

Dopamine Modulated Connectivity as a Function of Schizotypy Scores

To determine whether the main effect of treatment on iFC between the VSs and the right and left fusiform gyri was associated with score differences among SPQ subscales, we used a GLM that compared the SPQ scores from each subject to examine the actual iFC values within the supra-threshold cluster.

A significant interaction of subscores with the coupling was found between the right VSs and the cluster in both fusiform gyri for positive scores (right $T = 2.36$, $P\text{-}FDR = .022$, left; $T = 2.41$, $P\text{-}FDR = .022$) and disorganized scores (right; $T = -3.29$, $P\text{-}FDR = .002$, left; $T = -3.41$, $P\text{-}FDR = .002$). For the negative scores, we only found a significant interaction from the right VSs and the right fusiform gyrus (right; $T = -2.70$, $P\text{-}FDR = .019$, left; $T = -1.96$, $P\text{-}FDR = .056$).

We then analyzed the coupling separately in each group. In the placebo group, the coupling between the right VSs and the left fusiform gyrus was significantly affected by SPQ positive score (ß = 0.001, $T = 2.72$, 2-sided $P = .006$) (figure 2A) and disorganized score (ß = 0.02, $T = 2.84$, 2-sided $P = .006$) (figure 2E). Looking at these positive and disorganized scores, participants with low scores showed anticorrelated connectivity that deteriorated as the score increased. No significant pattern emerged for

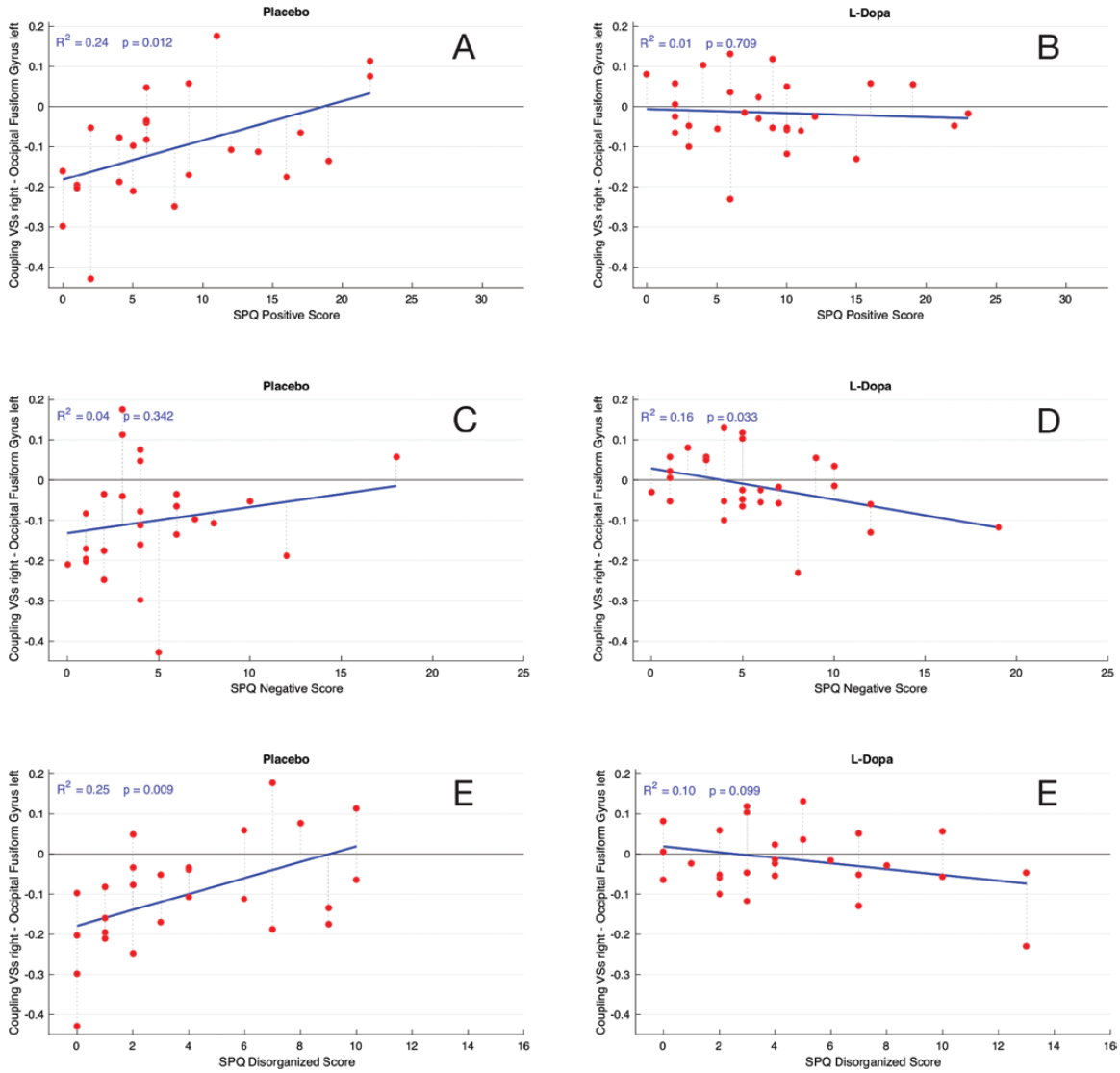

Fig. 2. Scatter plots showing association between absolute intrinsic functional connectivity (iFC) (coupling between right VSs and left occipital fusiform gyrus) and Schizotypal Personality Questionnaire (SPQ) sub-scores: positive (ie, cognitive-perceptual), negative (ie, interpersonal) and disorganized (ie, disorganized) for both, placebo group (A, C, E) and L-DOPA group (B, D, F). Each red dot represents an individual SPQ sub-score on the *x*-axis and its corresponding iFC (coupling) value on the *y*-axis. The range of the *x*-axis shows the max. Possible score for each sub-score. The blue line represents a linear regression of all subjects, showing a dopamine-induced decoupling primarily in subjects with low SPQ scores (B, D, F). Interestingly subjects with high positive and disorganized SPQ scores showed decoupling indifferently of L-DOPA treatment (A, B; E, F).

associations with negative scores (ß = 0.007, T = 0.97, 2-sided P = .170) (figure 2C).

In the L-DOPA group, no comparable influence on the anticorrelation was observed by the positive score (ß = −0.001, T = −0.38, 2-sided P = .709) (figure 2B) or disorganized score (ß = −0.007, T = −1.71, 2-sided P = .099) (Figure 2F). However, there is a significant increase in coupling directly associated with the SPQ negative score (ß = −0.008, T = −2.25, 2-sided P = .033), where participants with a low SPQ negative score are decoupled, but with increasing score an anticorrelation manifests (figure 2D).

The difference of the correlation coefficients between the L-DOPA and placebo group was significant for all subscores (SPQ positive: 2-tailed P = .028; SPQ negative: 2-tailed P = .030, SPQ disorganized: 2-tailed P = .002).

The association between the coupling of the right VSs and the right occipital fusiform gyrus closely resembled that between the coupling to the left occipital fusiform gyrus (supplementary figure 2).

Discussion

We here show that dopaminergic modulation iFC of 6 striatal seeds resulted in a significant functional decoupling from the right ventral caudate to both occipital fusiform gyri in participants with low SPQ scores, while participants with high positive SPQ scores showed decoupling indifferently of L-DOPA treatment.

When looking at change in iFC it is important to understand, that an absolute increase (eg, +1) can be interpreted as a stronger correlation (eg, 0 to 1) or a weaker anticorrelation (eg, −1 to 0). An absolute decrease (eg, −1) can likewise reflect weaker correlation (eg, 1 to 0) or stronger anticorrelation (eg, 0 to −1). That is why we refer to more correlation or anticorrelation as coupling, and less correlation or less anticorrelation as decoupling. Coupling can mean either correlation or anticorrelation as both represent a form of communication (supplementary figure 3).[50]

During the resting state, the striatum and fusiform gyrus seem to form a functionally antagonistic relationship in healthy individuals. Thus, the clusters are coupled, as both, correlated and anticorrelated networks represent a form of functional interaction.[50] With increased dopamine availability, as represented in our L-DOPA group, this (anticorrelated) coupling is disrupted (figure 2).

These results are in accordance with previous studies, reporting a L-DOPA-related decoupling from the VSs to the medial occipital cortex,[37] and no L-Dopa induced change in iFC from the putamen.[51] In contrast to our findings, Kelly et al[37] described a decrease in connectivity to the default mode network areas, as well as a marked increase in connectivity from the left VSi and the bilateral putaminal seeds to the cerebellum, while Flodin et al[51] additionally found an increase in fronto-striatal iFC. However, the study by Flodin et al was limited to the left VSs and 1 putaminal seed. Due to an equally important role for the caudate,[16] we covered the whole striatum including caudate areas in our analysis. Other incongruities could likely be ascribed to differences in the sample of participants, as former studies decided on more heterogeneous study sample (ie, gender), smaller sample size,[37,51] or methodology (eg, more liberal thresholds for cluster size[37]). Further, both studies regressed out the global mean signal, a procedure that can artificially introduce anticorrelations.[52]

As regards the expected associations between schizotypal traits and dopamine-dependent iFC, participants in the placebo group manifested a positive association between positive SPQ scores and decoupling of the VSs and the fusiform gyrus. Whereas persons with low scores were anticorrelated, those with higher scores lacked a comparable anticorrelation. Likewise, under the influence of L-DOPA, the participants with lower scores exhibited a similar disruption of anticorrelation between VSs and the fusiform gyrus. Comparable, in nonclinical psychosis, a general increase in iFC between the cingulo-opercular network and the visual cortex was found in association to the level of positive symptoms.[25] Although these results cannot be compared directly to those from our study because we investigated schizotypal traits within mentally healthy volunteers, instead of nonclinical psychosis, all of these reports suggest that an aberrant connectivity to visual areas can be traced to the lower end of the psychosis continuum. In schizotypy, on the other hand, a study found reduced iFC between the left insula and the putamen,[26] an association which we were unable to replicate. However, unlike us, they included the morphometrics of grey matter before comparing iFC. The interaction of SPQ positive scores with decoupling of the striatum with sensory areas seems to be especially important, as there are results pointing into a similar direction in patients with a history of hallucinatory symptoms (ie, trait).[53,54]

The role of aberrant iFC from the striatum to the fusiform gyrus has not been explored within the context of schizophrenia or schizotypy. The dopaminergic sensitive striatum incorporates information from different areas of the brain via segregated, parallel cortico-striatal loops to modulate adequate cognitive and emotional responses.[55,56] Among other loops, the striatum is thought to receive input from frontal regions and sensory areas. The influence of frontal cortical input on the striatum is associated with the top-down processing of internal, self-generated mental information.[11,57] Moreover, the striatum receives external, sensory information through direct cortico-striatal projections that originate in sensory and association areas,[58–60] as well as via thalamostriatal projections.[61–63] This dual cortico-striatal circuitry is crucial for formulating appropriate, adaptive reactions to both internal motivation and external context. Specifically, sensory inputs from the fusiform gyrus, in its role as an associative part

of the visual sensory pathway, has an important function in emotion-processing.[64] This region is also considered the processing center for facial stimuli and recognition of facial emotion,[54,65,66] as well as for expert object recognition, although under debate.[67]

With reference to our hypothesis, we found a decoupling of the right VSs and the fusiform gyri associated with L-DOPA-induced hyperdopaminergia, as well as with high SPQ positive scores in the placebo group. This result, if replicated, could be support both the dopamine and the disconnection hypothesis, as an increase of dopamine might result in a disruption of sensory information flow to the striatum, which in consequence has missing contextual information for modulating intrinsic frontal inputs and formulating adequate responses.[22,23]

We might also infer from this that dopaminergic availability was also enhanced for individuals within the placebo treatment group who manifested positive schizotypal traits. Winton-Brown et al previously described a dopamine-dependent explicit misattribution of salience to neutral stimuli, leading to errors in prediction and, therefore, a psychotic-like reaction.[16] Thus, the decoupling of the fusiform gyrus to the striatum, could ultimately be responsible for the misinterpretation of perception and further inadequate responses observed in psychotic individuals. This could be crucial to the pathophysiological development of positive symptoms.

The L-DOPA-induced changes in iFC in association with negative SPQ scores demonstrate a positive interaction in the placebo group. There, participants with lower scores presented an anticorrelation between the VSs and the fusiform gyrus, which disappeared in participants with higher negative scores. However, the reverse trend was found in the L-DOPA group, where low-scorers showed decoupling and participants with higher scores achieved anticorrelation. Hence, L-DOPA seems to be somewhat beneficial for schizotypal negative symptoms. This suggests that, under placebo conditions, the association between iFC and SPQ scores behaves similarly for positive and negative subscores. As dopamine availability increases, high SPQ-positive scorers seem unaffected as they remain decoupled while participants with high negative SPQ scores exhibit a phenomenon of *restitutio ad integrum*. Likewise, major-depressive disorder is related to abnormal reactions to the presentation of images of emotional faces even before onset of the first episode.[68] Greater availability of dopamine may potentially reinstitute coupling to the fusiform gyrus. Nevertheless, this also suggests that schizotypy and its single factors (ie, positive, negative, and disorganized), are a heterogeneous group of symptoms whose pathogenesis is accordingly diverse.

Our study had some limitations. We included only men, which meant that, while our sample was more homogenous and stable in terms of hormonal fluctuations, our choice limits external validity. Because we opted to keep the seed-based correlational analyses to a necessary minimum, we utilized only 6 bilateral striatal seeds. Although this allowed us to test our hypothesis without inflating the number of false positives, such a strategy also restricted our investigation to iFC between pre-specified regions in the striatum and the rest of the brain.

Future research should involve longitudinal, higher-powered studies with within-subject design to assess changes in iFC over time relative to the development of symptoms. Such efforts would provide new insight into disorders in persons on the lower end of the psychosis continuum, thereby contributing to a better understanding of the pathomechanisms of schizophrenia.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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