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# Functional Dysconnectivity in Ventral Striatocortical Systems in 22q11.2 Deletion Syndrome

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**22q11.2 deletion syndrome (22q11.2DS) is a genetic neurodevelopmental disorder that represents one of the greatest known risk factors for psychosis. Previous studies in psychotic subjects without the deletion have identified a dopaminergic dysfunction in striatal regions, and dysconnectivity of striatocortical systems, as an important mechanism in the emergence of psychosis. Here, we used resting-state functional MRI to examine striatocortical functional connectivity in 22q11.2DS patients. We used a 2 × 2 factorial design including 125 subjects (55 healthy controls, 28 22q11.2DS patients without a history of psychosis, 10 22q11.2DS patients with a history of psychosis, and 32 subjects with a history of psychosis without the deletion), allowing us to identify network effects related to the deletion and to the presence of psychosis. In line with previous results from psychotic patients without 22q11.2DS, we found that there was a dorsal to ventral gradient of hypo- to hyperstriatocortical connectivity related to psychosis across both patient groups. The 22q11.2DS was additionally associated with abnormal functional connectivity in ventral striatocortical networks, with no significant differences identified in the dorsal system. Abnormalities in the ventral striatocortical system observed in these individuals with high genetic risk to psychosis may thus reflect a marker of illness risk.**

*Keywords:* schizophrenia/functionalconnectivity/22q11DS/dopaminergic systems/striatal connectivity/genetic risk to psychosis

## Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2DS) or velocardiofacial syndrome is a neurodevelopmental disorder caused by a microdeletion at the q11.2 locus of chromosome 22,[1] which occurs in approximately 1 out of 4000 live births.[2] This syndrome may present with a diverse phenotype that includes somatic, cognitive, and psychiatric features.[3] Importantly, it represents one of the greatest known genetic risk factors for psychosis, with 30%–40% of patients developing schizophrenia.[4,5] Moreover, duplications of the same chromosomal segment have been found to be a protective factor for schizophrenia.[6] Understanding the biological underpinning of the 22q11.2DS may provide valuable insight into the mechanisms underlying schizophrenia and its vulnerability.

Dopamine dysfunction in striatal regions has been proposed as a central mechanism underlying the emergence of psychotic symptoms.[7] The genetic mechanism underlying the vulnerability to psychosis in the 22q11.2DS are likely to be complex, however one should also acknowledge that the deletion includes important genes in dopamine pathways such as COMT.[8,9] Growing evidence from positron emission tomography (PET) studies also suggests that patients with 22q11.2DS have a dysfunctional striatum, showing changes in dopamine transporter concentration,[10] and increased presynaptic dopaminergic activity.[11] In schizophrenia, these molecular abnormalities

are thought to relate to dysfunction of extended cortico-striato-thalamic networks,[12–14] although the function of such networks has not been extensively investigated in 22q11.2DS patients.

Two striatocortical circuits have been proposed to be relevant for psychosis: the ventral and dorsal systems.[13,15] These circuits topographically connect cortical regions with the striatum, with feedback loops passing through the pallidum and thalamus.[13,16] The ventral system connects the nucleus accumbens and ventral striatum with limbic regions, and its dysfunction has long been associated with psychosis.[17,18] Patients with a first episode of psychosis present increased coupling in the ventral striatofrontal circuit,[12] although the replication of these results remains equivocal.[14] Alterations in the ventral system have been correlated with the severity of psychotic symptoms in patients (particularly connectivity between ventral caudate and left dorsolateral prefrontal cortex),[12] but not with the severity of psychotic-like experiences in healthy subjects.[19]

The dorsal system links regions of dorsolateral prefrontal cortex and dorsal caudate/putamen, and it is involved in cognitive and associative functions.[13,16] Consistent with recent evidence for a primary role of the dorsal striatum in the pathogenesis of psychosis,[20] which is particularly supported by PET studies,[21] reduced functional coupling of the dorsal striatocortical system has proven to track psychotic symptom expressions across a broad spectrum of severity.[12,19,22,23] Accordingly, dysconnectivity of both dorsal and ventral striatocortical circuits have been proposed to represent a candidate risk phenotype. Particularly, functional decoupling of dorsal frontostriatal systems has been associated with genetic risk for psychosis, as it has been described in first-degree relatives of psychotic patients,[12] and in ultra-high risk for psychosis subjects.[24] On the other hand, alterations in the ventral system have been described for first-degree relatives[12] but not for ultra-high risk subjects.[24]

We here explored striatocortical connectivity in patients with 22q11.2DS as a way to shed further light on the neural mechanisms underlying the vulnerability to psychosis. We included a group of 125 subjects comprised by healthy controls, 22q11.2DS without a history of psychosis, 22q11.2DS with a history of psychosis, and subjects with a history of psychosis without the deletion. Thus, we were able to perform a 2 × 2 factorial design, examining the effect of the 22q11.2 deletion (as a genetic vulnerability) and of psychosis.

We hypothesized that carriers of the 22q11.2 deletion would present abnormal connectivity in a dorsal striatocortical network, related to a genetic vulnerability to psychosis. We also expected to find changes in ventral circuitry related to psychosis, particularly in the connectivity between the ventral caudate and dorsolateral prefrontal cortex.

## Methods

### *Participants*

We recruited patients with 22q11.2DS who had been part of previous studies of our group[25] or were in contact with support groups such as "Fundación Chilena del Niño con Síndrome Velocardiofacial." Subjects with and without history of psychosis with the deletion were included, assessed using the Mini International Neuropsychiatric Interview (MINI).[26,27] For subjects with a history of psychosis, current psychotic symptoms were measured using the Positive and Negative Syndrome Scale (PANSS).[28] For those subjects with the 22q11.2DS who did not have a history of psychosis, we assessed the presence of subthreshold symptoms using the Scale of Prodromal Symptoms.[29] We also recruited a group of subjects with early psychosis (within the first 2 years of the onset of psychosis, confirmed with the MINI) from the Psychiatric Institute "Dr José Horwitz Barak," matching this group to the 22q11.2DS group with psychosis according to their symptoms (PANSS total score). Healthy control subjects without any current psychiatric disorder or lifetime history of psychotic disorder, according to the MINI, or prodromal symptoms according to the SOPS, were also included.

In all participants, comorbid affective symptoms were measured using the Hamilton Depression Rating Scale (HDRS)[30] and the Young Mania Rating Scale (YMRS).[31] Intelligence quotient (IQ) was assessed using the WAIS-IV test. Also, all participants underwent MLPA (multiplex ligation-dependent probe amplification) to either confirm or discard 22q11.2DS. All participants gave written consent for this study, which was approved by the Ethics committee of the Pontificia Universidad Católica de Chile.

A total of 10 subjects across all groups (1 from 22q11.2DS, 5 from early psychosis and 4 healthy controls) were excluded due to scan artifacts or failures in the preprocessing pipeline. The final sample with complete cognitive and neuroimaging data consisted in 125 subjects (38 with 22q11.2DS: 10 of which had a history of psychosis; and 87 subjects without 22q11.2DS: 55 healthy controls and 32 patients with early psychosis).

### *Image Acquisition and Preprocessing*

Images were acquired with a Philips Ingenia 3T MRI scanner with a 16-channel brain coil. Resting-state functional MRI were acquired with the following scanning parameters: total scan time 8.33 min, single shot echo-planar imaging (EPI), repetition time (TR) 2.5 s, time to echo (TE)35 ms, flip angle of 82°, field-of-view (FOV) of 220 × 220 × 110 mm, and an isotropic spatial resolution of 2.75 mm. Subjects were asked to remain still and with their eyes opened. A structural T1-weighted image was also acquired with a voxel size of 1.0 $mm^3$

isotropic, a inversion time delay of 965.2 ms, TE 3.6 ms, TR 7.7 ms, and flip angle of 8°.

Preprocessing of the functional images followed previously published pipelines,[32] which included the following steps: (1) removal of the first 4 volumes of each acquisition; (2) slice-time correction using SPM12[33]; (3) 2-pass realignment of all volumes to the first volume (first pass) and then to the mean volume (second pass) using SPM12; (4) coregistration of EPI data to the structural image using ANTs[34,35]; (5) application of the nonlinear transform derived from the T1-weighted image processing pipeline to the coregistered EPI data using ANTs; (6) linear detrending of the spatially normalized BOLD time series; and (7) intensity normalization of the EPI data to mode 1000 units. The images were then spatially smoothed with a 6 mm FWHM Gaussian kernel, and bandpass-filtered between 0.008 and 0.08 Hz using the fast Fourier transform. Management of residual movement was performed based on an automated-ICA method: ICA-AROMA.[36] Following results of Parkes et al[32] for a dataset of patients with schizophrenia, regression of mean white matter and cerebrospinal fluid signals was also included as a denoising procedure.

### *Definition of Seeds, Regions of Interest*

Following previous studies,[12,37] 6 bilateral striatal regions of interest (ROIs) based on 3.5-mm radius spheres were used. Coordinates for each seed are defined in the Montreal Imaging Institute (MNI) stereotaxic space.

For the caudate, 3 ROIs were seeded:

- DC: dorsal caudate ($x = \pm13$, $y = 15$, $z = 9$),
- sVC: superior ventral caudate ($x = \pm10$, $y = 15$, $z = 0$),
- iVC: inferior ventral caudate/nucleus accumbens ($x = \pm9$, $y = 9$, $z = 28$).

As for the putamen, the 3 ROIs were:

- DCP: dorsocaudal putamen ($x = \pm28$, $y = 1$, $z = 3$),
- DRP: dorsorostral putamen ($x = \pm25$, $y = 8$, $z = 6$),
- VRP: ventrorostral putamen ($x = \pm20$, $y = 12$, $z = 23$).

The dorsal striatocortical system is comprised by DC, DRP, and the DCP, whereas seeds in the ventral system are iVC (nucleus accumbens), sVC, and VRP.

### *Statistical Analysis*

The statistical analysis was implemented as in previous studies.[12,19] Mean time series of each seed ($TS_{seed\ i}$) were used for seed-related functional connectivity mapping between such seeds and each voxel within a gray matter mask, which included all cortical regions and the thalamus.

In a first-level analysis, for each participant, a general linear model containing time series for each of the 6 seeds as covariates was used to model blood oxygen level-dependent signal fluctuations in each voxel of the gray matter mask ($TS_{voxel\ i}$):

$$TS_{voxel\ i} = \alpha + \beta_1 TS_{seed\ 1} + \beta_2 TS_{seed\ 2} + \ldots + \beta_6 TS_{seed\ 6} + \varepsilon \quad (1)$$

Gray matter $t$-maps estimated in the first-level analysis were then passed to a second-level general linear model to generate groupwise functional connectivity maps for each seed. Group effects were estimated using a 2 × 2 factorial ANOVA model with categorical variables *psychosis* and *22q11.2DS (deletion)*, as well as their interaction. Separate models were used for each seed, and nuisance covariates were included: age, age squared, sex, IQ, and mean framewise displacement (fd) as a measure of in-scanner motion (as in Sabaroedin et al[19]).

$$\begin{aligned} t_{seed\ 1} = \ & \alpha + \beta_1\, age + \beta_2\, age^2 + \beta_3\, sex + \beta_4\, fd + \beta_5\, IQ \\ & + \beta_6\, deletion + \beta_7\, psychosis + \\ & \beta_8\, psychosis \times deletion + \varepsilon \end{aligned} \quad (2)$$

To identify relevant changes in striatal functional connectivity, we used a clusterwise-corrected threshold of $P < .01$ determined using the AlphaSim permutation procedure implemented in the REST toolbox.[38]

## Results

One hundred and twenty-five subjects were included in this study. Thirty-eight subjects were carriers of the 22q11.2 deletion, 10 of which had a history of psychosis. Eighty-seven subjects without the deletion were also included: 55 corresponded to healthy controls and 32 were patients with a history of psychosis (early psychosis) who were symptom matched to the 22q11.2DS patients with psychosis, according to their PANSS total scores ($P = .5121$). Demographic and clinical information of each group can be found in table 1. Groups differed in age, with analyses showing that 22q11.2DS patients were significantly older than the early psychotic group ($P = .0275$). There was also a significantly larger number of women in the group with the deletion compared to the early psychosis group ($P = .0104$). From the 28 subjects with the deletion that had no history of psychosis, 3 fulfilled criteria for attenuated psychotic syndrome. All groups displayed low levels of affective symptoms (manic and depression symptoms); however this was slightly higher in patients than healthy controls (YMRS post hoc $t$ test for early psychosis vs healthy controls: $P = .009$). As expected, patients with the deletion also had a lower IQ than subjects from the early psychosis group and healthy controls ($P = 4.71e{-}15$ and $P = 1.10e{-}23$, respectively). Regarding in-scan movement, we compared mean FD across groups and found a significant difference between 22q11.2DS and healthy controls groups ($P = 5.70e{-}5$). Other clinical characteristics of the 22q11.2DS sample are reported in supplementary table 1. All subsequent reported analyses include age (as well as age squared), sex, IQ, and mean FD as covariates of no interest.

**Table 1.** Demographic and Clinical Information

| | Early Psychosis | 22q11.2DS (Psychosis/No Psychosis) | Healthy Controls | $F/t/\chi^2$ | $P$ |
|---|---|---|---|---|---|
| $N$ (125) | 32 | 38 (10/28) | 55 | — | — |
| Age | 20.03 ± 3.03 | 23.66 ± 8.66 (23.4 ± 9.43/23.75 ± 8.55) | 22.91 ± 3.59 | 2.74 | .046 |
| Sex (% female) | 25% | 55% (50%/57%) | 36% | 7.17 | .067 |
| PANSS Total score | 43.16 ± 13.66 | 46.50 ± 14.92 — | — | −0.66 | .512 |
| PANSS Positive symptoms | 8.03 ± 1.26 | 9.70 ± 3.56 — | — | −2.28 | .028 |
| Fulfills attenuated-positive symptom syndrome according to SOPS (Number of subjects) | — | — 3 | 0 | (Fisher's exact test) | .036 |
| HAM-D | 2.54 ± 3.56 | 2.70 ± 3.94 | 1.25 ± 2.29 | 2.816 | .06 |
| YMRS | 1.16 ± 2.07 | 0.62 ± 1.62 | 0.13 ± 0.48 | 5.28 | .006 |
| IQ | 94.19 ± 7.04 | 65.50 ± 14.03 69.75 ± 12.50 | 107.25 ± 13.82 | 76.46 | .000 |
| Mean FD | 0.43 ± 0.32 | 0.54 ± 0.28 (0.52 ± 0.28/0.55 ± 0.29) | 0.35 ± 0.16 | 6.99 | .001 |
| Antipsychotic medication (CPZ equivalent) | 448.12 ± 263.50 | 56.91 ± 138.424 (208.75 ± 208.33/[a]) | 0 | 2.62 ($t$-stat early psychosis vs 22q11.2DS psychosis) | .012 |

*Note*: CPZ, chlorpromazine; FD, framewise displacement; HAM-D, Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SOPS, Scale of Prodromal Symptoms; YMRS, Young Mania Rating Scale.
[a]One subject in the 22q11DS group was prescribed antipsychotic medication (75 mg CPZ equivalent) for other reasons (management of impulsivity), not because of past or current psychosis.

*Functional Connectivity Analyses*

Analyses of striatocortical connectivity for each seed across groups replicated similar patterns as seen in previous studies (supplementary figure S1).[37]

*22q11.2DS-Related Changes in Striatocortical Functional Connectivity* 22q11.2DS was associated with changes in the ventral striatocortical system (figure 1). Carriers of the deletion showed a decreased functional connectivity between sVC and 2 voxel clusters. The first one was located at the right dorsolateral prefrontal cortex, also extending into the right ventrolateral prefrontal cortex and right ventromedial orbitofrontral cortex. The second cluster included the left superior visual cortex and temporoparietal junction.

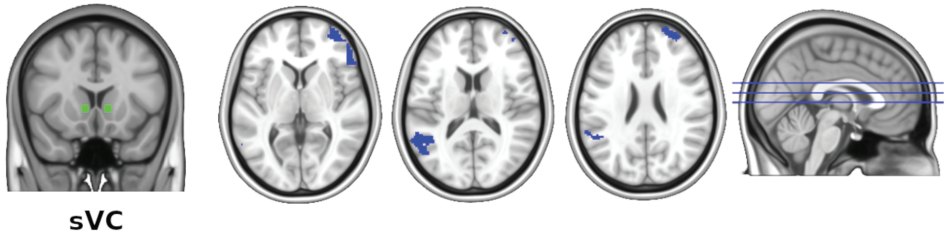
For the iVC, 22q11.2DS patients showed increased functional connectivity with right dorsolateral motor cortex and right dorsolateral somatosensory cortex.

*Psychosis-Related Changes in Striatocortical Functional Connectivity* Psychosis was associated with alterations both in the dorsal and the ventral circuits (see figure 2). Reduced functional connectivity from the DCP seed was found for 2 different clusters. The first one was identified at the bilateral somatosensory and motor cortex, expanding into the bilateral cingulate cortex. The second cluster that showed hypoconnectivity with DCP in psychosis was the left somatosensory and motor cortex, with the cluster extending into the left superior parietal cortex.

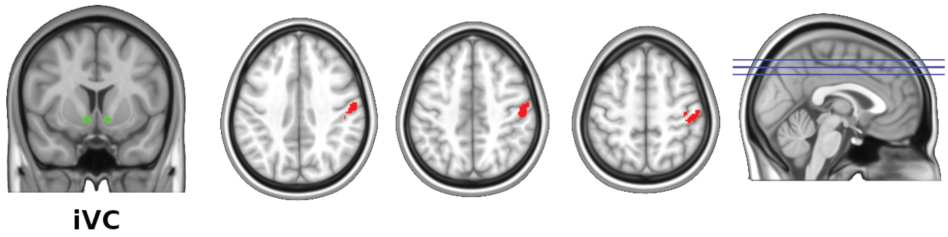
For the sVC seed, hypoconnectivity was found with 3 clusters. The first included the right medial, ventromedial, and dorsal prefrontal cortex, extending into the bilateral anterior cingulate cortex. The second cluster included right ventromedial orbitofrontal cortex and right dorsolateral prefrontal cortex. The third cluster encompassed left temporal and temporoparietal cortex.

For iVC seed, altered functional connectivity was found in 2 regions: bilateral medial visual cortex and cuneus, which showed hypoconnectivity; and right dorsal and dorsomedial prefrontal cortex, which showed hyperconnectivity.

*Psychosis and 22q11.2DS Interaction* We also performed an interaction analysis between psychosis and 22q11.2DS for striatocortical connectivity. Significant interactions were found for 3 seeds: DCP, DC, and sVC (figure 3). As shown in the interaction plots (figure 3, right), psychosis in the presence of the 22q11.2DS was associated with increased functional connectivity between DCP, DC, and sVC and several cortical regions. For the DCP, hyperconnectivity to bilateral dorsomedial motor and premotor cortex was found; for the DC, increased connectivity was seen with right ventral somatosensory cortex; and for the sVC seed, we found hyperconnectivity




| Region | Cluster size (number of voxels) | MNI coordinates (peak) | | | p-value (clusterwise-corrected, peak) |
|---|---|---|---|---|---|
| | | x | y | z | |
| Right dorsolateral PFC | 568 | 34 | 58 | 2 | 5,53E-05 |
| Left superior visual cortex | 362 | -48 | -50 | 28 | 0,0001 |




| Region | Cluster size (number of voxels) | MNI coordinates (peak) | | | p-value (clusterwise-corrected, peak) |
|---|---|---|---|---|---|
| | | x | y | z | |
| Right dorsolateral motor cortex | 411 | 52 | -18 | 44 | 5,88E-05 |

**Fig. 1.** 22q11.2DS-related changes in striatocortical functional connectivity. *Note*: iVC, inferior ventral caudate; sVC, superior ventral caudate. Cortical regions highlighted in the upper panel represent decreased functional coupling with the sVC. For the lower panel, highlighted regions represent increased functional connectivity with iVC. All depicted regions are clusterwise corrected at a threshold of $P < .01$.

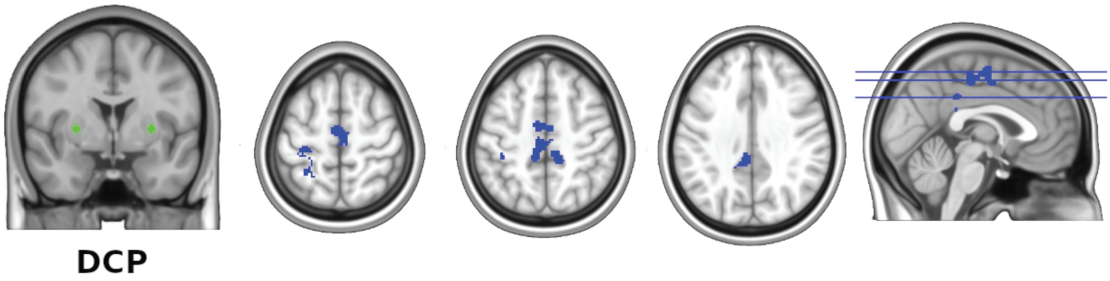
to the right dorsolateral prefrontal cortex. Increased connectivity between these regions was not seen in subjects with psychosis who were not carriers of the deletion.

*Effect of Antipsychotics* We repeated all the analyses above covarying for antipsychotic use. As shown in supplementary figures S2–S4, the results were very similar for the main effect of the deletion, or the interaction. The psychosis-related changes in the dorsal circuit (from DCP seeds) were no longer significant, nor were the hyperconnectivity from iVC to right dorsal pre-frontal cortex .

## Discussion

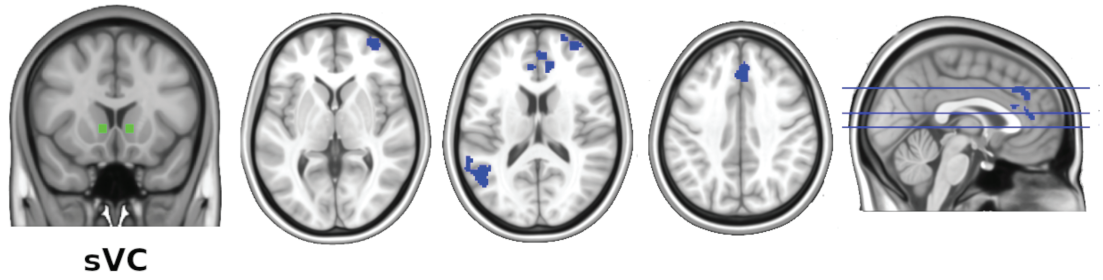
We here examined striatocortical connectivity associated with a genetic change related to a very high risk to develop psychosis, namely the 22q11.2 deletion. Our main finding was a dysfunction of the ventral striatocortical system related to the deletion, which might explain the higher risk of psychosis seen in this population. Contrary to our hypothesis, we did not find significant differences in dorsal striatocortical systems in patients with 22q11.2DS. Dorsal changes were only present in subjects with a known history of psychosis, which accompanied ventral system dysconnectivity in this group. Our results point toward a dysfunction of ventral striatocortical networks in people at high genetic risk for psychosis, along with a more global dysfunction in striatocortical systems in people experiencing psychosis.

22q11.2DS was associated with decreased connectivity between the sVC seed and an extensive frontal region comprising parts of the dorsolateral prefrontal cortex, as well as ventromedial and ventrolateral prefrontal cortex. Decreases in functional connectivity were also seen between this seed and the temporoparietal junction. Previous studies have suggested an increase in ventral striatum connectivity to frontal regions and a decreased connectivity to temporoparietal regions in relatives of psychotic patients,[12] although this pattern did not appear to be present in subjects with ultra-high risk to psychosis.[24] It is interesting to note that these cortical regions showing abnormal connectivity with the ventral striatum have been involved in social cognition,[39] and are known to be abnormal in schizophrenia.[40] Their connectivity with midbrain dopaminergic regions has also been related to social amotivation in patients.[41] Moreover, activation of the temporoparietal junction has been shown to be abnormal in response to a social task eliciting trust in



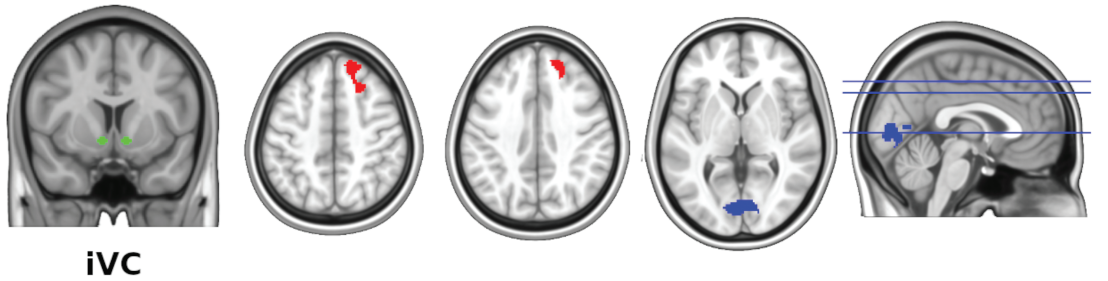
DCP

| Region | Cluster size (number of voxels) | MNI coordinates (peak) | | | p-value (clusterwise-corrected, peak) |
|---|---|---|---|---|---|
| | | x | y | z | |
| Bilateral dorsomedial somatosensory cortex | 742 | -8 | -34 | 52 | 2,00E-04 |
| Left dorsomedial somatosensory cortex | 421 | -28 | 30 | 72 | 7,90E-07 |



sVC

| Region | Cluster size (number of voxels) | MNI coordinates (peak) | | | p-value (clusterwise-corrected, peak) |
|---|---|---|---|---|---|
| | | x | y | z | |
| Right rostral medial prefontal cortex | 536 | 4 | 34 | 34 | 1,73E-05 |
| Right ventromedial orbitofrontal cortex | 497 | 30 | 64 | -8 | 2,31E-05 |
| Left caudal middle temporal cortex | 383 | -50 | -62 | 14 | 1,29E-04 |



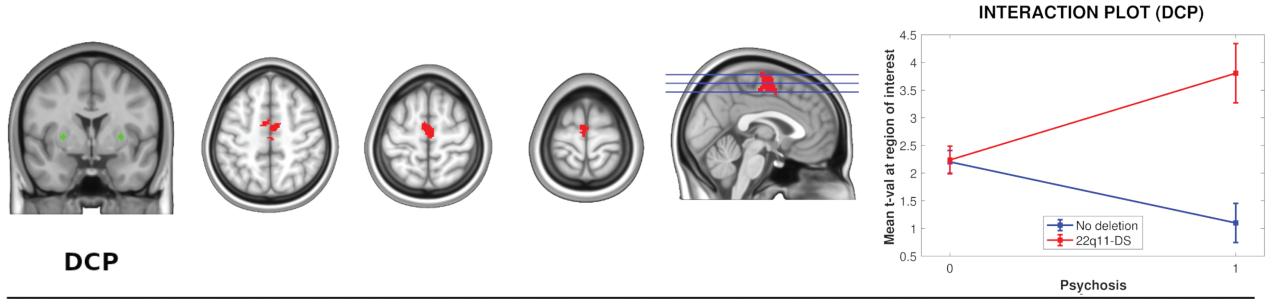
iVC

| Region | Cluster size (number of voxels) | MNI coordinates (peak) | | | p-value (clusterwise-corrected, peak) |
|---|---|---|---|---|---|
| | | x | y | z | |
| Bilateral caudal medial visual cortex | 598 | -2 | -84 | 2 | 1,00E-04 |
| Right rostral dorsal PFC | 400 | 20 | 42 | 42 | 9,81E-07 |

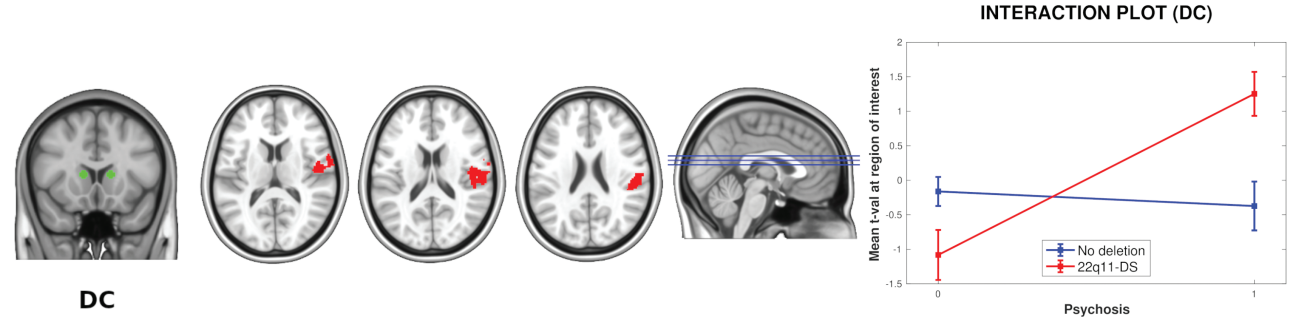
**Fig. 2.** Psychosis-related changes in striatocortical functional connectivity. *Note*: DCP, dorsocaudal putamen; iVC, inferior ventral caudate; sVC, superior ventral caudate. Cortical regions highlighted in upper and middle panels correspond to decreased functional coupling with DCP and sVC respectively. Bottom panel shows decreased cortical functional connectivity in the occipital cortex with iVC, and an increased coupling in frontal regions. All depicted regions are clusterwise corrected at a threshold of $P < .01$.

subjects at high clinical risk of psychosis.[42] Abnormalities in this system could therefore be the mechanism providing a higher risk to psychosis in patients with 22q11.2DS.

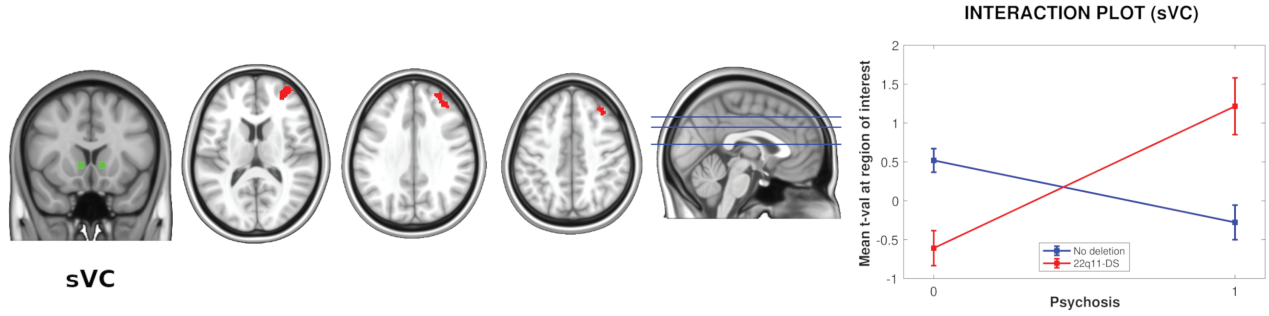
Patients with 22q11.2DS also presented increased connectivity between the iVC and sensorimotor regions. In line with this finding, subjects at ultra-high risk for psychosis




| Region | Cluster size (number of voxels) | MNI coordinates (peak) | | | p-value (clusterwise-corrected, peak) |
|---|---|---|---|---|---|
| | | x | y | z | |
| Bilateral dorsomedial motor and premotor cortex | 574 | -4 | -8 | 66 | 4,03E-05 |




| Region | Cluster size (number of voxels) | MNI coordinates (peak) | | | p-value (clusterwise-corrected, peak) |
|---|---|---|---|---|---|
| | | x | y | z | |
| Right ventral somatosensory cortex | 601 | 48 | -12 | 16 | 2,15E-05 |




| Region | Cluster size (number of voxels) | MNI coordinates (peak) | | | p-value (clusterwise-corrected, peak) |
|---|---|---|---|---|---|
| | | x | y | z | |
| Right rostral dorsolateral PFC | 556 | 32 | 54 | 8 | 4,76E-06 |

**Fig. 3.** Psychosis and 22q11.2DS interaction. Striatocortical functional connectivity. Cortical regions where a significant interaction was found are highlighted. The right column shows visual representations of the interactions between the effects of psychosis and 22q11.2DS at each region of interest. *Note*: DC, dorsal caudate; DCP, dorsocaudal putamen; sVC, superior ventral caudate. All regions showed are clusterwise corrected at a threshold of $P < .01$.

also show hyperconnectivity of the ventral striatal system (ventral putamen specifically) and the postcentral gyrus.[24] The association observed with motor areas resonates with findings of abnormal motor development in subjects who later develop schizophrenia,[43] supporting its role in the genetic risk to the disorder. However, it might also reflect vulnerabilities to develop other disorders in the 22q11DS, like Parkinson's disease among others.[4,5,44–47]

Our findings in psychosis partially support the proposed dorsal to ventral gradient of hypoconnectivity to hyperconnectivity.[12] Thus, we observed decreased connectivity in the dorsal putamen with the midcingulum and nearby sensorimotor areas (although such differences were no longer significant when covarying for antipsychotic medication, as shown in supplementary figure S3). A similar pattern of reduced functional connectivity between DCP and motor regions has been described in healthy subjects with psychotic-like experiences and it was associated with the severity of such symptoms.[19] In our study, psychosis was also associated with an increased connectivity between the iVC/ventral tegmental area (VTA) and the prefrontal cortex. These findings echo the functional connectivity abnormalities elicited by ketamine infusion, which have been shown to correlate with psychotic symptoms.[22] However, striatal dysconnectivity in psychosis seems to be more complex than the gradient would suggest. We also found reduced connectivity between the sVC (ventral system) and the anterior cingulate cortex. Both anatomic and functional abnormalities of the anterior cingulate have been associated to psychotic disorders,[48–50] and they have been implicated in the impaired integration of cognition, emotion, and motivational drive of schizophrenic patients. In the same manner, psychosis was also associated to hypoconnectivity between the iVC/VTA and occipital visual areas, alterations which are similar to those found in another study in first-episode psychotic patients.[12]

Several studies have shown that 22q11.2DS is associated with brain changes that are not frequently seen in patients with schizophrenia who are not carriers of the deletion, such as localized increased cortical thickness or increased fractional anisotropy.[51,52] By including patients with psychosis with or without the deletion, we were also able to explore potential differences in striatal connectivity, albeit with a relatively low power. Our findings associated with psychosis across deletion and nondeletion groups, that were discussed above, show that there are many similarities. However, as our interaction analyses show, there are differences as well. Overall our results point toward a lower presence of hypoconnectivity in the dorsal striatum in psychosis in the 22q11.2DS, and an increased hyperconnectivity in the ventral striatum.

Our study is limited by its relatively small sample size. This is not unusual for a relatively rare disorder such as the 22q11.2DS. Nonetheless, our 2 × 2 factorial analysis allowed us to boost its power by looking orthogonally at the effect of psychosis and the deletion, increasing its sample size with healthy controls and patients with early psychosis. Power analysis could help us understand to what extent our study was under-powered. However, power analyses for imaging experiments require many assumptions that are not necessarily easy to make, and post hoc power analyses could be considered uninformative.[53] One can still get a sense by observing that a total sample of 125 in a 2-way balanced ANOVA would have the power to detect medium size differences (Cohen's *f* around 0.25). Considering the multiple correction approach used, based on the spatial clustering of significant voxels (using AlphaSim[38]), this would be a medium size effect that affects a volume of at least 348 voxels. The unbalanced nature of our design makes this an overestimation. It is also likely that the power for the interaction effects is particularly smaller, enough to identify large to medium differences that are clustered together. And that power might only be for disordinal or reversal interactions (as found in our study), being even smaller for ordinal or attenuation effects.[54]

As another limitation, the 22q11.2DS also confers a higher risk to other neuropsychiatric disorders, as well as a cognitive delay, and therefore not all brain changes might be associated with a higher vulnerability to psychosis. In order to account for some of this heterogenic presentation, we covaried for IQ as a way to control for cognitive impairment.

In summary, we here show that 22q11.2DS is related to abnormal connectivity in the ventral striatocortical network, highlighting the importance of this network in relation to the risk to psychosis.

## Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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