Original Investigation

Striatal Response to Reward Anticipation Evidence for a Systems-Level Intermediate Phenotype for Schizophrenia

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IMPORTANCE Attenuated ventral striatal response during reward anticipation is a core feature of schizophrenia that is seen in prodromal, drug-naive, and chronic schizophrenic patients. Schizophrenia is highly heritable, raising the possibility that this phenotype is related to the genetic risk for the disorder.

OBJECTIVE To examine a large sample of healthy first-degree relatives of schizophrenic patients and compare their neural responses to reward anticipation with those of carefully matched controls without a family psychiatric history. To further support the utility of this phenotype, we studied its test-retest reliability, its potential brain structural contributions, and the effects of a protective missense variant in neuregulin 1 (NRG1) linked to schizophrenia by meta-analysis (ie, rs10503929).

DESIGN, SETTING, AND PARTICIPANTS Examination of a well-established monetary reward anticipation paradigm during functional magnetic resonance imaging at a university hospital; voxel-based morphometry; test-retest reliability analysis of striatal activations in an independent sample of 25 healthy participants scanned twice with the same task; and imaging genetics analysis of the control group. A total of 54 healthy first-degree relatives of schizophrenic patients and 80 controls matched for demographic, psychological, clinical, and task performance characteristics were studied.

MAIN OUTCOMES AND MEASURES Blood oxygen level–dependent response during reward anticipation, analysis of intraclass correlations of functional contrasts, and associations between striatal gray matter volume and NRG1 genotype.

RESULTS Compared with controls, healthy first-degree relatives showed a highly significant decrease in ventral striatal activation during reward anticipation (familywise error–corrected P < .03 for multiple comparisons across the whole brain). Supplemental analyses confirmed that the identified systems-level functional phenotype is reliable (with intraclass correlation coefficients of 0.59-0.73), independent of local gray matter volume (with no corresponding group differences and no correlation to function, and with all uncorrected P values > .05), and affected by the NRG1 genotype (higher striatal responses in controls with the protective rs10503929 C allele; familywise error–corrected P < .03 for ventral striatal response).

CONCLUSIONS AND RELEVANCE Healthy first-degree relatives of schizophrenic patients show altered striatal activation during reward anticipation in a directionality and localization consistent with prior patient findings. This provides evidence for a functional neural system mechanism related to familial risk. The phenotype can be assessed reliably, is independent of alterations in striatal structure, and is influenced by a schizophrenia candidate gene variant in NRG1. These data encourage us to further investigate the genetic and molecular contributions to this phenotype.

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Several lines of evidence suggest a crucial role for striatal dysfunction in the pathophysiology of schizophrenia. For humans, a widely used strategy has been the study of reward anticipation with neuroimaging.\(^1\)\(^,\)\(^2\) Functional magnetic resonance imaging (fMRI) experiments typically show attenuated ventral striatal activation in drug-naïve and unmedicated schizophrenic patients\(^3\)\(^-\)\(^5\) and then link this anomaly to symptom severity.\(^3\)\(^,\)\(^4\) Treatment with atypical, but not first-generation, antipsychotics may partially normalize ventral striatal dysfunction in schizophrenia,\(^4\)\(^,\)\(^6\) highlighting a potential dopaminergic mechanism relevant for therapy. In agreement with this, molecular neuroimaging demonstrates increased striatal dopamine synthesis\(^7\) and dopamine release in schizophrenia,\(^8\) while the density of presynaptic dopamine terminals is unaltered.\(^9\) In support of a link between striatal hypoactivation and dopamine dysregulation, the blood oxygen level–dependent response during reward anticipation (detected by fMRI) is correlated with dopamine synthesis capacity.\(^10\)

Based on these observations, it has been proposed that functional, but not structural, alterations of the striatum are a core feature of schizophrenia.\(^11\) Specifically, abnormal representation of environmental salience in a circuit (including the dopaminergic midbrain, striatum, and prefrontal cortex) has been linked to schizophrenia susceptibility.\(^12\)\(^-\)\(^13\) This proposal is supported by evidence suggesting striatal hypoactivation in individuals at high clinical risk for psychosis\(^14\) and associations between altered dopamine activity and the severity of prodromal symptoms.\(^15\) Further evidence comes from studies relating the sensitivity of the human reward system to genetic variation in dopamine-regulating genes.\(^16\) These data raise the possibility for a role for striatal dysfunction in the genetic risk architecture of the illness. More fundamentally, given the high heritability of schizophrenia, the question arises whether abnormal striatal activation during reward anticipation is a potential intermediate phenotype (or “endophenotype”) of the disorder (i.e., a systems-level feature that mediates genetic risk).\(^17\)

Among several criteria that have been proposed for candidate intermediate phenotypes, the demonstration of abnormalities in unaffected first-degree relatives is a particularly important piece of evidence.\(^17\) First-degree relatives have a strongly increased risk for the illness and share an enriched set of schizophrenia susceptibility genes.\(^18\) Studying these individuals circumvents a number of confounders that complicate the interpretation of patient data, in particular the effects of medication, substance use, and institutionalization on brain physiology. Using this research strategy, abnormal prefrontal activation and prefrontal-hippocampal connectivity have been identified as intermediate phenotypes.\(^19\)\(^-\)\(^20\) In the striatum, increased dopamine synthesis is evident in healthy first-degree relatives of schizophrenic patients, similar to the anomalies observed in manifest psychosis.\(^7\)\(^-\)\(^21\) Given the ties between dopaminergic neurotransmission, striatal function, and schizophrenia risk, blunted striatal activation during reward anticipation is a plausible candidate intermediate phenotype for the genetic risk for schizophrenia, but no data on relatives are available that would support this hypothesis.

We examined a large sample of unaffected first-degree relatives of schizophrenic patients who underwent fMRI and compared their neural response to reward anticipation to that of a sample of healthy matched controls who had no family history of psychiatric illness. Consistent with our prior work, we used a well-established reward anticipation paradigm that is known for robustly engaging the ventral striatum\(^1\)\(^-\)\(^3\)\(^,\)\(^5\) and effective in uncovering attenuated striatal response in antipsychotic-naïve schizophrenic patients.\(^22\) We hypothesized a blunted neural response in our sample at high familial risk, thereby providing initial evidence that striatal dysfunction during reward processing is a potential intermediate phenotype for schizophrenia. We also investigated the relationship between activation and striatal volume here, we expected to provide evidence for a primarily functional, but not structural, abnormality because the role of structural abnormalities in the striatum remains unclear. Specifically, although some studies demonstrate reduced striatal volume in early psychosis,\(^23\)\(^-\)\(^24\) increased striatal volume is reported in patients with chronic illness receiving antipsychotic treatment,\(^25\)\(^-\)\(^27\) a finding that is not related to heritable risk,\(^23\) and thus possibly reflective of treatment effects and not genetic risk. Furthermore, because the reliability of the target measure used is an important consideration in estimating specific genetic and therapeutic effects, we performed a test-retest reliability analysis to quantify the robustness of the functional phenotype. Finally, to test the utility of the phenotype for genetic studies, we examined the effects of a well-established candidate gene of the disorder, \(\text{NRG1}\)\(^26\)\(^-\)\(^27\) encoding neuregulin 1. This protein is a ligand for the tyrosine kinase receptor \(\text{ErbB4}\), a neurodevelopmental regulator that is highly expressed in the midbrain and the striatum,\(^28\)\(^-\)\(^29\) and it has recently been linked to abnormal dopamine signaling and cognitive deficits in a schizophrenia rodent model.\(^30\) We studied a nonsynonymous (and thus likely functional) variant that is supported by a meta-analysis of schizophrenia association studies (rs10503929, Met/Thr).\(^31\)

**Methods**

**Participants**

A total of 134 participants were studied: 80 healthy individuals recruited from local residents’ registration offices in Mannheim, Bonn, and Berlin, Germany, and 54 unaffected first-grade relatives of schizophrenic patients recruited from the same areas through psychiatric hospitals, support groups, and media advertisement. All participants provided written informed consent for protocols approved by the institutional review boards of the universities in Mannheim, Bonn, and Berlin. Psychological assessments included tests for visual-motor attention (part A of the Trail Making Test) and cognitive set shifting (part B of the Trail Making Test).\(^32\) See Table 1 and the eAppendix in the Supplement for further details on the sample characteristics and diagnostic procedures.

**Reward Task**

Brain function during reward anticipation was studied using fMRI and a well-established monetary incentive delay paradigm\(^1\)\(^-\)\(^3\)\(^,\)\(^5\) with 4 experimental conditions: a win condi-
tion, a loss avoidance condition, a verbal feedback condition, and a neutral condition. Ten trials per condition were presented in a pseudorandomized order over the course of the experiment. Further details on the methods used are given in Figure 1A and the eAppendix in the Supplement.

### Table 1. Demographic, Clinical, and Task Performance Characteristics

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<tr>
<th>Characteristic</th>
<th>Controls (n = 80)</th>
<th>Relatives (n = 54)</th>
<th>P Value</th>
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<td>(n = 51)</td>
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<td>(n = 53)</td>
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<td>Win</td>
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<td>229.57 (39.17)</td>
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<td>Loss</td>
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<td>Verbal</td>
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<td>247.71 (47.49)</td>
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<td>(n = 80)</td>
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<td>.26</td>
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<tr>
<td>Sum absolute rotations, degrees</td>
<td>8.91 (4.469)</td>
<td>10.29 (8.12)</td>
<td>.25</td>
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</table>

**Abbreviations:** MWTB, multiple-choice vocabulary test; RT, reaction time; SCL-90, Symptom Checklist 90; SPQ, Schizotypical Personality Questionnaire; SRSS, Social Readjustment Rating Scale; TMT-A, part A of the Trail Making Test.

* Raw scores were standardized into age-adjusted T-scores.

### Data Acquisition

Data acquisition was performed on 3 matching 3-T MRI systems (Siemens Trio) using identical experimental protocols. Further details are provided in the eAppendix in the Supplement.
Figure 1. Reward Anticipation Task and Group-Dependent Striatal Activation Differences

A, A scheme of the 8- to 9-minute reward anticipation task is shown. Four different conditions are shown in the leftmost column. Each condition (trial) was repeated 10 times in pseudorandom order. The conditions are sorted as belonging to the “money” or “control” class. The 6-second presentation of each cue (arrow) was followed by a target stimulus (flashing of the screen). Participants responded by pressing the button as fast as possible. A reaction time–dependent feedback followed after the response (rightmost column). Please note that the feedbacks depicted do not include all possible outcomes. B, A significant increase in striatal activation can be seen in healthy controls compared with relatives (z = 4.13, familywise error–corrected P = .013 for multiple comparisons across the whole brain) displayed on a transversal section of a structural magnetic resonance imaging template (money > control contrast). The threshold of the functional map was set at t > 3 for presentation purposes. The color bar represents t values. The map coordinates refer to the standard space as defined by the Montreal Neuroimaging Institute. L indicates the left side of the brain.

Functional Image Processing and Analysis
The fMRI data were processed following previously published procedures, using standard processing routines in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) (see the eAppendix in the Supplement for details on the preprocessing and first-level modeling). Consistent with our a priori hypothesis and prior work in schizophrenia, contrast images were calculated to identify brain regions with greater activation during the anticipation of monetary salient events relative to control events (contrast: [win + loss] > [verbal + neutral]) that we refer to as “money > control” in the following). In addition, because prior evidence suggests a link between schizophrenia and altered striatal response to loss avoidance, contrast images were calculated for the [loss > neutral] condition. Group differences between relatives and controls in brain activation to reward anticipation were examined using random-effects group statistics at the second level. Specifically, linear regression models were defined that included a group variable (relatives vs healthy control) as a covariate of interest, and age, sex, and site as nuisance covariates. Significance was measured at familywise error (FWE)–corrected P < .05 for multiple comparisons across the whole brain. Because the subsequent reliability, morphometry, and imaging genetics analyses relate to the core intermediate phenotype region identified here, we obtained a striatal region-of-interest mask from the familiarity analysis for all subsequent studies, as detailed in the eAppendix in the Supplement.

Structural Image Processing and Analysis
Automated image processing was performed using the voxel-based morphometry (VBM) toolbox (VBM8 [http://dbm.neuro.uni-jena.de/vbm8/]) and, for cross-software validation, FreeSurfer version 5.1.0 (https://surfer.nmr.mgh.harvard.edu/fswiki/ReleaseNotes). In the VBM analysis, we examined the striatal region-of-interest mask derived from the functional analysis to test for the possibility that the observed functional differences may relate to preexisting group differences in striatal volume. Details of the VBM and FreeSurfer analyses are provided in the eAppendix in the Supplement. To maximize sensitivity, a significance threshold of P < .05, uncorrected, was adopted.

Test-Retest Reliability of Striatal Activation Measures
The robustness of activation measures was quantified by foci analysis of the test-retest reliability data reported in Plichta et al, a study that did not quantify the reliability of the functional contrasts examined here. Further details are provided in the eAppendix in the Supplement.

NRG1 Analysis
We tested the utility of the identified functional phenotype for genetic analyses in a subsample of 78 healthy volunteers from the control group with available genotypes for a missense mutation in NRG1 (ie, rs10503929). Consistent with prior evidence, we expected to see a protective effect (ie, a relative activation increase in the striatal core intermediate phenotype region) in carriers of the minor (C) allele. Details of the genotyping procedures and imaging analysis are given in the eAppendix in the Supplement. Details of the participants’ demographics, neuro-psychology, and fMRI task performance stratified by NRG1 genotype are provided in the eTable 1 in the Supplement.

Results
Demographic and Behavioral Variables
All groups were well matched for demographics and task performance (Table 1; Figure 2). For cognitive set shifting (part B of the Trail Making Test), a significant impairment was seen in the healthy first-degree relatives (P = .003; Table 1). More-
over, for the controls included in our imaging genetics analysis, a trend-level superiority in cognitive set shifting ability was seen in the healthy carriers of the protective rs10503929 C allele (P = .06; eTable 1 in the Supplement).

Functional Neuroimaging Data
In line with our expectations, we detected a significant activation decrease during reward anticipation in first-degree relatives compared with controls in the money > control contrast in the left (Montreal Neurological Institute coordinates: x = −18, y = 23, z = −6; z = 4.48, FWE-corrected P < .03 for multiple comparisons across the whole brain) and right ventral striatum (x = 12, y = 20, z = −9; z = 4.74, FWE-corrected P < .13 for multiple comparisons across the whole brain [Figure 1B; Figure 2A]). Moreover, the relatives showed a significant decrease in activation in the loss > neutral contrast in the left (x = −12, y = 23, z = 3; z = 4.61, FWE-corrected P < .03 for multiple comparisons across the whole brain) and right ventral striatum (x = 9, y = 20, z = −6; z = 4.86, FWE-corrected P < .006 for multiple comparisons across the whole brain). No significant effects were seen outside the striatum. See eTable 2 in the Supplement for the outcome of other functional contrasts. Supplementary analyses did not provide any evidence for significant effects of head motion or type of first-degree kinship (see eAppendix in the Supplement for details). Across all participants, correlation analysis of striatal β estimates from the money > control contrast and part B of the Trail Making Test performance demonstrated a significant association, with higher striatal activation predicting better (ie, less time needed for) cognitive set shifting (r = −0.23, P = .006).

Effects of NRG1 rs10503929 Genotype
In the healthy control group, we detected a significant striatal activation decrease in homozygotes of the risk-associated T-allele relative to C-allele carriers in the money > control contrast (FWE-corrected P < .03; see Figure 3 and eAppendix in the Supplement for details).

Test-Retest Reliability of Reward Anticipation Contrasts
Our test-retest analysis of an independent sample of healthy controls provided evidence for good robustness of the striatal activation estimates derived from the money > control (with intraclass correlation coefficients of 0.68-0.73) and loss > neutral (with intraclass correlation coefficients of 0.59-0.60) contrasts. In light of the test-retest reliability of fMRI studies (with a mean intraclass correlation coefficient of 0.50) reported in a prior meta-analysis,16 this indicates fairly good reliability of the reward anticipation task in the specific region and functional contrasts where anomalies were detected in the unaffected relatives. Further details of the calculated intraclass correlation coefficients and the spatial distribution of reliable voxels are given in Table 2 and Figure 2D.
patients, and to our own study using the same paradigm, we found that striatal function could be measured reliably and thereby providing initial evidence for a systems-level inter-

tative C allele (Thr) showed a significant increase in striatal 

Discussion

Voxel-Based Morphometry

In our study, we investigated the potential of striatal response during reward anticipation as an intermediate phenotype for schizophrenia. Our key finding is a regionally specific and highly significant attenuation of striatal activation during reward anticipation in unaffected first-degree relatives of schizophrenic patients. Both the directionality and the localization of this result conform well to previous results of drug-naïve, unmedicated, and chronic schizophrenic patients and to our own study using the same paradigm, thereby providing initial evidence for a systems-level intermediate phenotype. Supporting the utility of this phenotype, we found that striatal function could be measured reliably and was not confounded with potential preexisting structural abnormalities in the striatum, differences in task performance, or head motion. We further demonstrate that in the healthy controls, the identified phenotype is affected by a genetic variant in NRG1 that has been linked by meta-analysis to the genetic risk for schizophrenia. Here, the carriers of the protective C allele (Thr) showed a significant increase in striatal activation relative to the carriers of the risk allele (T, Met), a finding that conforms to the directionality seen in both our relatives here and our prior work in manifest schizophrenia.

Two key cognitive processes have been associated with ventral striatal function: salience and reward processing. Current schizophrenia models propose that a dysregulated hyperdopaminergic state linked to altered midbrain-striatal-prefrontal function promotes the development of delusions through an aberrant assignment of salience to unimportant elements of perception. Antipsychotics are expected to “dampen the salience” of these abnormal experiences, thereby advancing the resolution of positive symptoms. In addition, reward-related signaling in the striatum has been linked to negative schizophrenia symptoms such as anhedonia or reduced volition. Consistent with prior data, we observed attenuation of striatal responses in unaffected relatives in contrasts reflecting the anticipation of desirable and unpleasant monetary consequences and loss avoidance. Owing to the purely monetary nature of our paradigm, the present data do not allow for a final conclusion on the kind of cognitive process that drives the observed dysfunction. However, given that in prior work we observed an association between striatal hypofrontality during reward anticipation in the current paradigm and the increased attribution of salience to stimuli in a task devoid of monetary incentives, we propose that the detected striatal hypofrontality may reflect a genetic mechanism involving salience processing, a proposal that is in good agreement with fMRI evidence linking striatal signaling to the salience, and not the valence, of stimuli.

Because our data support a familial component to striatal signaling in schizophrenia, we further investigated the test-retest reliability of this phenotype because our previous reliability work on this paradigm did not examine the contrasts that provided the basis of the striatal signaling deficits detected here. Our analysis proved the robustness of the de-
rived activation estimates, relative to both previously established criteria and the reliability of fMRI studies reported in prior meta-analytic work. These data support future work on this risk phenotype with this paradigm, particularly in the context of pharmacogenetic studies.

Our study also addressed several important potential confounders. Consistent with established standards of imaging genetics, our samples did not exhibit significant differences in any of the assessed demographic variables or clinical ratings. We also carefully controlled for potential between-group differences in task performance, thereby ensuring that the detected neural abnormalities are not reflective of differences in overt behavior. The observed effects were still very strong, which supports the idea that methods capable of surveying the intermediate neural level (eg, fMRI) are sensitive to alterations that may be missed in neurocognitive behavioral tests. Finally, given the inconsistent literature on striatal structure in schizophrenia, we further studied the relationship between striatal volume and activation in our sample. Here, no evidence emerged suggesting that the striatal hypoactivations are rooted in preexisting volumetric differences. Our data therefore support the hypothesis that striatal abnormalities related to schizophrenia risk are primarily functional, consistent with our prior findings indicating that striatal volume abnormalities are not heritable and likely related to the exposure to antipsychotics.

Our study does not support any conclusions on the specific molecular processes that promote the observed blood oxygen level–dependent activation deficits. Even so, it is tempting to speculate that striatal presynaptic disinhibition of dopamine signaling may contribute to the observed functional anomalies. This molecular phenotype is well established in schizophrenia and already present prior to the onset of frank psychosis, and a familial risk component to striatal dopamine synthesis has previously been reported. In our study, striatal activation related to cognitive set shifting, a function that is impaired in manifest schizophrenia, has been linked to striatal presynaptic dopamine synthesis capacity and was observed in our healthy first-degree relatives. Consistent with this, reduced striatal function and cognitive set shifting were seen in the carriers of a likely functional NRG1 risk variant, a gene whose product has been linked to the (mal)development of the dopaminergic system and related hyperdopaminergic states and cognitive deficits in a rodent model of schizophrenia. Although not a direct proof, these data thus support the idea that the identified striatal phenotype reflects facets of schizophrenia susceptibility that are influenced by genetic risk, possibly through alterations in presynaptic dopaminergic function.

On the systems level, our findings are certainly compatible with a primary striatal risk mechanism, as proposed by Kellendonk et al, but may as well be reflective of downstream effects of disturbances in higher-order nodes of the salience system. The striatum and prefrontal cortex are anatomically highly connected, and abnormalities in these structures and their interconnecting pathways have been linked to the development of cognitive symptoms in schizophrenia, which may be mediated by dopamine. Because the prefrontal cortex projects directly to the striatum and ventral tegmentum, a primary dysfunction of the prefrontal cortex or of its glutamatergic efferents could lead to abnormal striatal function and could increase schizophrenia risk. Previous work supports a relationship between striatal dopamine synthesis capacity and prefrontal cortex function in healthy volunteers, prodromal patients, and patients with manifest schizophrenia. Future work with relatives is necessary to study the molecular and connectivity alterations that could contribute to the altered striatal signaling during the reward anticipation that we report here.

Our study has several limitations. Although our samples were relatively large (the detected effects were strong and were not affected by the type of kinship), we included first-degree relatives of several generations, whereas previous experiments in other domains studied siblings only. Also, although all samples were carefully matched, we cannot exclude the potential effect of factors that we might have missed. Specifically, although our data on unaffected relatives and NRG1 risk allele carriers suggest that the phenotype is indeed modulated by genetic rather than just familial influences, we cannot rule out the influences of a shared environment. Furthermore, we did not study index patients with neuroimaging, which would have allowed for more formal measurements of heritability. However, we demonstrate the presence of the same blunted activation phenotype in relatives with the same paradigm that we previously used for antipsychotic-naive first-episode patients.

**Conclusions**

In summary, we provide the first evidence that striatal hypoactivation during reward anticipation is a robust functional intermediate phenotype for schizophrenia that is useful for imaging genetics analyses. Our data provide the basis for further studies on the genetic architecture of more proximal mechanisms that contribute to the observed systems-level abnormalities, such as alterations in dopamine and glutamate neurotransmission and their relationship to higher-order prefrontal functional deficits. In addition, because risk mechanisms are attractive systems-level targets for early treatment...
and prevention, the effect of established and novel treatments on this circuitry should be further investigated and explored for genetic contributions. Finally, our data strongly support the study of the effect of genome-wide–significant genetic variants for schizophrenia on the striatal risk phenotype that we describe.

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