Reduced ventral striatal (vST) activation during reward anticipation is a well-established phenotype in patients with schizophrenia (SZ) (1). Blunted vST activation has been detected in unaffected first-degree relatives of patients with SZ (2) and linked to polygenic risk (PGR) scores for psychotic disorders (3), suggesting a genetic underpinning of this phenotype. While a growing number of studies reported vST activation to be reduced during reward anticipation across severe mental disorders (4–6), e.g., major depressive disorder (MD) (7,8) and bipolar disorder (BP) (9,10), alterations were more compelling and consistent on the psychosis end of the mood-psychosis spectrum (11). vST alterations have been related to positive symptoms (12,13) and linked to reduced differentiation between reward-indicating and neutral cues, a measure of aberrant salience (1,14). While previous functional magnetic resonance imaging (fMRI) studies on reward processing alterations in SZ mostly focused on the vST in isolation, a large body of work has defined dense cortical and subcortical connections of the vST [e.g., (15)] that underpin reward-related behavior. This basic neuroscience information has been linked to the pathophysiology of SZ. Specifically, Grace suggested that impaired hippocampal modulation leads to an abnormal reward (or salience)-related response in the vST (16) through a dopaminergic mechanism (17–19), which was also highlighted as a druggable circuit in a recent review (20). Context-dependent regulation of the vST has been related to parvalbumin-expressing GABAergic (gamma-aminobutyric acidergic) interneurons in the ventral hippocampus (16), which are reduced in mouse models of SZ (21,22) and postmortem studies in SZ (23,24). While the substantial evidence implicating structural and functional hippocampal alterations in SZ (25–31) supports this model, the underlying cellular mechanisms cannot be studied directly in humans in vivo. Functional connectivity during fMRI has recently been used to study altered hippocampal-striatal circuit dysfunctions in subjects at high risk for psychosis (32). However, fMRI studies...
investigating transdiagnostic reward-network dysfunction and its link to altered vST-hippocampus connectivity are missing. To close this gap, we investigated the functional interactions between the vST and the hippocampus during reward processing using a well-established monetary incentive delay task (33,34) in a large, transdiagnostic sample. Thus, this study applies ideas introduced by the Research Domain Criteria initiative (35,36) of the National Institute of Mental Health to characterize core neurobiological and neuropsychological mechanisms across psychiatric conditions. This approach aims to complement current psychiatric nosology by a dimensional conceptualization of core functions (i.e., reward processing alterations) that are investigated along the full range of human behavior from normal to abnormal and across diagnostic entities on multiple observational levels, starting from clinical group comparisons and moving to dimensional (neuro)psychological associations and to more biologically related levels (e.g., genetic). Hence, we investigated the transdiagnostic relevance of functional reward-related vST-hippocampus coupling by exploring whether 1) patients with different diagnostic entities show similar alterations compared with a designated control group and 2) alterations are associated with dimensions of psychopathology across disorders (37). Specifically, we probed the following research questions: First, we tested whether vST-hippocampus connectivity was altered in SZ and whether these alterations were specific for SZ or extend transdiagnostically to mood disorders, such as BP and MD. Second, we explored whether the identified phenotype was associated with dimensions of psychopathology across disorders by specifically focusing on the three major symptom domains in SZ: positive, negative, and cognitive symptoms. To this end, we used the Schizotypal Personality Questionnaire (SPQ) (38), which measures psychotic-like experiences in the general population and has consistently been related to SZ on a genetic, behavioral, and neurobiological level (38), and extracted factors related to positive and negative symptoms as previously described (38,39). With respect to cognitive dysfunction, we specifically focused on memory functioning, given 1) its significance in psychosis (40,41); 2) its pivotal role in hippocampal activation (42), structure (40), and connectivity (43); and 3) the direct link of parvalbumin-expressing interneurons between the hippocampus and nucleus accumbens and memory function in rodents (44). Dimensional analyses were done across all groups, thereby exploring the full range of symptom domains from health to disease (35,36). Third, we tested the familiality of this phenotype by examining whether unaffected first-degree relatives of patients with SZ, BP, and MD (see Table 1). Data were collected in two acquisition waves (1: 2008–2012; 2: 2014–2018) at the Central Institute of Mental Health in Mannheim, the Medical Faculty of the University of Bonn, and the Department of Psychiatry and Psychotherapy at Charité Universitätsmedizin Berlin. All participants provided written informed consent for protocols approved by the institutional ethics review boards at each site. Psychiatric diagnoses were confirmed by trained clinical interviewers using the German version of the Structured Clinical Interview for DSM-IV-TR Axis I disorders (45). To target the potentially confounding effect of medication (46,47), we followed an established procedure for transdiagnostic studies (11,48) and performed partial correlation analyses to show that results were not related to proxies of medication, including chlorpromazine dose equivalents (49) and an index of medication load following the procedure outlined by Hassel et al. (48) (see Supplemental Methods). Psychological assessments included the SPQ (38) to assess individual schizotypy levels and the verbal learning memory test (VLMT) (50) to assess individual memory performance. See Table 1 and Supplemental Methods for details on sample characterization.

Neuroimaging Paradigm, MRI Data Acquisition, and First-Level Analyses

Brain function during reward anticipation was studied using fMRI and a well-established monetary incentive delay paradigm (2,34,51,52) (see Supplemental Methods for details). Functional MRI data were acquired using 3T Siemens Trio scanners (Siemens Medical Systems) in Mannheim, Berlin, and Bonn following the identical scanning protocols as described previously (2,51) and preprocessed using standard routines in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) (see Supplemental Methods for details). Consistent with previous work (2), the contrast of interest reflects the anticipation of monetary salient (win and loss avoidance) cues as compared with control (neutral and verbal) cues (see Supplemental Methods). Functional connectivity was assessed using a seeded connectivity approach with individual general linear models for the first eigenvariate of the time series extracted from the right vST (see Supplemental Methods).

Observation Level 1: Diagnostic Group Differences in Functional vST-Hippocampus Connectivity

We conducted between-group analyses on individual contrast images for functional connectivity using full-factorial designs (for the activation analyses of vST reactivity, see Supplemental Methods). We included diagnostic group (HC, SZPatient, BPPatient, MPatient) as between-subject factor together with age, sex, site, acquisition wave, and head motion (mean framewise displacement) (53) (see Table 1) as covariates of no interest (see Supplemental Methods). In line with our hypothesis of aberrant vST-hippocampus connectivity (16), significance was defined a priori as \( p < .05, \) familywise error (FWE) corrected at the peak level within a well-established hippocampus mask extracted from the automated anatomical labeling atlas (54). In case of a significant main effect of group, \( F \) tests were followed up by post hoc \( t \) tests where the three patient groups were compared with HC subjects and corrected for the number of group comparisons (i.e., HC vs. SZ, BP, and MD (see Table 1). Data were collected in two acquisition waves (1: 2008–2012; 2: 2014–2018) at the Central Institute of Mental Health in Mannheim, the Medical Faculty of the University of Bonn, and the Department of Psychiatry and Psychotherapy at Charité Universitätsmedizin Berlin. All participants provided written informed consent for protocols approved by the institutional ethics review boards at each site. Psychiatric diagnoses were confirmed by trained clinical interviewers using the German version of the Structured Clinical Interview for DSM-IV-TR Axis I disorders (45). To target the potentially confounding effect of medication (46,47), we followed an established procedure for transdiagnostic studies (11,48) and performed partial correlation analyses to show that results were not related to proxies of medication, including chlorpromazine dose equivalents (49) and an index of medication load following the procedure outlined by Hassel et al. (48) (see Supplemental Methods). Psychological assessments included the SPQ (38) to assess individual schizotypy levels and the verbal learning memory test (VLMT) (50) to assess individual memory performance. See Table 1 and Supplemental Methods for details on sample characterization.

METHODS AND MATERIALS

Sample

We assessed 728 participants, including healthy individuals, unaffected first-degree relatives, and affected patients with SZ, BP, and MD (see Table 1). Data were collected in two acquisition waves (1: 2008–2012; 2: 2014–2018) at the Central Institute of Mental Health in Mannheim, the Medical Faculty of the University of Bonn, and the Department of Psychiatry and Psychotherapy at Charité Universitätsmedizin Berlin. All participants provided written informed consent for protocols approved by the institutional ethics review boards at each site. Psychiatric diagnoses were confirmed by trained clinical interviewers using the German version of the Structured Clinical Interview for DSM-IV-TR Axis I disorders (45). To target the potentially confounding effect of medication (46,47), we followed an established procedure for transdiagnostic studies (11,48) and performed partial correlation analyses to show that results were not related to proxies of medication, including chlorpromazine dose equivalents (49) and an index of medication load following the procedure outlined by Hassel et al. (48) (see Supplemental Methods). Psychological assessments included the SPQ (38) to assess individual schizotypy levels and the verbal learning memory test (VLMT) (50) to assess individual memory performance. See Table 1 and Supplemental Methods for details on sample characterization.

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Correlates of vST-Hippocampus Coupling and Psychosis

Table 1. Sample Description

| Group | HC | SZPat | BPPat | MDPat | SZRel | BPRel | MDRel |
|-------|----|-------|-------|-------|-------|-------|-------|
| n     | 396| 46    | 45    | 60    | 46    | 50    | 85    |
| Site | Bonn | 130 | –     | –     | –     | 14    | 28    | 32    |
|     | Mannheim | 141 | 25    | 20    | 30    | 17    | 10    | 27    |
|     | Berlin | 125 | 21    | 25    | 30    | 15    | 12    | 26    |
| Age, Years | 32.09 (10.2) | 33.70 (9.9) | 33.04 (9.3) | 34.30 (11.7) | 31.91 (12.5) | 28.80 (9.2) | 27.46 (8.6) |
| Sex, Female/Male | 207/189 | 16/30 | 25/20 | 41/19 | 30/16 | 29/21 | 53/32 |
| Framewise Displacement | 0.19 (0.07) | 0.19 (0.08) | 0.19 (0.08) | 0.18 (0.06) | 0.24 (0.08) | 0.20 (0.07) | 0.21 (0.08) |
| Medication Value, Mannheim Only | – | 2.50 (2.5) | 2.77 (1.3) | 1.75 (1.4) | – | – | – |
| CPZ-e, Mannheim Only | – | 390.75 (337.2) | 142.00 (206.5) | 19.40 (49.8) | – | – | – |
| CGI | – | 4.24 (1.1) | 3.72 (1.0) | 3.93 (1.2) | – | – | – |
| VLMT | 60.72 (7.7) | 52.54 (10.0) | 58.49 (9.1) | 60.17 (6.4) | 58.33 (7.0) | 59.37 (9.7) | 60.75 (7.9) |
| SPQpositive | –0.15 (0.8) | 1.35 (1.5) | 0.77 (1.3) | –0.09 (1.0) | –0.19 (0.8) | –0.25 (0.6) | –0.08 (0.8) |
| SPQnegative | –0.29 (0.7) | 0.55 (1.0) | 0.93 (1.3) | 1.08 (1.3) | –0.17 (0.8) | –0.06 (0.8) | –0.07 (0.8) |
| PANSS, Total | – | 52.43 (14.4) | 41.84 (10.4) | 44.65 (8.4) | – | – | – |
| PANSS, Positive | – | 12.09 (4.4) | 8.82 (2.4) | 8.43 (2.4) | – | – | – |
| PANSS, Negative | – | 13.80 (5.8) | 10.21 (4.2) | 10.23 (3.8) | – | – | – |
| HAM-D | – | 6.64 (3.9) | 7.47 (6.0) | 13.27 (6.5) | – | – | – |
| YMRS | – | 0.78 (1.3) | 3.96 (5.0) | 0.59 (1.1) | – | – | – |

Values are presented as mean (SD) or n and statistical between-group comparisons. For nonparametric test, we used the Kruskal-Wallis test; for parametric tests, analysis of variance was computed. The CGI scale ranges from 1 (no mental disorder) to 7 (extreme mental disorder). SPQpositive and SPQnegative scores were extracted from a principal component analysis using the nine subscores of the SPQ (mean [SD] = 1 [0]).

HC vs. BP, HC vs. MD) using the Bonferroni-Holm correction. Exploratory between-patient comparisons are reported in the Supplemental Results. To probe the transdiagnostic relevance of the identified phenotype for psychosis, we additionally separated patients based on reported current positive symptoms in the positive subscale of the Positive and Negative Syndrome Scale (55) into no (n = 106) and moderate (n = 40) psychosis groups and tested whether the extracted vST-hippocampus coupling estimates differed between the two patient populations (see Supplemental Methods).

Observation Level 2: (Neuro)psychological Correlates of vST-Hippocampus Coupling

To explore underlying brain-behavior relationships, we tested the association between vST-hippocampus coupling and traits related to positive, negative, and cognitive symptoms. Factors for positive and negative symptoms were extracted from a principal component analysis implemented in SPSS (version 27; IBM Corp.) using the nine subscores of the SPQ (38) (see Supplemental Methods). As expected (39), this revealed 2 uncorrelated factors (SPQpositive and SPQnegative) covering aspects of negative (e.g., blunted affect, lack of close friends) and positive (e.g., magical thinking, ideas of reference) symptoms (see Table 1). The validity of the SPQpositive and SPQnegative factors was confirmed by their significant association with the respective subscales of the Positive and Negative Syndrome Scale (56) in patients (see Supplemental Methods). For the association between vST-hippocampus coupling and cognitive functions related to memory, we used the VLMT (50) to assess verbal short-term memory performance.

In a first step, we included individual SPQpositive, SPQnegative, and VLMT levels as covariates of interest in separate one-sample t tests on vST brain connectivity along with the above-named covariates of no interest. In a second step, we included all 3 variables into one unified model to investigate whether associations are explained by shared variance between the variables. The same statistical thresholds and a Bonferroni-Holm correction within the second analysis step were applied as outlined above. In a last step and only in case of significant associations, we tested whether individual SPQpositive, SPQnegative, or VLMT levels were predictive of vST-hippocampus coupling beyond the effect of diagnostic category. To this end, and in line with our previous study (11), we converted the variable coding for the four diagnostic groups into three dummy variables using HC as the reference category. We extracted peak voxel estimates within significant vST-hippocampus clusters and used these measures as dependent variables in post hoc multiple regression analyses, including the dummy variables together with the dimensional measures and our covariates of no interest as independent variables.
Ventral Striatal–Hippocampus Coupling and Psychosis

Observation Level 3: Familiality and Genetic Underpinning of vST-Hippocampus Coupling

Familiality: In line with the between-group analyses on observational level 1, individual seeded connectivity estimates were subjected to a full-factorial design including unaffected first-degree relatives of patients with SZ, BP, and MD together with HC subjects (matched for age and sex) as between-subject factors along with the above-named covariates of no interest. The same statistical thresholds and a Bonferroni-Holm correction for the three included group comparisons were applied as outlined above.

PGR score calculation: To further validate our intermediate phenotype, we used a PGR approach in a subset of HC subjects ($n = 295$, mean age: $32.1 \pm 9.8$ years, 154 males). For the preprocessing of genetic data, see Supplemental Methods. The SZ PGR score was computed using Psychiatric Genomics Consortium summary statistics taken from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (57) following the method developed by Purcell and colleagues (58) and using the PRSice software (59). Briefly, PGR scores were calculated by summing schizophrenia-associated alleles, weighted by the natural log of the odds ratio. To ensure that single nucleotide polymorphisms were not in high linkage disequilibrium with one another, clumping was applied on the genotype data using a linkage disequilibrium $D^2$ threshold of 0.1 and a genomic distance threshold of 250 kb. PGR scores were constructed based on genome-wide significant variants ($p = 5 \times 10^{-8}$). Polygenic risk scores in high versus low vST-hippocampus couplers: We used a median split to group HC subjects according to their vST-hippocampus connectivity in low ($n = 148$) and high ($n = 147$) couplers. We subsequently performed analysis of covariance analyses including coupling group as a covariate of interest and age, sex, site, mean framewise displacement, acquisition wave, and the first 10 principal components extracted from genome-wide association data as covariates of no interest.

RESULTS

Observation Level 1: Diagnostic Group Differences in Functional vST-Hippocampus Connectivity

Consistent with our previous study (11), vST activation was reduced in patients with SZ and BP but not MD (see Supplemental Results and Figure S4 for details). In line with the dopamine dysregulation model in SZ (16), we detected group differences in vST-seeded connectivity with the left hippocampus during reward processing (main effect of group: $p_{FWE} < .012$, small-volume corrected [SVC]) (Figure 1 and Table 2). Post hoc tests indicated that compared with HC subjects, vST-hippocampus coupling was reduced in patients with SZ ($p_{FWE} = .025$, SVC) and BP ($p_{FWE} = .001$, SVC) but not MD (see Table 2). In addition, patients with moderate positive symptoms showed lower vST-hippocampus coupling than patients with no positive symptoms ($F_{1,140} = 5.715$, $p = .018$) (Figure S6). In addition, vST-hippocampus connectivity was not modulated by medication values (see Table S6).

Observation Level 2: (Neuro)psychological Correlates of vST-Hippocampus Coupling

Higher $SPQ_{positive}$ values related to lower vST-seeded connectivity with the bilateral hippocampus across diagnostic groups (left hippocampus: $p_{FWE} = .002$, SVC; right hippocampus: $p_{FWE} = .028$, SVC) (see Figure 2) whereas no significant results emerged for $SPQ_{negative}$ values ($p_{FWE} > .05$). Moreover, memory performance was positively associated with vST connectivity in the left hippocampus ($p_{FWE} = .006$, SVC) (see Figure 2). When including all variables in a unified model, the negative association with $SPQ_{positive}$ remained significant ($p_{FWE} < .010$, SVC) (see Table 2) while the association with the VLMT dropped below the Bonferroni-Holm corrected significance threshold ($p_{FWE} < .029$, SVC) (see Table 2), suggesting a stronger relationship between the vST-hippocampus connectivity and positive symptomatology that is not explained by cognitive deficits. Further, post hoc multiple regression analyses revealed that dimensional factors predicted vST-hippocampus coupling beyond the effect of diagnostic group for $SPQ_{positive}$ (right hippocampus: $\beta = -0.118$, $p = .012$; left hippocampus: $\beta = -0.130$, $p = .006$) and memory performance (left hippocampus: $\beta = 0.142$, $p = .002$). See Supplemental Results for more detailed information.

Observation Level 3: Familiality and Genetic Underpinning of vST-Hippocampus Coupling

Familiality. vST activation was reduced in relatives with SZ but not BP or MD (2) (see also Supplemental Results and Figure S4 for details). Further, we detected group differences in vST-seeded connectivity with the left hippocampus during reward processing (main effect of group: $p_{FWE} < .05$, SVC).

Figure 1. Observation level 1—diagnostic group differences in functional ventral striatal (vST)-hippocampus connectivity. Left: depiction of the main effect of group in vST-hippocampus connectivity during reward processing. For illustration purposes, a significance threshold of $p_{corrected} < .005$ was applied. Right: plotted contrast estimates (mean, SE) of the peak voxel in the left hippocampus. *Significance between patient group compared with healthy control (HC) group. BP, bipolar disorder; con, connectivity; MD, major depressive disorder; Pat, patients; SZ, schizophrenia.
Table 2. vST–Hippocampus Coupling

| Observational Level | Effect/Region | k  | x  | y  | z  | F/t | pFWE | pFWE |
|---------------------|---------------|----|----|----|----|-----|------|------|
| Observational Level 1: Diagnostic Group Differences | Main effect of group | | | | | | | |
| Hippocampus L | 36 | -18 | -25 | -10 | 7.54 | .050 | .012 |
| Post hoc group comparisons | | | | | | | | |
| HC > BP Pat | | | | | | | | |
| Hippocampus L | 41 | -21 | -22 | -16 | 4.16 | .017 | .001 |
| Hippocampus R | 15 | 36 | -22 | -13 | 3.51 | .017 | .015 |
| HC > SZ Pat | | | | | | | | |
| Hippocampus L | 10 | -33 | -28 | -10 | 3.35 | .025 | .025 |
| Observational Level 2: (Neuro)Psychological Correlates | SPQpositive | | | | | | | |
| Hippocampus L | 43 | -24 | -34 | -7 | 3.61 | .017 | .010 |
| VLMT | | | | | | | | |
| Hippocampus L | 18 | -30 | -28 | -10 | 3.29 | .025 | .029 |
| Observational Level 3: Familiality and Genetic Underpinning | Main effect of group | | | | | | | |
| Hippocampus L | 2 | -24 | -40 | 2 | 6.28 | .050 | .024 |
| Post hoc group comparisons | | | | | | | | |
| HC > SZ Rel | | | | | | | | |
| Hippocampus L | 3 | -24 | -40 | 2 | 3.46 | .017 | .017 |
| Hippocampus L | 8 | -21 | -22 | -19 | 3.31 | .017 | .027 |
| HC > BP Rel | | | | | | | | |
| Hippocampus L | 2 | -24 | -40 | 2 | 3.33 | .025 | .026 |

Cluster extent k is given at p < .05, familywise error corrected (FWE) for multiple comparisons within the hippocampus region of interest using small-volume correction. pFWE indicates the p threshold for an additional Bonferroni–Holm correction for the number of post hoc group comparisons (observational levels 1 and 3) and the number of included dimensional measures (observational level 2). x, y, and z coordinates (Montreal Neurological Institute) and statistical information refer to the peak voxel in the corresponding cluster.

BP, bipolar disorder; HC, healthy control; L, left; Pat, patient; R, right; Rel, relative; SPQ, Schizotypal Personality Questionnaire (38); SZ, schizophrenia; VLMT, verbal learning memory test (50); vST, ventral striatum.

(Figure 3 and Table 2). Post hoc tests indicated that compared with HC subjects, vST-hippocampus coupling was reduced in SZ relatives (pFWE < .017, SVC) and BP relatives (trend-level when adjusting for the number of post hoc comparisons; pFWE < .026, SVC) (see Table 2).

PGR for SZ. As expected, HC subjects with a low vST-hippocampus coupling had higher PGR scores for SZ than subjects with a high coupling (\(F_{1,277} = 4.467, p = .035\)) (Figure S7).

DISCUSSION

To our knowledge, we provide the first evidence that vST-hippocampus coupling during reward processing is an endophenotype for psychotic disorders, supporting the model outlined by Grace (16). Our data indicate that vST-hippocampus coupling is 1) specific for psychotic disorders, 2) associated transdiagnostically with measures of positive symptoms and memory performance, and 3) familial and relates to the genetic risk for SZ.

Observation Level 1: Diagnostic Group Differences in Functional vST–Hippocampus Connectivity

As a proof of concept and in line with our previous reports (11), we show blunted vST activation during reward anticipation in patients with SZ and BP, but not MD, providing further evidence of the transdiagnostic relevance of this intermediate phenotype for psychosis (5). Prominent mechanistic theories have linked blunted vST activation to striatal dopamine release (60–62) and psychotic symptomatology (63) via a deficient modulation by the hippocampus (16,27). While our systems-level measure of coupling cannot define underlying cellular processes, our findings align with animal models (21,64,65) and postmortem studies (29), suggesting that (reward-related) alterations in the vST and associated behaviors are related to the functioning of the hippocampus through a dopaminergic mechanism. The disrupted hippocampal rhythmicity observed in SZ (66,67), which has been related to the reduced number of inhibitory parvalbumin-expressing interneurons (16), might reduce the hippocampal modulation of vST oscillatory activity, thereby leading to the investigated blunted vST-hippocampus coupling. Consistent with this, a recent review highlights the pivotal role of the hippocampal-vST-ventral tegmental area axis for aberrant salience processing in SZ and its potential for the development of novel therapeutic treatments (20). Our finding extends to the previous evidence provided by imaging research in patients with SZ showing structural and functional alterations in the hippocampus (25,26,29) and the striatum (1,68) and the functional connectivity between the two regions (32,69,70). While future studies have to further unravel the link between cellular abnormalities in the hippocampus, especially a loss of parvalbumin-expressing interneurons, and functional imaging phenotypes such as vST-hippocampus coupling, our results highlight the importance
of vST-hippocampus coupling in reward processing (71), specifically in psychosis.

**Observation Level 2: Dimensional Association of vST-Hippocampus Coupling and Symptom Domains for SZ**

We further show associations between functional vST-hippocampus coupling and psychosis-relevant traits related to positive and cognitive but not negative symptoms across diagnoses, thereby indicating a dimensional impact of the introduced phenotype on the symptomatology of SZ. Specifically, higher SPQ positive scores related to lower vST-hippocampus coupling. This is in line with the theoretical framework outlined above, which suggests that deficient hippocampal modulation of the vST leads to positive symptoms in SZ (16). Further evidence showed that alterations in hippocampal functioning relate to psychosis level (30) and positive symptoms (72). We extend these findings by showing that the functional vST-hippocampus coupling is related transdiagnostically to clinically relevant trait measures related to SZ.

In addition to positive symptoms, reduced functional vST-hippocampus coupling was also linked to impaired verbal memory performance. This aligns with previous findings implicating the relevance of memory performance for both psychosis and hippocampal functioning (40–43). Specifically, memory impairment was related to psychotic disorders (73), especially for memory processes that depended on the hippocampus (74–76). Mechanistically, parvalbumin-expressing
interneurons in the hippocampus have been associated with network plasticity and long-term memory consolidation (77). Accumulating evidence further points to a tight interaction between networks implicated in memory and reward processing [e.g., (71,78,79)]. Specifically, reciprocal connections between the hippocampus and the mesolimbic reward system are thought to strengthen memory encoding based on the valence of a stimulus (80). Recently, a direct connection from the hippocampus to the nucleus accumbens through parvalbumin interneurons was shown to enable place reward memories in mice (44). Overall, these findings lend further support to the functional and clinical relevance of vST-hippocampus coupling observed in this study.

While our diagnosis-related analyses on observational level 1 link alterations in vST-hippocampus coupling to psychotic disorder categories, our dimensional analyses show that brain-behavior relationships extend across nosological boundaries. Thus, a reduction in vST-hippocampus coupling links to positive symptoms and cognitive dysfunctions even when they do not reach the threshold required for a categorical diagnosis of SZ or BD, thereby highlighting the sensitivity of a dimensional approach (35,36).

**Observation Level 3: Familiality and Genetic Underpinning of vST-Hippocampus Coupling**

We further found that vST-hippocampus coupling could be an intermediate phenotype for psychosis, given the observed reductions in unaffected first-degree relatives of patients with SZ and trend-level BP. This suggests that a low functional vST-hippocampus coupling could be related to the genetic risk for psychosis. This notion is supported by our observation that reduced coupling was related to higher PGR scores for SZ in our HC sample. This extends to previous studies associating genetic risk for SZ to structural and functional alterations in the hippocampus (29,72,81) and suggests that the functional vST-hippocampus coupling represents a heritable intermediate phenotype for psychosis.

**Strengths and Limitations**

First, as stated, we cannot measure underlying biochemical or cellular processes using blood oxygen level–dependent fMRI. This also means that we cannot prove that the observed coupling reduction is inhibitory. Future studies are warranted to investigate the mechanisms linking structural, neurochemical, oscillatory, and functional alterations in the hippocampus to reward-network dysfunctions. In addition, this study faced several challenges common to clinical imaging. Throughout analyses, we controlled for basic demographic variables in which groups were naturally heterogeneous (e.g., higher number of females in the HC group and higher number of males in the SZ group). With respect to medication, we carried out additional analyses in a subset of patients that showed that medication level was not related to vST-hippocampus coupling. However, larger-scale studies that allow for the comparison of medicated and unmedicated patients, ideally within and across diagnostic groups, are warranted to rule out the possibility that medication influenced our results. This is especially true because information on detailed medication dosage was only available for a subset of patients. With respect to imaging quality, we carefully balanced our sample for several head motion and signal-quality parameters (see Supplemental Methods) and included a proxy for head motion (mean framewise displacement) as a covariate across all analyses. However, we acknowledge that we cannot rule out the possibility of unaddressed influences of some of these confounders. Overall, effect sizes of dimensional brain-behavior relationships were rather small but in the range of other dimensional transdiagnostic reward-related fMRI studies [e.g., (5,11)]. In fact, true correlations tend to be rather small, especially in larger samples (83). In addition, we controlled for multiple comparisons using 1) stringent FWE correction for the imaging analyses and 2) Bonferroni-Holm correction for the number of tests within each observational level, while restricting the number of post hoc tests by only comparing patient groups against HC subjects for which we explicitly hypothesized between-group differences (and reporting exploratory between-patient comparisons in the Supplemental Results). Although the multiplicity of tests within our multilevel approach increases the risk for false positive findings, we believe that the diversity of included measures across different SZ-associated observational level is at the heart of the Research Domain Criteria approach (35,36) and will inform the replication and further characterization of the introduced intermediate phenotype in future larger-scale studies. Thereby, the inclusion of even more diagnostic groups known to show alterations in reward processing (e.g., substance use disorder) as well as larger samples, which ideally are matched on demographic characteristics, and longitudinal investigations over the course of the disorders would have been desirable but were beyond the feasible scope of this study. However, despite all methodological challenges, the investigation of different patient and first-degree relative groups in the same study comes with the valuable advantage of ruling out methodological differences when comparing results between diagnostic entities.

**Conclusions**

In summary, we provide evidence that vST-hippocampus coupling during reward processing is an endophenotype for psychotic disorders and relates to dimensional, behaviorally meaningful measures of positive symptoms and memory performance across the psychiatric spectrum. Besides informing current disorder-specific mechanistic theories of vST dysfunction, our results can inform the development of pharmacological and therapeutic interventions, e.g., by trainings targeting vST-hippocampus connectivity through neurofeedback or by indirect therapeutic interventions that enhance cognitive control abilities in SZ.

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