Received: 15 September 2020 | Revised: 5 July 2021 | Accepted: 21 July 2021
DOI: 10.1002/hbm.25613

RESEARCH ARTICLE

WILEY

Task-related neural mechanisms of persecutory ideation in schizophrenia and community monozygotic twin-pairs

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Funding information
National Association Research in Schizophrenia and Depression/Brain Behavior Research Foundation's Francoeur Investigator Award; National Institute of Mental Health, Grant/Award Numbers: F31MH102997, R21MH112918

Abstract

Perceptions of spiteful behavior are common, distinct from rational fear, and may undergird persecutory ideation. To test this hypothesis and investigate neural mechanisms of persecutory ideation, we employed a novel economic social decision-making task, the Minnesota Trust Game (MTG), during neuroimaging in patients with schizophrenia ($n = 30$) and community monozygotic (MZ) twins ($n = 38$; 19 pairs). We examined distinct forms of mistrust, task-related brain activation and connectivity, and investigated relationships with persecutory ideation. We tested whether co-twin discordance on these measurements was correlated to reflect a common source of underlying variance. Across samples persecutory ideation was associated with reduced trust only during the suspiciousness condition, which assessed spite sensitivity given partners had no monetary incentive to betray. Task-based *activation* contrasts for specific forms of mistrust were limited and unrelated to persecutory ideation. However, task-based *connectivity* contrasts revealed a dorsal cingulate anterior insula network sensitive to suspicious mistrust, a left frontal–parietal (lF-P) network sensitive to rational mistrust, and a ventral medial/orbital prefrontal (vmPFC/OFC) network that was sensitive to the difference between these forms of mistrust (all $p < .005$). Higher persecutory ideation was predicted only by reduced connectivity between the vmPFC/OFC and lF-P networks ($p = .005$), which was only observed when the intentions of the other player were relevant. Moreover, co-twin differences in persecutory ideation predicted co-twin differences in both spite sensitivity and in vmPFC/OFC–lF-P connectivity. This work found that interconnectivity may be particularly important to the complex neurobiology underlying persecutory ideation, and that unique environmental variance causally linked persecutory ideation, decision-making, and brain connectivity.

KEYWORDS
decision-making, functional connectivity, monozygotic twins, persecutory ideation, schizophrenia, trust

1 | INTRODUCTION

Persecutory delusions are fixed false beliefs that someone will harm you. They are the most common form of delusions (Appelbaum, Robbins, & Roth, 1999), are associated with negative affect (Bentall et al., 2009), violence (Coid et al., 2013), and treatment noncompliance (Moritz, Hunsche, & Lincoln, 2014). Still, little is known about their underlying neural mechanisms or etiology, which limits the development of specific interventions. Importantly, persecutory delusions appear at one extreme of a dimension of *persecutory ideation*, with transient suspicions in the middle, and beliefs in others' benevolence at the opposing extreme (Freeman & Garety, 2014). To advance understanding of this dimensional phenomena, the current study examined task-based brain activation and functional connectivity to probe the neural mechanisms involved in persecutory ideation in schizophrenia patients and community members who were monozygotic twins.

Persecutory ideation is affectively charged with threat, impacts social interactions and important life events, and may involve dysfunctional perception or reasoning (Corlett, Taylor, Wang, Fletcher, & Krystal, 2010; Wible, 2012). While studies of resting-state brain functioning or brain structure can be used to examine associations with persecutory ideation (Decross et al., 2019; Kuroki et al., 2006; Kwon et al., 1999; Lui et al., 2009; Zhu et al., 2017), these studies are unable to distinguish the cognitive processes underlying the association. Importantly, the identification of process-specific brain functioning related to particular symptoms could facilitate development of targeted interventions such as brain stimulation or cognitive training. Toward this goal, carefully designed paradigms can be employed during neuroimaging to elicit brain functioning involved in cognitive processes hypothesized to be relevant to target symptoms. However, few studies have specifically examined brain functioning related to persecutory ideation with well-controlled paradigms in clinical samples with psychosis. Due to the content of persecutory ideation, such studies have tended to focus on basic social or threat processes or social decision-making.

Theory of mind studies, which assess understanding of others' mental states, rarely show neural patterns related to persecutory ideation. This may be due to lack of threat, lack of first-person perspectives, or psychometric confounds such as when differences in the measures of interest show relationships with nonspecific factors such as age, general intelligence, motivation, or speed (Corcoran et al., 2011). More successfully, studies of explicit threat (e.g., rating persons' trustworthiness) and implicit threat (e.g., rating irrelevant attributes) using faces expressing negative affect report abnormal activations associated with persecutory ideation in medial temporal lobe, lateral temporal gyri, insula, medial prefrontal cortex (PFC), and lateral PFC (Hooker et al., 2014; Phillips et al., 1999; Pinkham et al., 2015; Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2008a; Pinkham, Hopfinger, Ruparel, & Penn, 2008b; Russell et al., 2007; Williams et al., 2004, 2007). However, these threat paradigms did not differentiate persecution from general anxiety. Another approach has used game theory and social decision-making with financial stakes, such as the prisoner's dilemma, trust, and ultimatum games (Rilling & Sanfey, 2011). While these paradigms reveal patients make more erratic and fewer strategic choices (Billeke & Aboitiz, 2013; Robson, Repetto, Gountouna, & Nicodemus, 2020) such performance is difficult to distinguish from generalized deficits, which are broad behavioral impairments not isolated to one cognitive process or condition, that could be a consequence of insufficient understanding of, or engagement with, the task (MacDonald, 2015). Perhaps for these reasons, specific associations of brain functioning with persecutory ideation are still limited.

The Minnesota Trust Game (MTG) (Johnson, Rustichini, & MacDonald, 2009) is a noniterative variant of the Trust Game (Berg, Dickhaut, & McCabe, 1995) that addresses these drawbacks by recognizing mistrust can occur for several reasons. Fearing someone will harm you despite having no other incentive describes *spite sensitivity*, which is distinct from believing you will be harmed by another's selfishness, and may therefore undergird persecutory ideation. By parametrically manipulating risk and incentives, the MTG dissociates *suspiciousness* (fear of partner being spiteful) which is a construct relevant to persecution, from *rational mistrust* (fear of partner being selfish) and *risk aversion* (fear of loss due to chance) which are two constructs not particularly related to this symptom. Given that MTG provides no feedback or information about the other player, the partner conditions assess pre-existing beliefs or biases about other people, which distinguishes it from other social decision-making tasks that involve learning. An initial study in a nonpatient sample confirmed high persecutory ideation was associated with reduced trust only in the suspiciousness condition; in comparison, high harm avoidance anxiety was associated with reduced trust only in the risk aversion condition (Johnson et al., 2009). These results, the specificity of the MTG to distinguish spite sensitivity from other processes, and particularly the potential to contrast processes involved in spite sensitivity and rational mistrust, suggest the MTG would be useful for investigating specific neural mechanisms underlying persecutory ideation in schizophrenia.

Previous threat studies examining persecutory ideation, as described above, implicate temporal and frontal brain functioning. These align with two models of delusions implicating (a) abnormalities in the representations of self and others that involve temporal–parietal and hippocampal regions (Wible, 2012), and (b) abnormalities in prediction error and learning that involve frontal and striatal/midbrain regions (Corlett et al., 2010). Given multiple implicated regions and cognitive processes, standard activation analyses may be inadequate for identifying brain functions most relevant to spite sensitivity mistrust and persecutory ideation. Investigations of network connectivity may also be necessary that include the interactions between networks during the task in order to capture subtle changes over time. For this reason our study employed standard activation analyses as well as data-driven connectivity methods with established reliability and reproducibility (Poppe et al., 2013; Wisner, Atluri, Lim, & MacDonald, 2013) that have also shown sensitivity to task (Moodie, Wisner, & MacDonald, 2014; Poppe, Carter, Minzenberg, & MacDonald, 2015), familiality (Moodie et al., 2014;

Poppe et al., 2015), and psychopathology (Wisner, Patzelt, Lim, & MacDonald, 2013b). These data-driven methods assess how network *coherence*, which is the degree voxels within the network show similar fluctuations in the hemodynamic response, is impacted by changing task demands. These methods also quantify the strength of *connectivity* between networks that interact to influence behavior. In the current study, which is the first neuroimaging investigation of the MTG, the analyses proceeded at three levels. First, the basic brain functioning elicited by overall task demands was examined to initially validate the MTG imaging paradigm. Second, we examined a priori contrasts of brain functioning during specific decisions to test our key hypotheses regarding spite sensitivity and rational mistrust in schizophrenia. Only significant findings from the a priori contrast analyses were then passed forward for individual differences testing using persecutory ideation. Taken together, this study uses complementary neuroimaging methods to examine whether localized activation or network connectivity best characterize brain functioning involved in distinct forms of mistrust, and how such brain functioning may be associated with persecutory ideation.

One of the shortcomings of such neuroimaging studies is that they employ inherently correlational methods, which limits the ability to examine causal or etiological variance contributing to the findings. However, twin methods can be combined with neuroimaging to probe etiological sources, due to the enriched characteristics of twin samples. While clinical psychosis is strongly associated with both genetic and environmental factors (MacDonald & Schulz, 2009), current evidence suggests persecutory ideation itself is more influenced by the environment relative to other symptoms of psychosis (Cardno, Sham, Murray, & McGuffin, 2001), with substantial environmental influence also associated with persecutory ideation in community twin samples (Zavos et al., 2014). To investigate the role of unique environmental variance in the neural mechanisms underlying persecutory ideation we extended our study to also include a sample of community monozygotic (MZ) twins using a *co-twin control* design (also referred to as a *discordant twin pair* design) (McGue, Osler, & Christensen, 2010). This design allows examining whether exposure to unique environmental factors (that are nonshared within twin pairs) influences both neuroimaging and behavioral phenotypes, while controlling for the shared genetic and shared environmental factors by testing the *discordance* within the MZ twin pairs (hereafter referred to as co-twin discordance or co-twin differences). The method applied here consequently tests for evidence of *unique environmental causes* that links variance in brain functioning to variance in persecutory ideation and decision-making.

The current study therefore employed the MTG and task-based functional neuroimaging methods to test hypotheses that: (a) elevated persecutory ideation would be specifically associated with spite sensitivity mistrust in schizophrenia patients and twins; (b) brain functioning associated with spite sensitivity would be distinct from that associated with other forms of mistrust; (c) variation in brain functioning associated with spite sensitivity would predict variation in persecutory ideation; and (d) that co-twin discordance on these brain and behavior measures would be correlated, reflecting a common source of unique environmental variance. Importantly, the current study aimed to isolate a particular symptom of mental illness, deconvolved from the heterogeneity of the disorder itself, to identify potential intervention targets for the symptom. Therefore, we first examined brain functioning linked to persecutory ideation in patients with schizophrenia to validate the hypothesized associations in a sample with relevant clinical variance of the symptom and to which the paradigm was targeted. Those findings then guided investigations in the community twins, where the co-twin control design was used to test whether the same measures of brain functioning were associated with subclinical persecutory ideation using twin discordance to examine the role of environmental influences on both characteristics.

2 | MATERIALS AND METHODS

2.1 | Participants and assessment

The *patient sample* included 38 individuals with schizophrenia or schizoaffective disorder. Eight patients were removed due to incomplete data, scanning difficulties, or excessive movement during the scan (see Appendix S1). The final sample included 30 patients [mean age of 32.7 (*SD* 7.5, range 18–46); 69% male; 81% Caucasian]. Persecutory ideation in patients was measured with the suspiciousness rating from the Brief Psychiatric Rating Scale-Extended Version (BPRS) (Lukoff, Liberman, & Nuechterlein, 1986). The following are the descriptive statistics for this critical item in this sample: mean = 3.77, *SD* = 2.03, and range = 1–7. While patients vary widely in severity of persecutory ideation, our individual differences approach takes advantage of this by investigating how variance in persecutory ideation related to variance in both trusting behaviors and brain functioning. Accordingly, we focused on persecutory ideation, not schizophrenia as a whole. In this way patients without persecutory ideation can be thought of as closely-matched controls for patients with persecutory ideation, in that the subjects had more in common with each other (e.g., illness related factors such as medication) than patients would have with healthy volunteers. To this end, we confirmed that persecutory ideation in patients was unrelated to age ($r = .03$, $p > .5$), premorbid intelligence using the WRAT ($r = -.19$, $p > .3$) and sex ($t = 1.29$, $p > .1$), which suggests analyses were not confounded by basic characteristics.

A community *twin sample* was also collected using the MTG in order to extend the current study's generalization and to examine the impact of nonshared environment on brain and behavior. The twin sample included MZ twin pairs previously recruited by the Minnesota Twin Study (Kramer, Patrick, Krueger, & Gasperi, 2012), an epidemiological study during which participants completed the Multidimensional Personality Questionnaire (MPQ) (Patrick, Curtin, & Tellegen, 2002). Twins were re-contacted for the current study based on their MPQ Alienation scale, the community-level measure of persecutory ideation examined in this sample. Recruitment prioritized a sample with a distributed degree of co-twin discordance on this measure. Once enrolled, participants completed a second MPQ for current analyses. The sample included 52 twins (26 pairs). Seven pairs were removed due to incomplete data, scanning difficulties, or excessive movement in one or both twins. The final sample included 38 twins [19 pairs, mean age of 25.18 (SD 5.4, range 20–34); 53% male; 100% Caucasian]. The following are the descriptive statistics for the Alienation scale in this sample: *T*-score mean = 59.29, *SD* = 11.32, and range = 43–78. Due to nonindependence, all twin analyses were corrected to an effective sample size of 19 or used co-twin differences (twin1–twin2) in discordance analyses assessing the role of unique environmental variance. All participants provided informed consent and both studies were approved by the institutional review board at University of Minnesota. See Appendix S1 for details.

2.2 | Behavioral procedures and analyses

Participants completed the Minnesota Trust Game (MTG) (Johnson et al., 2009) during functional neuroimaging after training. The MTG is a two-player economic social decision-making task that is a non-iterative variant of the Trust Game (Berg et al., 1995). The MTG is composed of two types of trust games differentiated by decision-agent (the other player or a coin flip), with each game subdivided into two conditions, resulting in a total of four conditions (Figure 1a). During each trial the participant chooses to either *not trust* the decision-agent and take assured financial outcomes for both players, or *to trust* the decision-agent to determine financial outcomes for both players (Figure 1b). If the participant chooses to trust, the decision-agent can

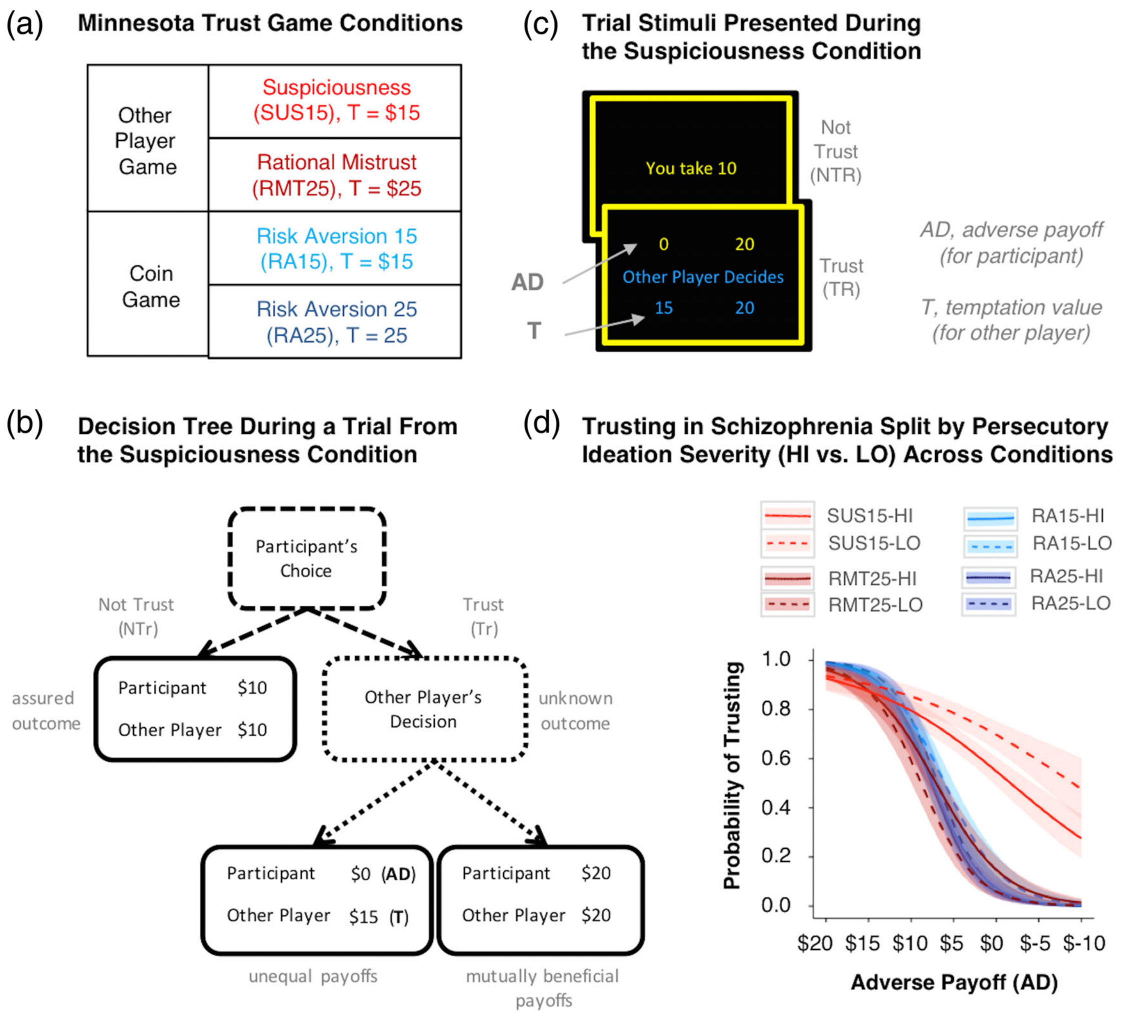

FIGURE 1 (a) Minnesota Trust Game (MTG) divisions based on experimental manipulations of decision-agent (other player or coin-flip) and temptation value, T. Decisions during the suspiciousness condition measures spite sensitivity; remaining conditions serve as different controls. (b) During each trial the participant takes one action: to trust (Tr) or not trust (NTr) the decision-agent (here shown as the other player). If the participant chooses not to trust, they receive an assured outcome of equal payoffs to self and the other player. If the participant chooses to trust, they receive an unknown outcome based on the decision-agent's choice between two alternatives presented below. Participant's decision is based on the decision-agent, the temptation (incentive) payoff for the other player (T, $15 or $25), and the adverse payoff (risk) for the participant (AD, range: −$10 to $20). (c) Example stimuli with possible payoffs for participant (in yellow) and the other player (in blue). If participant decides to trust they select the bottom card; otherwise, the top card. (d) Behavioral findings in schizophrenia illustrating that only decisions during the suspiciousness condition (SUS15), which measures spite sensitivity, were related to individual differences in persecutory ideation using BPRS suspiciousness rating (LO = rating of 1–3, HI = rating of 4–7) in schizophrenia

choose from mutually beneficial payoffs that are greater than the assured outcome for both players, or unequal payoffs that are potentially risky for the participant if less than the assured outcome. For the participant, the unequal payoff is the adverse payoff (AD), which varies but includes a few trials where AD is greater than the assured outcome; the latter serve as validity trials to detect if the components of the task were understood and increase the likelihood of observing at least some trust responses from each participant across all conditions. By varying the temptation value (T) offered to the other player, the Other Player Game is split into two important conditions: one measures *suspiciousness* (fear of other player being spiteful, i.e., spite sensitivity) when $T = \$15$, and one measures *rational mistrust* (fear of other player being selfish) when $T = \$25$. These conditions are based on how the values differ from the mutually beneficial payoffs ($20) and serve as incentives assuming players act in self-interest. In the patient sample, participants received supplemental training to ensure comprehension of these different contexts, and stimuli were designed to minimize cognitive load using an updated version of the task (Figure 1c). See Appendix S1 and Figure S1 for details and differences about task design, presentation, and training in the two samples.

Given the aim of the MTG is to examine processes related to persecutory ideation, the *rational mistrust* condition functions as an active control for interpersonal trust processes when examining effects in the *suspiciousness* condition. Parallel conditions in the Coin Game, resolved with a coin flip if the participant chooses to trust, serve as controls for human agency (of decision-agent) and anxiety relating to chance-level outcomes that measure *risk aversion* (fear of loss due to chance). In turn, while participants can choose to *not trust* the decision-agent in the *suspiciousness*, *rational mistrust*, or *risk aversion* conditions, the underlying reasons are designed to be different. Based on task design and previous MTG findings that high persecutory ideation was related to reduced trust only in the *suspiciousness* condition, while high harm avoidance was related to reduced trust only in *risk aversion* conditions (Johnson et al., 2009), key neuroimaging analyses for hypothesis-driven tests focused on the Other Player Game conditions after replicating previous behavioral effects across all trials and validating overall brain functioning during the MTG, as described below.

Behavioral analyses were completed with R (http://www.r-project.org). First, we employed hierarchical repeated-measures logistic regression ("glmer," "lme4" package) to examine how experimental manipulations (decision-agent; temptation; and adverse payoff) and persecutory ideation predicted trust decisions. The four variables were fixed-effects with subject (or twin pair) entered as the random-effect. Additionally, "trust scores" based on trial-by-trial risk [specifically the adverse payoff (AD)] and participant's decision were calculated for each of the four conditions (see Appendix S1) and used in one-tailed individual differences analyses to further examine phenotypic effects of persecutory ideation and co-twin difference. Robust regression was used for all individual differences analyses to down-weight outliers.

2.3 | Neuroimaging procedures and analyses

Participants were scanned in a Siemens Trio 3T while completing the task. See Appendix S1 for acquisition details for the two samples. Standard preprocessing of functional magnetic resonance imaging (fMRI) scans was completed with FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/); preprocessing steps were completed in parallel manners for the two analysis types in patients (activation and connectivity), and preprocessing steps were identical across the two samples. In addition to excluding subjects with excessive movement, applications beyond motion correction were employed to further reduce the influence of movement in both methods. See Appendix S1 for processing details.

2.3.1 | Time course specification for task-relatedness

The neuroimaging analyses aimed to identify patterns of brain activation/connectivity that were engaged in the (a) overall demands during the task, and (b) specific forms of mistrust during the task. Accordingly, event-related analyses modeled specific time courses. For each scan, task time courses were modeled using matrixes of the onset and duration of the decision phase, plus event codes, for each trial where a response was given. Only the decision phase for each response trial was modeled, which began when the participant was presented trial options and ended once a decision (response) was made. Resulting matrixes were convolved by the double-gamma hemodynamic response function using FSL.

The two types of time courses were differentiated by event inclusion. First, *overall* task-relatedness time courses modeled all response trials within the game type regardless of condition or decision. These were performed for the Other Player Game and Coin Game separately, and were used for initial validation of the overall brain activation/connectivity during the MTG. Second, *specific* task-relatedness time courses modeled trials for specific decision and condition combinations. These were focused on response trials within the Other Player Game and were used for specific hypothesis-driven tests of brain activation/connectivity during the MTG. That is, they were used to examine three a priori contrasts of *specific* task-relatedness, which compared the brain functioning associated with specific decisions in order to investigate the neural responses differentiating distinct forms of mistrust, which may be most likely to be related to persecutory ideation. Contrasts compared the neural responses of: (a) *no trust* and *trust* decisions during the suspiciousness condition (SUS15 NTr–SUS15 Tr) termed the "suspiciousness contrast," (b) *no trust* and *trust* decisions during the rational mistrust condition (RMT25 NTr–RMT25 Tr) termed the "rational mistrust contrast," and (c) *no trust* decisions during the suspiciousness and rational mistrust conditions (SUS15 NTr–RMT25 NTr) termed the "no trust contrast" which is the most critical analysis related to persecutory ideation. The same "overall task-relatedness" and "specific task-relatedness" time courses were employed in both activation and connectivity analyses.

Note, the neuroimaging a priori contrasts of specific task-relatedness were designed to isolate decision-making processes associated with acceptable vs. unacceptable (e.g., intolerable) risks. These contrasts did not control for the adverse payoff (AD) that varies across trials because the decisions (to trust or not trust) are inherently related to the AD. While the AD itself is a noisy measure of subjective risk, each individual's decision reflects how subjective risk is applied and acted upon, making the decision a less noisy and more interpretable index. All conditions contained the same levels of AD, and AD was manipulated similarly in all conditions and never repeated within a condition, which allowed us to equally probe decision-making.

2.3.2 | Activation analyses

General linear model (GLM) analyses were performed to identify brain activations associated with the task using *patient sample* data ($n = 30$) and were completed with FSL's FEAT (fMRI Expert Analysis Tool; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT). For each analysis, the event time courses and their temporal derivatives were entered in the model in addition to motion parameters as confound variables. Group-level analyses were thresholded at voxelwise $z > 3.09$ and employed a corrected cluster extent threshold of $p < .05$ to control for brainwise error during significance testing. Thresholds to examine significance were based on recent published recommendations (Eklund, Nichols, & Knutsson, 2016; Woo, Krishnan, & Wager, 2014).

There were three phases of analysis. First, initial validation of brain activation during the MTG was examined with whole-brain analyses to identify regions showing engagement in the general demands of the task, referred to as overall task-relatedness. Other Player Game versus baseline and Coin Game versus baseline analyses were tested as two separate experimental questions. A comparison of overall task-relatedness across the two games was not part of the hypotheses; however, by request, this was included in supplemental analyses.

Second, for hypothesis-driven tests that were the main focus of this study we examined the three a priori contrasts of specific task-relatedness to identify activation patterns associated with distinct forms of mistrust; each of the three contrasts were considered separate experimental questions as described in Section 2.3.1. To make the search extent parallel across activation and connectivity methods, the a priori contrasts of activation were performed within a combined spatial mask of the 10 a priori selected networks derived from connectivity analyses below. However, exploratory analyses expand these contrasts to whole brain tests. Third, significant findings for the a priori contrasts were further examined by extracting percent signal change values for each subject for use in individual differences analyses focused on persecutory ideation in R. Robust regression was used for individual differences analyses to down-weight outliers.

2.3.3 | Generation of networks

Data-driven probabilistic independent component analysis (ICA) was used to derive task-based connectivity networks. This method was chosen so that findings would not be constrained to a single or circumscribed set of seeds (Cole, Smith, & Beckmann, 2010), which may be beneficial for studying individual differences (Smith et al., 2014). *Patient sample* fMRI data ($n = 30$; preprocessed registered and motion regressed) was entered into a meta-ICA procedure to generate consistent components representing functional networks and isolated noise variance (Poppe et al., 2013; Smith et al., 2009; Wisner, Atluri, et al., 2013). Briefly, 25 temporal concatenation (model-free and multisubject) group-level probabilistic ICAs were completed using FSL's MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) (Beckmann, DeLuca, Devlin, & Smith, 2005; Beckmann & Smith, 2004). Each ICA employed a unique and randomly generated subject order for data input and was constrained to 60 components based on prior neurometric research showing the spatial networks were optimized for dimensionalities between 50 and 70 using the meta-ICA procedure (Poppe et al., 2013). This prior work suggested an array of consistent and reproducible canonical networks can be achieved at these dimensionalities, compared with lower and higher dimensionalities, and that the dimensionality of 60 produces connectivity maps well aligned with meta-analytic task-based co-activation networks reported by Smith et al., 2009 and Laird et al., 2011 (Laird et al., 2011; Smith et al., 2009; Wisner, Atluri, et al., 2013). In the current study, input data for the ICAs was limited to the second scan of each game type (second other player scan and second coin scan) to ensure steady-state. For the meta-ICA, components form each MELODIC were concatenated into a single file and employed in the single meta-level MELODIC (meta-ICA) to generate the 60 most consistent group-level components. For additional rationale pertaining to our chosen methods, please refer to the introduction where rationale is provided regarding (a) the use of the meta-ICA method given its proven neurometric properties and sensitivity (paragraph 5), and (b) the choice to derive networks from the current patient sample while engaged in specific cognitive processes during the MTG (paragraph 2), as opposed to employing publicly available resting-state networks from a nonpatient sample.

2.3.4 | Generation of connectivity metrics

Using the full set of meta-ICA components derived from *patient data*, dual regression was used to generate time courses and spatial maps for each component for each scan (Beckmann, Mackay, Filippini, & Smith, 2009; Filippini et al., 2009). We note that following this step the influence of motion has been addressed using several methods to remove its impact on subsequent connectivity metrics: (a) preprocessing and (b) how the dual regression procedure calculates time courses for each component in a way that controls for the influence of all other components (including artifact components) (Leech, Kamourieh, Beckmann, & Sharp, 2011). The resulting time courses were used to calculate three connectivity metrics based on network coherence, which is the degree to which voxels within the network show similar fluctuations in the hemodynamic response; higher network coherence indicates more homogeneity in fluctuations across the voxels in the network, whereas lower network coherence indicates less homogeneity across the voxels. Metrics were calculated and analyzed using R (http://www.r-project.org), and included (a) overall task-relatedness of network coherence, (b) specific task-relatedness of network coherence, and (c) metrics representing the degree of connectivity between pairs of networks which we term interconnectivity. Overall task-relatedness metrics were calculated as the Pearson correlation between the overall task-relatedness time courses and network time courses (Moodie et al., 2014). Specific task-relatedness metrics were calculated as the Pearson correlation between the specific event task-relatedness time courses and network time courses (Moodie et al., 2014; Poppe et al., 2015). Interconnectivity metrics were calculated as the Pearson correlation between pairs of network time courses (Wisner, Patzelt, et al., 2013). All metrics underwent Fisher's z' transformation prior to analyses. All metrics were first calculated at the scan-level, then average subject-level metrics across the 2–3 scans per subject were calculated and employed for group and individual differences analyses in Fisher's z' form.

2.3.5 | Network selection

Artifacts were visually identified using standard methods (Kelly et al., 2010; Smith et al., 2009); these included signals due to cardiac or respiratory sources, or movement or other nonneural fluctuations in periphery. Nonartifact components are subsequently referred to as networks. The meta-ICA generated 24 nonartifact networks from patient fMRI data. Although derived from patients, they are visually similar to published canonical networks in foundational work from meta-analytic networks of co-activation and large-scale datasets (Laird et al., 2011; Smith et al., 2009). A priori networks were identified based on anatomical structures associated with neurobiological models of delusions. Specifically, frontal and striatal/midbrain networks were selected based on involvement in abnormalities in prediction error and learning (Corlett et al., 2010), while temporal–parietal networks were selected based on involvement in abnormalities in representations of self and others (Wible, 2012). Networks that appeared to combine these regions and represented canonical networks (e.g., frontal–parietal) were included. When multiple overlapping networks were observed, those aligning with foundational canonical networks were prioritized to improve validity and reduce multiple comparisons. A priori network selection resulted in 10 networks of interest (see results; top of Figure 3); therefore, all a priori network analyses used the significance threshold $p < .005$ to correct for multiple comparisons.

2.3.6 | Connectivity analyses

Group-level analyses examined connectivity metrics in a step-wise manner aiming to parallel the three phases of the activation analyses and controlled multiple comparisons by limiting analyses of interest to the 10 a priori networks selected based on anatomical structures identified by neurobiological models of delusions (Corlett et al., 2010; Wible, 2012).

First, for the initial validation of brain connectivity during the MTG, we tested the overall task-relatedness metrics to identify networks that showed engagement in the general demands of the task. Overall task-relatedness metrics for the a priori networks were examined for Other Player Game and Coin Game separately as two different experimental questions. Here, an omnibus repeated measures ANOVA including all 10 a priori networks' overall task-relatedness metrics (network was the independent variable) was completed for each game type separately and followed, as needed, by post-hoc tests for each network ($p < .005$, correcting for 10 networks) within the indicated game type. However, to parallel the whole brain overall task-relatedness activation analyses, these tests were expanded to the remaining nonartifactual brain networks to approximate whole-brain coverage in exploratory analyses. From these analyses we expected to additionally observe association with standard sensory and motor networks. A comparison of overall task-relatedness across the two game types was not part of the hypotheses; however, by request supplemental analyses include this comparison of connectivity metrics.

Second, for hypothesis-driven tests that were the main focus of this study we examined the three a priori contrasts of specific task-relatedness to identify networks associated with distinct forms of mistrust; each of the three contrasts were considered separate experimental questions as described in Section 2.3.1. *Contrast metrics* were calculated as subtractions of the Fisher's z' transformed specific task-relatedness metrics for distinct events (different types of decisions). An omnibus repeated measures ANOVA including all 10 a priori networks' *contrast metrics* (network was the independent variable) was completed for each contrast separately and followed, as needed, by post-hoc tests for each network ($p < .005$, correcting for 10 networks) within the indicated contrast. However, exploratory tests expand these procedures to the remaining nonartifactual networks to approximate whole brain coverage to parallel those in the activation analyses. Third, significant findings for the a priori contrasts were further examined by employing the subject-specific metrics in individual differences analyses focused on persecutory ideation in R. Additionally, interconnectivity metrics from pairs of networks showing significant contrasts of the specific task-relatedness were tested in individual differences analyses in R to examine how synchrony between implicated networks predicts persecutory ideation. Robust regression was used for these analyses to down-weight outliers.

2.3.7 | Neuroimaging analyses in twins

Results of the above imaging analyses in patients were then used to guide imaging analyses in the twin sample. Specifically, the methods that successfully revealed significant relationships between task-related brain functioning and persecutory ideation in patients were applied to the twin sample data to *extend* the investigation of individual differences using the same brain regions or networks. For example, masks resulting from the activation analyses in patients would be applied to the twins, or networks resulting from the connectivity analyses in patients would be applied to the twins via dual regression. The primary purpose of the twin analyses was to examine associations among co-twin differences to test for evidence of *unique environmental causes* that link variance in brain functioning to variance in persecutory ideation and decision-making using individual differences analyses. Due to these aims, reasons related to greater clinical variance and ability to test paradigm validity in the patients with schizophrenia, and the smaller effective sample size in twins (19 pairs), independent analyses to derive original activation or networks were not completed in this community twin sample.

3 | RESULTS

3.1 | Task effects and persecutory ideation in schizophrenia

3.1.1 | Task behavior and persecutory ideation

Behavioral effects showed the predicted interaction between persecutory ideation and task manipulations (Figure 1d and Table S1a). Persecutory ideation negatively influenced trust only during the Other Player Game (Table S1b,c); this was observed specifically in the suspiciousness condition (SUS15) but not rational mistrust condition (RMT25) (Table S1d,e). This affirmed specificity of the suspiciousness condition to persecutory ideation.

3.1.2 | Brain activation during MTG

Overall task-relatedness of activation for validation

Whole-brain GLM analyses were used to identify regions activated ($z > 3.09$) by overall task demands during each game, relative to baseline, in patients. Findings showed robust task-positive activations during the Other Player Game (Figure 2), where increased BOLD activations were observed in the ventral and dorsal lateral PFC, portions of the parietal and occipital cortex, as well as insula, striatum, thalamus, and cerebellum. Very similar activations were observed for the Coin Game and there was a high degree of overlap (Figure S2). See Appendix S1 for a comparison of Other Player Game and Coin Game activations.

Specific task-relatedness contrasts of activation for key hypothesis testing

Second, masked GLM analyses separately examined the three a priori specific task-relatedness contrasts to identify regions sensitive to distinct task decisions and forms of mistrust in patients. Each of the three contrasts were considered separate experimental questions as described in Section 2.3.1. Here the mask was a combination of the spatial extent of the 10 a priori selected networks in order for activation and connectivity contrast analyses to have similar spatial extent.

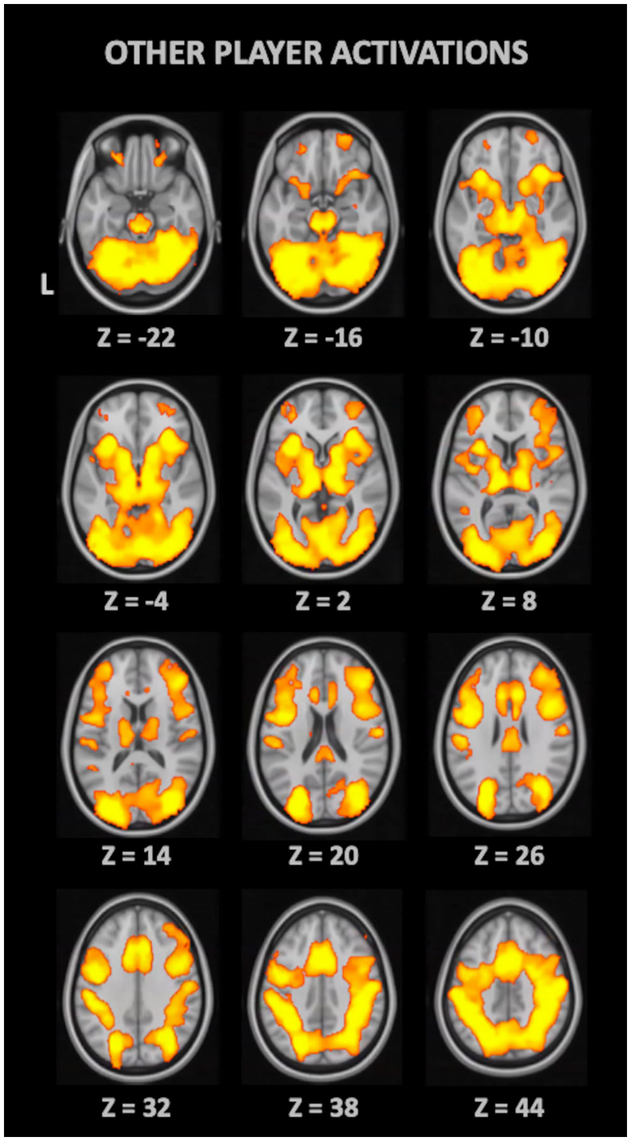

FIGURE 2 Whole-brain overall task-relatedness activation findings ($z > 3.09$) in schizophrenia during the Other Player Game of the MTG. Analyses included all trials regardless of condition or decision within this game type to assess bold oxygenation level dependent (BOLD) response to overall task demands. Several regions implicated in higher-level cognition and visuo-motor processing show greater BOLD response during the decision phase compared with baseline. Z under each brain above refers to slice location along the superior–inferior axis

Within this mask there were no significant ($z > 3.09$) findings for any of the three contrasts. Exploratory whole-brain analyses of the suspiciousness contrast (NTr SUS15–Tr SUS15) and the rational mistrust contrast (NTr RMT25–Tr RMT25) both showed significantly greater ($z > 3.09$) left sensorimotor activations associated with *no trust* decisions versus *trust* decisions (specifically pre-central and post-central gyrus, with max peaks at $x = -34$, $y = -26$, $z = 64$ and $x = -36$, $y = -24$, $x = 56$ for the two analyses, respectively); no other regions were significant in these contrasts. The critical no trust contrast (NTr SUS15–NTr RMT25) comparing neural response across the

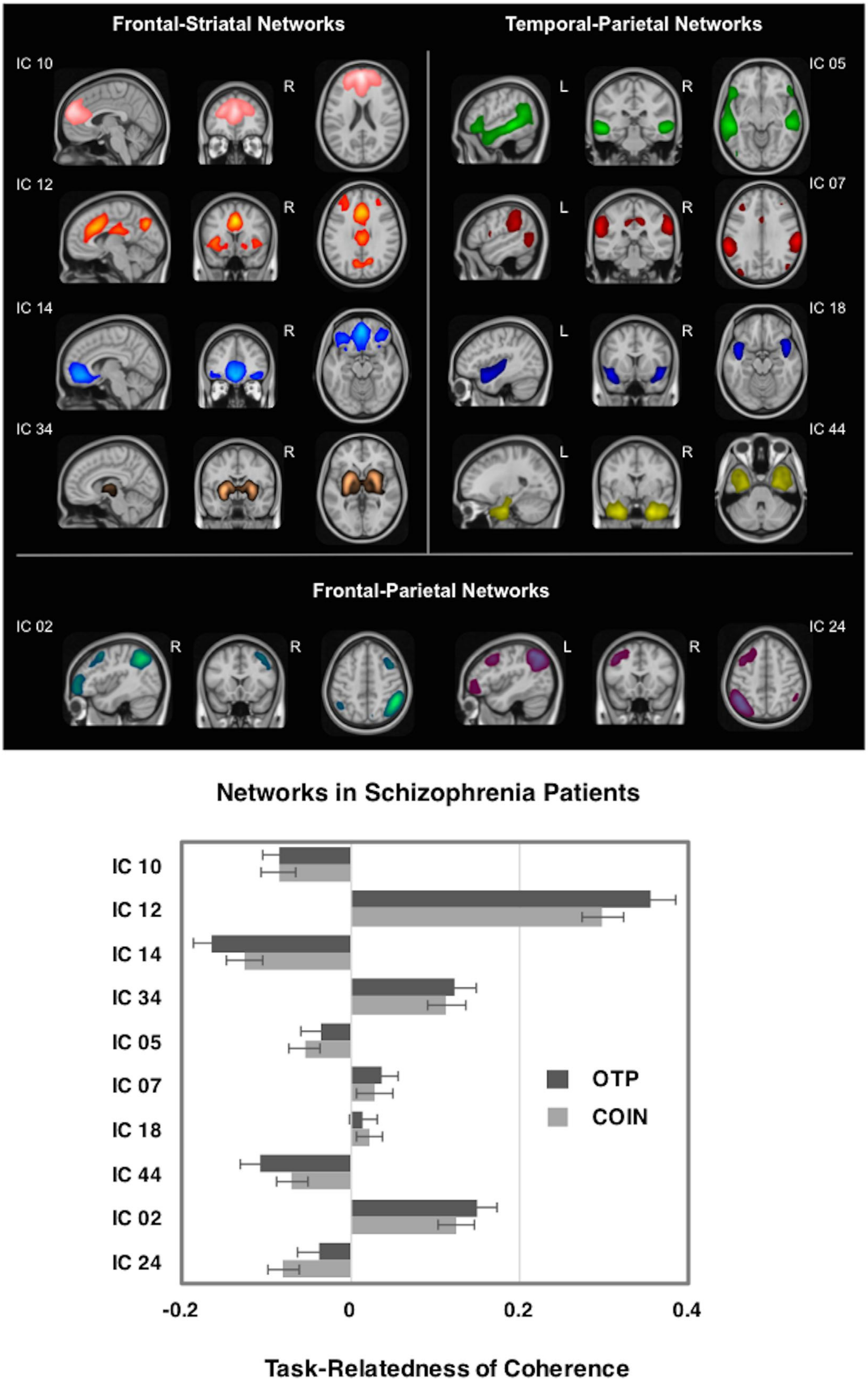

FIGURE 3 (Top) Ten a priori selected networks from the ICA completed on schizophrenia task fMRI data collected while completing the Minnesota Trust Game. (Bottom) Visualization of overall task-relatedness results for each a priori network during each game type separately in schizophrenia. Each bar indicates the degree to which fluctuations in the network's coherence were associated with task events, plotted as mean task-relatedness using Fisher's z'; error bars represent *SEM*. IC, independent component; OTP, Other Player Game; COIN, Coin Game

suspiciousness and rational mistrust conditions for *no trust* decisions yielded no significant ($z > 3.09$) activation differences in the exploratory whole-brain analysis.

3.1.3 | Brain connectivity during MTG

Overall task-relatedness of network coherence for validation

Ten networks were selected a priori for analyses as described above; these networks are shown in the top of Figure 3. Notably, while the network selection was based on the literature and independent of the activation findings, it is relevant to point out these networks consist of regions that showed robust activations in the whole-brain overall GLMs described above. First, connectivity analyses that intended to parallel the initial set of activation analyses aimed to identify networks with fluctuations sensitive to overall task demands during each game type in patients. For each game separately, an initial omnibus ANOVA ($p < .025$) with a priori networks as the independent variable assessed differences in overall task-relatedness metrics. Overall task-relatedness significantly varied across networks in the Coin Game ($F[9,261] = 49.33$, $p < .001$) and the Other Player Game ($F[9,261] = 50.53$, $p < .001$) (bottom of Figure 3 and top of Table S2). Within-game post-hoc tests controlling for multiple comparisons across networks ($p < .005$) highlighted that the dorsal cingulate and anterior insular network (IC 12), striatal and thalamic network (IC 34), and right frontal–parietal (IC 02) network demonstrated significant positive task-relatedness during both games. The dorsal medial PFC network (IC 10), ventral medial/orbital PFC network (IC 14), and medial temporal and temporal pole (IC 44) network demonstrated significant negative task-relatedness during both games. The left frontal–parietal network (IC 24) showed significant negative task-relatedness during the Coin Game. Exploratory analyses extended tests to the remaining 14 networks. As expected, robust positive task-relatedness was observed across the games for multiple non a priori networks likely involved in the sensory and motor demands of the task (see bottom of Table S2). See Appendix S1 for a comparison of Other Player Game and Coin Game overall task-relatedness for the networks.

Specific task-relatedness contrasts of network coherence for key hypothesis testing

Second, connectivity analyses that intended to parallel the second set of activation analyses aimed to identify networks with fluctuations sensitive to distinct task decisions and forms of mistrust in patients. The three a priori contrasts of specific task-relatedness were examined as separate experimental questions as described in Section 2.3.1 using contrast metrics. For each contrast separately, an initial omnibus ANOVA ($p < .016$) with a priori networks as the independent variable assessed for differences in the specific task-relatedness contrast metrics. Within-contrast post-hoc tests controlled for multiple comparisons across networks ($p < .005$). Analyses of the suspiciousness contrast metrics comparing *no trust* versus *trust* decisions within that condition (NTr SUS15–Tr SUS15) showed significant variation across networks ($F[9,216] = 2.45$, $p = .011$), with post-hoc tests highlighting significant changes in the dorsal cingulate and anterior insular network (dACC-AI) (IC12) ($p < .005$; Table S3a top and Figure 4a). Analyses of the rational mistrust contrast metrics comparing *no trust* versus *trust* decisions within that condition (NTr RMT25–Tr RMT25) showed significant variation across networks ($F[9,252] = 4.00$, $p < .001$), with post-hoc tests highlighting significant changes in the left frontal–parietal network (lF-P) network (IC24) ($p = .002$; Table S3b top and Figure 4b). Analyses of the critical no trust contrast metrics comparing *no trust* decision in the suspiciousness condition versus *no trust* decisions in rational mistrust condition (NTr SUS15–NTr RMT25) showed significant variation across networks ($F[9,216] = 2.47$, $p = .011$), with post-hoc tests highlighting significant changes in the ventral medial/orbital PFC network (vmPFC/OFC) (IC14) ($p < .005$; Table S3c top and Figure 4c). Thus, three different networks showed changes in coherence that were sensitive to distinct forms of mistrust within the MTG. See Appendix S1 for exploratory analyses of the above contrasts for the remaining 14 non a priori networks.

3.1.4 | Individual differences in behavior and brain functioning

Significant findings from behavioral and imaging analyses were tested for relationships with individual differences in trusting behavior or persecutory ideation in patients. First, a confirmatory test using calculated trust scores reproduced the behavioral effect observed with logistic regressions, where higher persecutory ideation was associated with reduced suspiciousness condition trust scores ($\beta = -0.35$, $t[28] = -1.98$, $p = .029$) (Figure 5a). Second, the connectivity contrast metrics for the a priori networks found to be sensitive to specific task decisions (dACC-AI, lF-P, and vmPFC/OFC) were not related to persecutory ideation ($p > .05$; Table 1a). Third, we tested how the interconnectivity metrics between the dACC-AI, lF-P, and vmPFC/OFC networks during the Other Player Game (based on our behavioral and connectivity findings above) were associated with persecutory ideation. Results demonstrated that reduced vmPFC/OFC–lF-P interconnectivity predicted greater persecutory ideation in schizophrenia ($\beta = -0.50$, $t[28] = -3.06$, $p = .005$) (Table 1b and Figure 5b). See Appendix S1 for requested tests of whether non a priori regions/networks identified in exploratory whole-brain contrast analyses (e.g., left sensorimotor activation and sensory/motor networks from the bottom half of Table S3) were associated with persecutory ideation in patients.

3.2 | Examination of environmental influences using discordance in community MZ twins

3.2.1 | Replication of task effects on behavior and overall task-relatedness

Logistic regression analyses across all trials in twins replicated behavioral findings in patients, demonstrating a similar interaction between persecutory ideation and task manipulations, with the negative

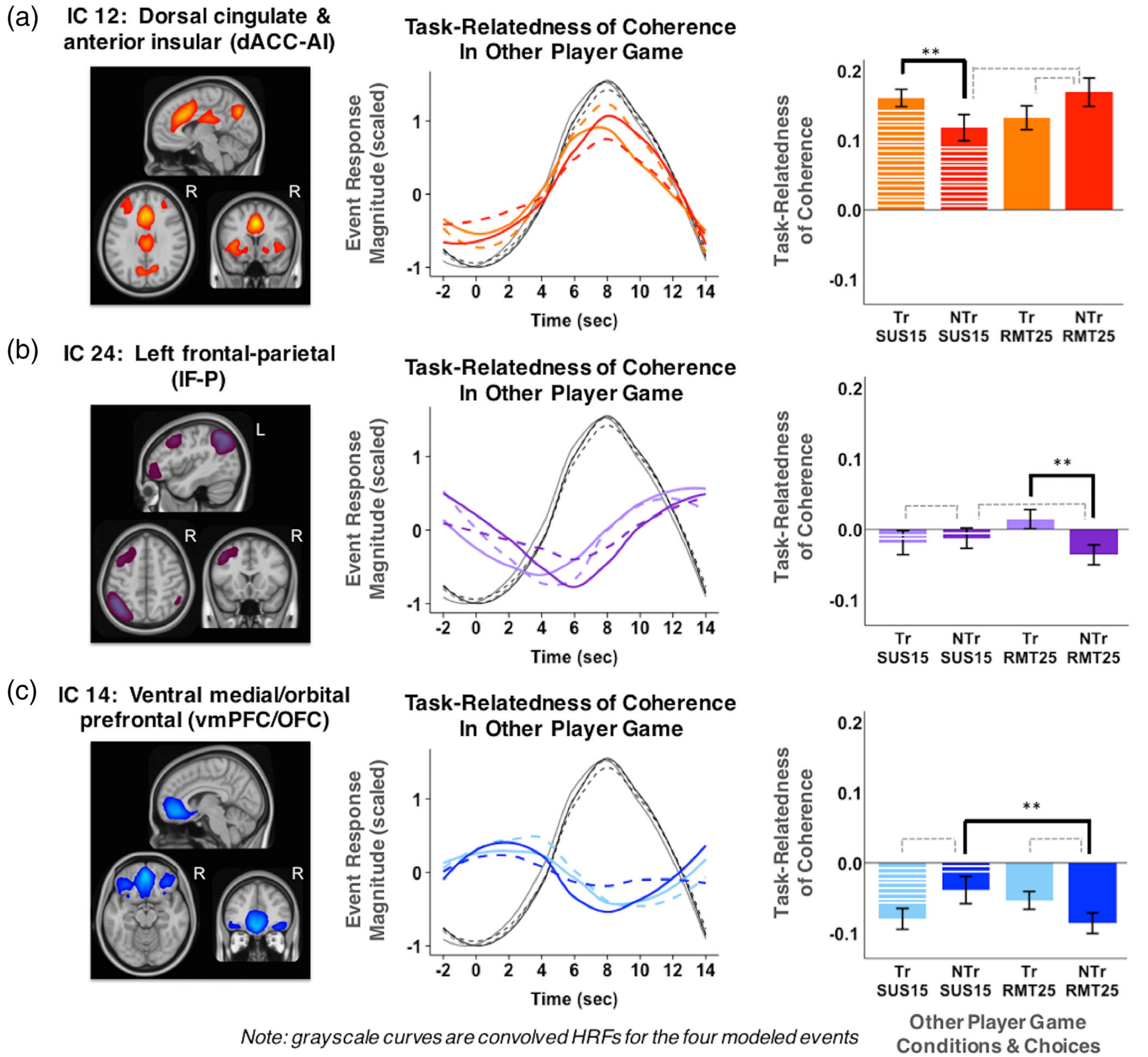

FIGURE 4 Results of a priori specific task-relatedness contrast analyses in schizophrenia. The three contrasts represent different experimental questions. (a) Finding for Suspiciousness Contrast, defined as NTr SUS15–Tr SUS15. (b) Finding for Rational Mistrust Contrast, defined as NTr RMT25–Tr RMT25. (c) Finding for No Trust Contrast, defined as NTr SUS15–NTr RMT25. *Left column* shows networks with significant findings for one of the contrasts. *Middle column* shows for the specific task events, the fluctuations in that network's coherence as colored curved lines and the predicted brain response based on task as grayscale curved lines. These plots thus visualize the time courses used to calculate specific task-relatedness metrics (the degree to which fluctuations in the network's coherence were associated with task events). *Right column* summarizes specific task-relatedness metrics for the different events for each network, with colored bars representing the means using Fisher's z' and error bars representing *SEM*. Note, colors and patterns of bars in the right column correspond to the colors and patterns of the lines on the middle column. The three a priori contrasts of specific task-relatedness are shown by the three lines between bars in the right column. Significant ($p < .005$) contrasts indicated by bold line and **. Nonsignificant contrasts for that same network shown by dashed gray lines. IC, independent component; Tr, Trust; NTr, Not Trust; SUS15, suspiciousness condition; RMT25 rational mistrust condition

influence of persecutory ideation limited to the suspiciousness condition (Table S4 and Figure S3a). Next, in the primary sample of patients with schizophrenia, our neuroimaging analyses highlighted the ability of connectivity methods to identify specific networks related to distinct forms of mistrust and persecutory ideation. Therefore, we examined the same connectivity networks in the twin sample. Specifically, the full set of networks derived in the patient sample were applied to the twin sample data at the dual regression stage of the pipeline to generate subject-specific network time courses for this sample. Event time courses and subsequent connectivity metrics in

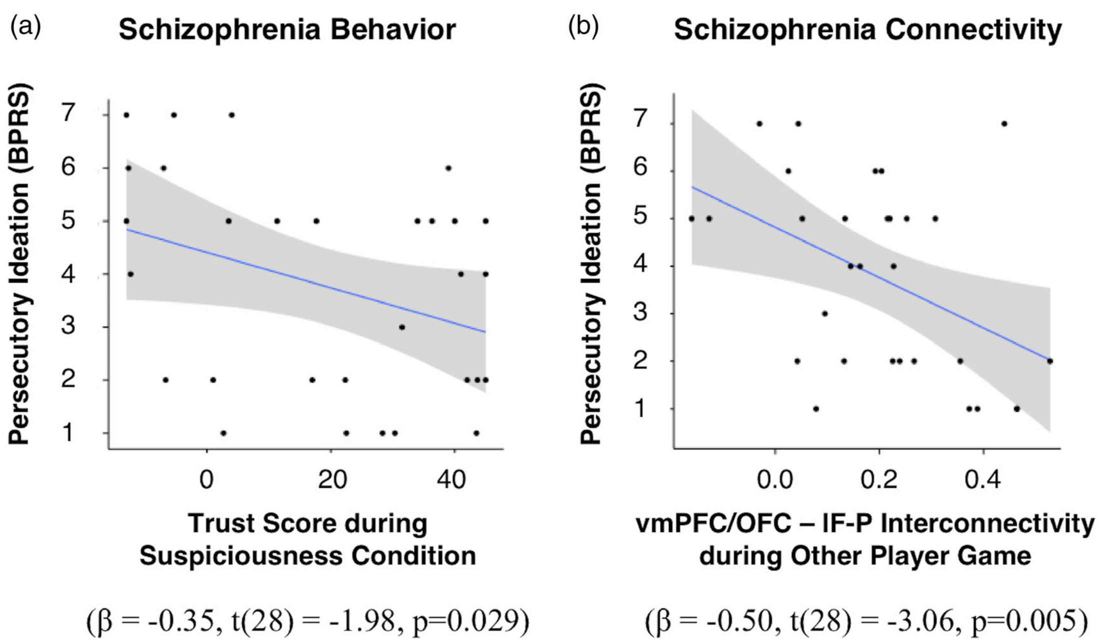

FIGURE 5 Relationship between task-related metrics and individual differences in persecutory ideation in schizophrenia. (a) Inverse association with Suspiciousness condition trust scores, where lower trust scores indicate reduced willingness to trust. (b) Inverse association with interconnectivity between ventral medial orbital prefrontal cortex (vmPFC/OFC) network and left frontal–parietal (lF-P) network during the Other Player Game (plotted using Fisher's *z*′), where reduced interconnectivity indicates reduced between-network communication. Analyses employed robust regression to down-weight outliers

TABLE 1 Prediction of persecutory ideation using key other player game neuroimaging metrics in schizophrenia

a. Connectivity contrast metrics	Coefficient (β)	*T*-stat	*p*-value
dACC-AI: Suspiciousness contrast	0.18	0.84	.411
lF-P: Rational mistrust contrast	−0.27	−1.34	.192
vmPFC/OFC: No trust contrast	0.08	0.39	.699
b. OTP interconnectivity metrics	**Coefficient (β)**	***T*-stat**	***p*-value**
dACC-AI∼vmPFC/OFC	0.12	0.63	.535
dACC-AI∼lF-P	−0.11	−0.56	.583
vmPFC/OFC∼lF-P	−0.50	−3.06	.005**

Note: Metrics from significant group-level contrasts, and the interconnectivity between networks showing significant contrasts, were tested for prediction of persecutory ideation. All tests used robust regression and were 2-tailed. dACC-AI, dorsal cingulate and anterior insula network; lF-P, left frontal–parietal; vmPFC/OFC, ventral medial/orbital prefrontal cortex network; OTP, other player game. ** significant after correction for six tests (p < .008).

twins were generated and analyzed using identical methods as in the patient sample. Results from these analyses showed overall task-relatedness metric findings in twins closely replicated those in schizophrenia patients. Six of the networks (ICs 12, 34, 02, 10, 14, 44) were significantly task-related in both games with the same directionality and similar magnitudes as in patients (Table S5 and Figure S3b).

3.2.2 | Individual differences in behavior and brain functioning with twin discordance

Confirmatory analyses in twins reproduced the behavioral effect observed in logistic regressions, where higher persecutory ideation was associated with reduced suspiciousness condition trust scores ($\beta = -0.55$, $t[17] = -3.96$, $p < .001$). Importantly, the discordance analysis revealed co-twin differences in trust scores negatively predicted co-twin differences in persecutory ideation ($\beta = -0.25$, $t[17] = -1.97$, $p = .033$) (Figure 6a). Next, confirmatory analyses in twins examined the negative relationship between vmPFC/OFC–lF-P interconnectivity and persecutory ideation previously observed in schizophrenia. Here in twins, interconnectivity was calculated across other player and coin trials due to their interleaved presentation in this sample only. Although in the predicted direction, this relationship was nonsignificant in twins ($\beta = -0.15$, $t[17] = -0.69$, $p = .248$) in part due to reduced power. Importantly, the discordance analysis was convergent with the patient findings, showing co-twin differences in

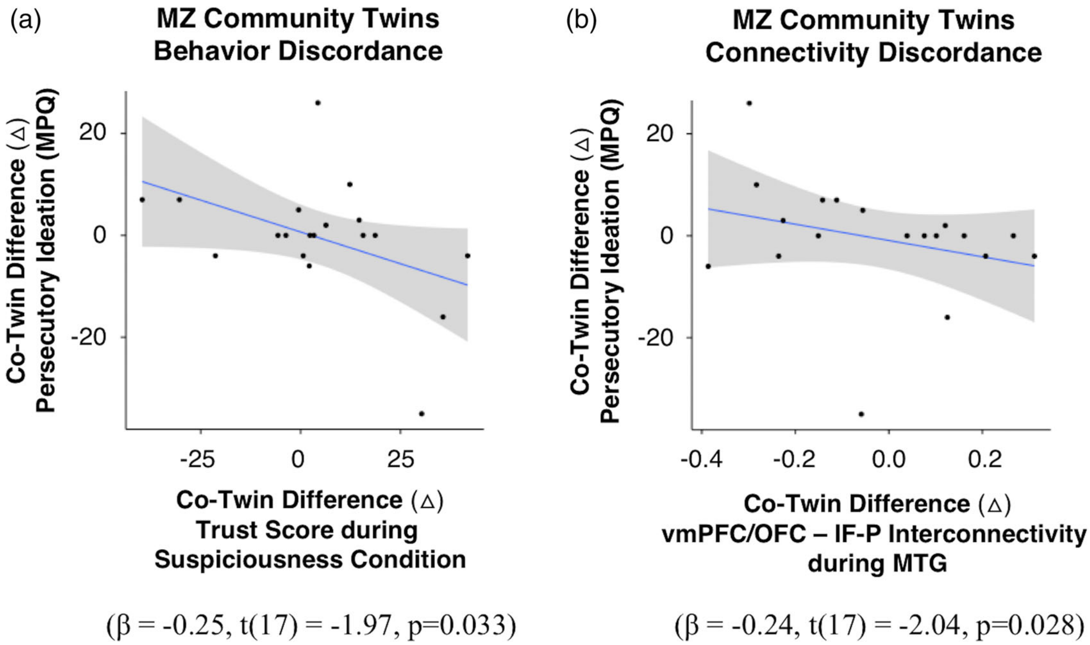

FIGURE 6 Relationship between task-related metrics and individual differences in persecutory ideation in community twins using MZ twin discordance (co-twin differences, $n = 19$ pairs). (a) Inverse association with Suspiciousness condition trust scores, where lower trust scores indicate reduced willingness to trust. (b) Inverse association with interconnectivity between ventral medial orbital prefrontal cortex (vmPFC/OFC) network and left frontal–parietal (lF-P) network (plotted using Fisher's z'), where reduced interconnectivity indicates reduced between-network communication. Interconnectivity in twins was calculated across other player and coin trials due to their interleaved presentation in this sample only. Analyses employed robust regression to down-weight outliers. For comparison to pattern of findings in schizophrenia, see Figure 5

vmPFC/OFC–lF-P interconnectivity negatively predicted co-twin differences in persecutory ideation ($\beta = -0.24$, $t[17] = -2.04$, $p = .028$) (Figure 6b), which suggests an influence of unique environmental variance in this brain–behavior relationship.

3.3 | Specificity analyses

Post-hoc analyses of the specific task-relatedness metrics examined new contrasts designed to parallel the three a priori contrasts to rule out potential confounds and examine the specificity of the network findings. Results are presented in Table S6 and Figure S4. Briefly, results highlighted specificity of the original contrast findings for the dACC-AI and vmPFC/OFC networks ($p < .05$); whereas, the lF-P network showed nominal but nonsignificant differences in contrast patterns when tested for specificity across conditions.

Post-hoc specificity analyses of individual differences findings in schizophrenia and twins were completed in order to rule-out potential confounds. Results are presented in Table S7. Briefly, these analyses confirmed specificity of the suspiciousness condition trust scores for association with persecutory ideation in both samples, confirmed specificity of the vmPFC/OFC–lF-P interconnectivity during the Other Player Game for association with persecutory ideation in patients, ruled out relationships with other symptoms as driving these effects in patients, and ruled out movement as an imaging confound for the key findings in both samples.

4 | DISCUSSION

Using the MTG during two fMRI studies with 30 patients with schizophrenia and 38 community MZ twins (19 pairs), we found spite sensitivity mistrust specifically predicted persecutory ideation across samples. Connectivity methods revealed three task-driven brain networks (dACC-AI; lF-P; and vmPFC/OFC) were sensitive to distinct forms of mistrust. Moreover, decreased connectivity between the task-driven vmPFC/OFC and lF-P networks predicted increased persecutory ideation in patients. Our extension into the twin sample further demonstrated unique environmental variance within MZ twin pairs influenced spite sensitivity, persecutory ideation, and the task-driven vmPFC/OFC and lF-P connectivity. Taken together, our findings illustrate the importance of network-based functional connectivity for understanding the neural mechanisms underlying persecutory ideation, and point to a multi-factor model that incorporates environmental causality in the mechanisms underlying persecutory ideation.

Behavioral findings in both patients with schizophrenia and community twins (Figure 1d and Figure S3a) replicated our prior MTG results in undergraduates (Johnson et al., 2009) in two critical ways. First, the probability of trusting decreased as the adverse payoff worsened and this effect was strongest in rational mistrust and risk aversion conditions. Second, and crucially, the trusting behaviors across individuals with high versus low persecutory ideation differed only in the suspiciousness condition, where decreased trust was driven by *fear of a partner's spite, that is showing disincentivized interpersonal* *malevolence*. Such patterns did not occur in rational mistrust or risk aversion conditions. This distinction supports a specific, rather than generalized, deficit (MacDonald, 2015) in social decision-making related to persecutory ideation, and implicates spite sensitivity as a liability for this phenomenological dimension.

Our neuroimaging analyses revealed that decreased connectivity between the task-related vmPFC/OFC and lF-P networks during the Other Player Game predicted increased persecutory ideation in schizophrenia (Figure 5b). During the MTG, these networks were associated with distinct forms of mistrust, which underscores the interpretation of this relationship. Specifically, contrast analyses highlighted the vmPFC/OFC's sensitivity to the key distinction between spite sensitivity mistrust and rational mistrust (Figure 4c). The vmPFC/OFC is an integrative hub for social/self-related thought and affect (D'Argembeau, 2013; Hiser & Koenigs, 2018; Lieberman, Straccia, Meyer, Du, & Tan, 2019; Roy, Shohamy, & Wager, 2012), as well as value and outcome comparisons (Grabenhorst & Rolls, 2011; Noonan, Kolling, Walton, & Rushworth, 2012; Rudebeck & Murray, 2011, 2014), that is sensitive to context (Losecaat Vermeer, Boksem, & Sanfey, 2014) and receives input from insula and amygdala which can drive negative bias (Fukuda et al., 2019; Ho, Gonzalez, Abelson, & Liberzon, 2012; Kim, Choi, & Jang, 2012; Rilling et al., 2008). During the MTG the vmPFC/OFC network appears to integrate these social, affective, contextual, and value signals, such that vmPFC/OFC changes in task-relatedness during MTG reflect changes in the subjective affect-infused valuation that differentiates these two types of *no trust* decisions. Contrast analyses also highlighted the lF-P's sensitivity to rational *trust* versus *no trust* decisions (Figure 4b). Here, changes in task-relatedness in the lF-P network likely reflected context maintenance and cognitive control (MacDonald, Cohen, Stenger, & Carter, 2000; Poppe et al., 2015) as well as computational reasoning (Zamarian, Ischebeck, & Delazer, 2009) supporting rational decisions, which are consistent with lF-P's influence during strategic social decision-making (Yoshida, Seymour, Friston, & Dolan, 2010). Therefore, our findings fit with prior literature suggesting vmPFC/OFC provides subjective valuation during affective decision-making (Grabenhorst & Rolls, 2011; Roy et al., 2012; Rudebeck & Murray, 2014), while lF-P provides broad executive control of functioning (MacDonald et al., 2000; Niendam et al., 2012).

Taken together the vmPFC/OFC and lF-P networks, whose interconnectivity predicts persecutory ideation, have been described as *opposing systems* supporting affective and logical reasoning, respectively (Goel & Dolan, 2003), that are both important for decision-making. Along these lines, our connectivity findings are consistent with dual process models proposing an intuitive/experiential "system 1" generates subjective, possibly instinctive, ideas that may require *correction* from a controlled/rational "system 2" for adaptive goal-directed behavior (Sanfey, Loewenstein, McClure, & Cohen, 2006). In healthy subjects, vmPFC – lF-P connectivity has already been shown to be critical for value modifications in affective and reward-based decision-making (Hutcherson, Plassmann, Gross, & Rangel, 2012). The important extension for the psychopathology of delusional ideation is that if this *correction by the rational "system 2"* does not occur, then the biased and subjective, potentially maladaptive, ideas would be allowed to persist (Risen, 2015) and possibly be reinforced by safety-seeking behaviors (Freeman et al., 2007; Gaynor, Ward, Garety, & Peters, 2013). In our data, the vmPFC/OFC processing may reflect the subjective, affect-infused expectations of the social interaction and value outcomes for oneself based on prior beliefs about how others will treat them. When these are not contextualized or "corrected" by top-down executive control processes from lF-P that facilitate rational and strategic decision-making, these "intuitive" ideas may produce suspiciousness-driven mistrust in predisposed individuals. Thus, the lF-P is relevant to persecutory ideation because impaired executive control involving lF-P may be a critical element in the development of this symptom. Indeed, behavioral evidence suggests individuals with persecutory ideation rely less on rational reasoning (e.g., hypothesis testing) and more on experiential reasoning (e.g., affect) (Freeman, Evans, & Lister, 2012). Individuals with persecutory ideation have increased negative affect and impaired affect regulation (Bentall et al., 2009; Westermann, Kesting, & Lincoln, 2012), with regulation abilities moderating the relationship between self-reported stress and persecutory ideation (Krkovic, Krink, & Lincoln, 2018). Furthermore, studies demonstrate stress and negative affect (such as that produced in situations perceived as threatening or suspicious) are detrimental to executive control (Clore & Huntsinger, 2007; Maier, Makwana, & Hare, 2015) and that vmPFC–lF-P connectivity is implicated in regulation of negative affect (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Ochsner, Silvers, & Buhle, 2012).

Importantly, our vmPFC–lF-P connectivity was not related to depression or anxiety and was not related to symptoms of disorganization, but rather appeared specific to persecutory ideation and this relationship was observed only in contexts where the other player's intentions were relevant to decision-making (not observed during Coin Game). The specificity of the interconnectivity finding points to the importance of beliefs about others' intensions rather than risk more generally for this dimension of psychopathology, and highlights the importance of eliciting a specific pattern of functioning using a cognitive task to study persecutory ideation. Taken together, these findings suggest context-dependent reductions in vmPFC/OFC–lF-P interconnectivity represents a neural mechanism underlying persecutory ideation and associated mistrust. This specification suggests interventions aiming to reduce persecutory ideation might include brain stimulation to the lF-P combined with targeted cognitive training (Filmer, Varghese, Hawkins, Mattingley, & Dux, 2017; Nejati, Salehinejad, & Nitsche, 2018) to improve the use of context processing and executive control during interpersonal situations (Rocha et al., 2020). Alternatively, training individuals to be more aware of and regulate their stress and emotions during interpersonal situations may be useful (Ludwig, Mehl, Schlier, Krkovic, & Lincoln, 2020). These interventions could be tested for reductions in the spite-sensitivity-driven mistrust and brain functioning linked to persecutory ideation using the MTG in future studies.

While the dACC-AI network did not predict individual differences in persecutory ideation, it showed strongest overall task-relatedness in both samples, and a main effect of task such that it was uniquely sensitive to spite sensitivity mistrust during the MTG. This dACC-AI salience network (Uddin, 2015) is involved in conflict and threat detection (Kalisch & Gerlicher, 2014; MacDonald et al., 2000; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003), and awareness of physiological and emotional arousal (Medford & Critchley, 2010). In our sample, it also included ventral striatum, posterior cingulate, and precuneus, which in psychosis show aberrant salience to neutral versus emotional stimuli (Kapur, 2003; Potvin, Tikàsz, & Mendrek, 2016) and are associated with delusions (Holt et al., 2011; Menon et al., 2011; Morris, Quail, Griffiths, Green, & Balleine, 2015; Perez et al., 2015; Roiser, Howes, Chaddock, Joyce, & McGuire, 2013). Here, the suspiciousness condition is the "neutral" condition with no explicit threat, and only during this condition did the dACC-AI show significant changes in task-relatedness (Figure 4a), which may reflect changes in perceived salience, perhaps driven by *inappropriate* mentalizing about the other player's intentions (Haroush & Williams, 2015; Liljeholm, Dunne, & O'Doherty, 2014) and resulting arousal (Medford & Critchley, 2010). Based on these findings, we hypothesize the dACC-AI salience network may contribute to observed task-related changes in the vmPFC/OFC or lF-P networks via arousal or similar mechanisms (Young et al., 2017), and thereby still be important in persecutory ideation (Krkovic et al., 2018). Future studies examining salience and arousal processes in independent paradigms alongside the MTG will clarify these interpretations.

An important piece of our findings is how the lF-P network supports executive control during the MTG. While our results are in line with previous work, the combined set of lF-P findings are complex. Previous studies show regions composing the lF-P network are engaged by tasks requiring context processing, working memory, computations, cognitive control, and rationale decision-making; in short, executive control (Niendam et al., 2012). We might expect the lF-P to show the greatest changes for decisions that draw on these executive functions the most, such as when changing contexts or risks require a strategic *switch away from the habitual response strategy* within a condition (MacDonald et al., 2000). This is most prominent in the rational mistrust condition, wherein only under certain circumstances (when the adverse payoff is above $10) does *a switch from the dominant no trust response to a trust response* yield high likelihood of a positive outcome for the participant. Indeed, the rational mistrust contrast singled out involvement of the lF-P (Table S3); however, specificity analyses comparing this to other contrasts were not significant (Figure S4). While unexpected, trends from these tests (Table S6) suggest larger samples may clarify. Specificity may have also been attenuated given all three contrasts involve a change from *no trust to trust* driven by risk and probability calculations, processes the lF-P is also implicated in (Poudel, Bhattarai, Dickinson, & Drummond, 2017; Rao, Li, Jiang, & Zhou, 2012). This highlights heterogeneity of conditions and lF-P responses, which have implications for the overall task-relatedness results. In particular, attenuated and nonsignificant overall task-relatedness for lF-P during the Other Player Game (Table S2) may be attributed to this metric collapsing across the varied lF-P responses during rational mistrust and suspiciousness conditions; whereas, this did not occur for the more homogenous lF-P responses during the Coin Game (Figure S4). Importantly, this does not undermine our interpretations that lF-P provides top-down executive control to contextualize or "correct" affect-infused intuitions in vmPFC/OFC which may otherwise contribute to persecutory ideation. As highlighted above, only vmPFC/OFC–lF-P interconnectivity during the Other Player Game, not the Coin Game, was related to individual differences in persecutory ideation. Rather these findings emphasize the importance of hypothesized a priori contrasts (e.g., rational mistrust contrast) that leverage task features for process-based investigations of neural mechanisms underlying complex symptoms.

While we expected overall task-relatedness of the lF-P network in twins to parallel observations in patients, our findings and existing literature suggest the lack of significance in the twins may be due to generally more intact executive control in this community sample. The lF-P overall task-relatedness in twins was more positive and closer to zero (leading to nonsignificance) than in patients, implying the twin's lF-P was less modulated by the MTG. Perhaps this is because non-psychotic individuals maintain relatively better coherence of the lF-P network across conditions, on par with their intact lF-P functioning in other studies (Niendam et al., 2014; Poppe et al., 2016). Whereas, the more negative task-relatedness of the lF-P in patients may reflect *fragmented engagement* of lF-P during the MTG, similar to patient findings in other imaging studies (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Nielsen et al., 2017; Poppe et al., 2016). Rather than reproduce all task effects from the patient study, the small sample of community MZ twins and co-twin control design (also referred to as discordant twin pair design) (McGue et al., 2010) was intended to extend the study to investigate a role for environmental influences in the current findings with a focus on individual differences. We demonstrated the same unique environmental variance influenced both the psychological and neural mechanisms underlying persecutory ideation. Specifically, co-twin differences in spite sensitivity negatively predicted co-twin differences in persecutory ideation (Figure 6a), and co-twin differences in vmPFC/OFC–lF-P interconnectivity negatively predicted co-twin differences in persecutory ideation (Figures 6b). These findings, via the co-twin control design employed here, suggest an environmental causality underlying these processes. While a number of environmental factors are linked to psychosis (MacDonald & Schulz, 2009), only obstetric complications, institutional care, neglect, and bullying have been specifically linked to persecutory ideation (Bentall et al., 2014; Catone et al., 2015; Guerra et al., 2002; Singham, Viding, Schoeler, Arseneault, & Ronald, 2017), though such studies are rare in twins to clarify. Continued work is needed examining environmental factors underlying persecutory ideation. Considering our findings, environmental factors interfering with executive control and affect regulation, such as chronic poor sleep (Simon et al., 2015) and early life stress (Duffy, McLaughlin, & Green, 2018; Hostinar, Stellern, Schaefer, Carlson, & Gunnar, 2012) warrant investigation and could be potentially important treatment considerations for paranoia.

Finally, our findings suggests that task-based network connectivity methods can be a useful complement to voxel-level task activation methods and may even be better suited for some applications. Based on our findings, it is possible that interconnectivity may be particularly important to persecutory ideation, as complex phenomena involving the interaction of multiple processes and therefore multiple networks in the brain. Our connectivity methods revealed three task-driven brain networks (dACC-AI; lF-P; vmPFC/OFC) were sensitive to distinct forms of mistrust and demonstrated vmPFC/OFC–lF-P connectivity predicted individual differences in persecutory ideation. While the overall task-relatedness of brain activation findings were robust, the key contrasts examining the distinct forms of mistrust identified only sensorimotor activations in this sample, which were unrelated to persecutory ideation, and likely driven by divergent button presses for the decisions. Given the subtlety of these contrasts, however, brain activation during the MTG should be further examined in larger samples. Taken together, the phenomenology of interest was related to network interactions rather than localized activations, which may be a more wide-spread observation with at least two previous studies reporting similar patterns in schizophrenia (Anticevic, Repovs, & Barch, 2012; Fonville et al., 2015).

Besides the limitation of relatively small samples in our study, there were some other limitations we acknowledge. This is the first imaging study employing the MTG and future studies will need to replicate these findings. The neuroimaging contrast analyses included validity trials (AD > $10), when a participant may choose to trust because they are guaranteed a better outcome regardless of other parameters, which could phenomenologically differ from trusting in the presence of greater risk and could be examined in larger samples. The smaller twin sample was not well suited for deriving a second independent set of networks during the MTG in a nonpsychotic sample. Future studies may wish to collect the MTG in larger community samples to examine networks in nonpsychotic populations with sufficient variance on the persecutory ideation dimension as well as test potential group differences between those with and without psychosis, which was not the aim of the current study. Additionally, such future studies will want to employ identical versions of the MTG across samples when testing group differences. Here data is combined from two independent studies, and in doing so slightly different versions of the task were employed due to task updates to reduce cognitive demands in the patients. Thus, it is possible such procedural differences could underlie any of the discrepancies in findings across the groups and replication with harmonization across samples is necessary. Pertaining to the twin analyses, we were unable to specify the environmental factors involved which will be beneficial to examine in future studies. While, a larger twin sample could have allowed us to test a more complete co-twin control model, a full biometric analysis was not conducted due to discordance-focused sampling of twin pairs. Another limitation of our study included operationalizing persecutory ideation differently across the two samples. Additionally, while the connectivity analyses were completed at a dimensionality of 60 components based on the recommendations from prior work (Poppe et al., 2013), future studies may wish to repeat these analyses at lower or higher dimensionalities. Finally, our study was cross-sectional; future investigations employing longitudinal studies and in vivo manipulations of persecutory ideation will be needed to reveal the how these relationships develop.

5 | CONCLUSION

In conclusion, we employed an innovative economic social decision-making task in two samples, revealed novel network relationships, and highlighted environmental causality underlying both the psychological and neural mechanisms of persecutory ideation. Specifically, our work demonstrated dACC-AI, lF-P, and vmPFC/OFC networks were associated with distinct forms of mistrust, but that only connectivity between the vmPFC/OFC and lF-P networks predicted persecutory ideation, suggesting a role of weakened top-down executive control on subjective valuation, and possibly *failure to correct* an "intuitive" idea (Risen, 2015) in this phenomena. Moreover, we established these mechanisms were associated with the same environmental variance using MZ twins, which is informative for future interventions. This work highlights a new brain-based perspective on dimensional persecutory ideation and identified potential treatment targets which require validation in larger samples.

ACKNOWLEDGMENTS

This work was supported by funding from National Association Research in Schizophrenia and Depression/Brain Behavior Research Foundation awards to AWM and National Institute of Mental Health grants R21MH112918 to AWM and F31MH102997 to KMW. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Brain Behavior Research Foundation. We thank the participants for their time and effort involved in the study. We also thank the Minnesota Center for Twin and Family Research, the Minnesota Supercomputer Institute, and the Center for Magnetic Resonance Research at the University of Minnesota, each for resources or support during different phases of the study.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Wisner, K. M., Johnson, M. K., Porter, J. N., Krueger, R. F., & MacDonald, A. W. III (2021). Task-related neural mechanisms of persecutory ideation in schizophrenia and community monozygotic twin-pairs. *Human Brain Mapping*, *42*(16), 5244–5263. https://doi.org/10.1002/hbm.25613