Mechanisms of Working Memory Impairment in Schizophrenia

Jared X. Van Snellenberg, Ragy R. Girgis, Guillermo Horga, Elsmarieke van de Giessen, Mark Slifstein, Najate Ojeil, Jodi J. Weinstein, Holly Moore, Jeffrey A. Lieberman, Daphna Shohamy, Edward E. Smith, and Anissa Abi-Dargham

ABSTRACT

BACKGROUND: The neural correlates of working memory (WM) impairment in schizophrenia remain a key puzzle in understanding the cognitive deficits and dysfunction of dorsolateral prefrontal cortex observed in this disorder. We sought to determine whether patients with schizophrenia exhibit an alteration in the inverted-U relationship between WM load and activation that we recently observed in healthy individuals and whether this could account for WM deficits in this population.

METHODS: Medicated (n = 30) and unmedicated (n = 21) patients with schizophrenia and healthy control subjects (n = 45) performed the self-ordered WM task during functional magnetic resonance imaging. We identified regions exhibiting an altered fit to an inverted-U relationship between WM load and activation that were also predictive of WM performance.

RESULTS: A blunted inverted-U response was observed in left dorsolateral prefrontal cortex in patients and was associated with behavioral deficits in WM capacity. In addition, suppression of medial prefrontal cortex during WM was reduced in patients and was associated with poorer WM capacity in patients. Finally, activation of visual cortex in the cuneus was elevated in patients and associated with improved WM capacity. Together, these findings explained 55% of the interindividual variance in WM capacity when combined with diagnostic and medication status, which alone accounted for only 22% of the variance in WM capacity.

CONCLUSIONS: These findings identify a novel biomarker and putative mechanism of WM deficits in patients with schizophrenia, a reduction or flattening of the inverted-U relationship between activation and WM load observed in healthy individuals in left dorsolateral prefrontal cortex.

Keywords: Cognitive impairment, Functional magnetic resonance imaging, Inverted-U, Schizophrenia, Short-term memory, Working memory

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Researchers have attempted for several decades to characterize the neurobiological mechanisms of deficits in working memory (WM) in patients with schizophrenia (1), which have been closely linked to poorer functional outcomes (2,3). Performance on WM tasks depends on dopamine function in dorsolateral prefrontal cortex (DLPFC) (4–7), which along with norepinephrine exerts a neuromodulatory influence on glutamatergic and gamma-aminobutyric acidergic networks that are critical to WM representations (6). Given the numerous dopaminergic abnormalities present in schizophrenia (4,9–11) and the mounting evidence for a disruption in glutamate (12,13) and gamma-aminobutyric acid (14,15) neurotransmission, disruption of WM representations in the DLPFC of patients with schizophrenia seems clear, although the precise nature of the disruption has yet to be elucidated.

A widely used approach to assaying DLPFC function during WM performance has been noninvasive in vivo hemodynamic imaging using functional magnetic resonance imaging (fMRI). Initial fMRI studies demonstrated reduced activation in DLPFC in patients during the performance of WM tasks (16–19), which was taken to be consistent with impaired dopamine function in DLPFC, given that dopamine in DLPFC had been shown to be critical for WM performance in nonhuman primates (20,21). However, subsequent studies failed to confirm these findings, instead showing greater DLPFC activation by patients (22–24), and our meta-analysis revealed no difference in DLPFC activation between patients and control subjects across 29 studies (25).

To account for these inconsistent findings, multiple authors proposed that the normal response of DLPFC to parametric variations in WM load may be nonmonotonic (i.e., an “inverted-U”) (26–28), such that DLPFC activation declines at higher WM loads, whereas patients with schizophrenia exhibit a “left shift” in this inverted-U, leading to greater DLPFC activation at lower WM loads and reduced activation at greater loads. Although this notion became prevalent and received considerable discussion (25,29–33), there has been no direct evidence thus far to support it. Jansma et al. (29) did observe a reduction in activation in DLPFC in patients from a 2-back load of the n-back task; however, their finding has not
been replicated in the very large literature using n-back tasks, their study was carried out with only 10 participants in each group and included error trials, and no inverted-U was observed in healthy participants. We propose that the failure thus far to demonstrate the hypothesized inverted-U may be due to the relative coarseness of the WM load manipulations allowed by commonly used WM tasks, such as the n-back and Sternberg tasks, where a limited number of steps restricts the ability of the task to demonstrate an inverted-U. Consequently, we adapted the self-ordered WM task (SOT), a classic neuropsychological test of DLPFC function (34), for use with fMRI. Our version of the task allows for a gradual increase in WM load from zero to seven items in a single trial, and SOT performance correlates with performance on a visual change detection task (35), the gold standard for estimating visual WM capacity. Critically, two independent cohorts of healthy individuals showed an inverted-U response in increasing WM load in the SOT in a network of regions including DLPFC (36).

We hypothesized that patients with schizophrenia would exhibit a similar but left-shifted variant of this inverted-U. Moreover, we hypothesized that this alteration would relate to task performance and WM deficit in patients. Consequently, we sought to determine whether either an inverted-U pattern of activation or the magnitude of activation (first in DLPFC, but also elsewhere in the brain) was 1) altered in patients with schizophrenia relative to matched control subjects and 2) predictive of performance on the task, as only regions showing evidence of both 1) and 2) can be taken as putative neuro-biological substrates explaining WM deficits in schizophrenia. Furthermore, because chronic dopamine D2 receptor antagonism by antipsychotic medications may affect DLPFC function, we included both unmedicated and medicated groups of psychiatrically stable patients in our study. Consistent with our work in healthy individuals, we restricted analysis of DLPFC activation to correct trials, to limit the impact of poor performance, which has been shown to produce reduced DLPFC activation in patients with schizophrenia (25,37).

### METHODS AND MATERIALS

#### Participants

All procedures were approved by the New York State Psychiatric Institute Institutional Review Board. Participants provided written informed consent, and patient participants were deemed to have capacity to provide consent by an independent psychiatrist. Patients were outpatients recruited from research facilities at the New York State Psychiatric Institute, and control participants were recruited via advertisements. The final sample included 21 unmedicated patients, 30 medicated patients, and 45 healthy control subjects (Supplemental Methods).

Inclusion criteria for patients were 1) lifetime DSM-IV diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder and 2) negative urine toxicoogy. Unmedicated patients were medication free for at least 2 weeks, whereas medicated patients were taking stable doses of risperidone, aripiprazole, lurasidone, paliperidone, or haloperidol for at least 4 weeks, with no antipsychotic polypharmacy and no psychiatric emergency department visit or hospitalization for at least 3 months. Inclusion criteria for healthy control subjects were 1) no history of a DSM-IV Axis I disorder, 2) no family history (first-degree relative) of psychotic illness, and 3) negative urine toxicoogy. Exclusion criteria for all groups included significant medical and neurologic illnesses, current misuse of substances other than nicotine, pregnancy, and nursing. Groups were matched for age, sex, and parental socioeconomic status. Table 1 summarizes demographic and clinical data.

#### Task Procedures

Task procedures are detailed in the Supplemental Methods and have been described previously (36). Briefly, eight line drawings of difficult-to- verbalize objects were presented, and participants were instructed to select each object once, in any order. After each object was selected, all objects were pseudorandomly rearranged on the screen. Participants then had to select an object not already selected so that at each step there was one more previously selected object to remember. A perceptual and motor control task was used following identical procedures except that one object was marked with an asterisk, and participants were instructed to select the marked object. Participants were paid $0.25 per correct response for both tasks. Our primary measure of performance was WM capacity, as estimated by a maximum likelihood model (Supplemental Methods) (35).

#### fMRI Procedures

**fMRI Acquisition, Preprocessing, and First-Level Modeling.** Data were acquired on a Philips 1.5T Intera scanner (Philips Healthcare, Andover, MA) and preprocessed as described elsewhere (36) and in the Supplemental Methods. Briefly, images were slice-timing corrected, motion realigned, normalized to a standard template, and smoothed. Time series values were transformed to percent signal change on a per-voxel basis. First-level modeling followed prior work (Supplemental Methods) (36). Regressors of interest were those reflecting correct trials in the control task or each of the first seven steps of the SOT, modeled separately. Step eight was excluded because of poor performance by patients. Incorrect trials were modeled separately and are not reported.

Two primary outcome measures were calculated for each subject. First, the fit to an empirical inverted-U shape obtained from an independent healthy sample [study 1 in our previous study (36)] was calculated at each voxel for each participant. This fit was obtained by regressing observed task activation at each step on the inverted-U shape, such that larger positive values indicate better fit. Second, a task minus control contrast was calculated as the average activation across the first seven steps of the SOT minus activation to the control task. Although we did not hypothesize a between-group difference in this contrast, it is a commonly used and straightforward measure of regional brain activation to the SOT relative to the control task.

**Second-Level Modeling.** Both outcome measures (regression betas indicating fit to the inverted-U pattern, and
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Table 1. Demographic and Clinical Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unmedicated Patients</th>
<th>Medicated Patients</th>
<th>Healthy Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>Age, Years (SD)</td>
<td>33.2 (10.6)</td>
<td>36.4 (7.5)</td>
<td>34.0 (8.9)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>11/10</td>
<td>17/13</td>
<td>21/24</td>
</tr>
<tr>
<td>Parental SES (SD)</td>
<td>43.4 (13.7)</td>
<td>41.0 (12.6)</td>
<td>42.1 (14.0)</td>
</tr>
<tr>
<td>Handedness, R/L</td>
<td>19/2</td>
<td>27/3</td>
<td>44/1</td>
</tr>
<tr>
<td>Age at Diagnosis (SD)</td>
<td>18.1 (4.9)</td>
<td>22.2 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic Medication History, DF/DN</td>
<td>12/9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Current CPE (mg) (SD)</td>
<td>—</td>
<td>270.6 (227.8)</td>
<td>—</td>
</tr>
<tr>
<td>PANSS General</td>
<td>29.7 (8.8)</td>
<td>29.2 (7.9)</td>
<td>—</td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>14.4 (5.9)</td>
<td>13.0 (6.6)</td>
<td>—</td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>15.9 (5.9)</td>
<td>14.8 (6.0)</td>
<td>—</td>
</tr>
<tr>
<td>SANS</td>
<td>8.8 (4.4)</td>
<td>8.4 (3.4)</td>
<td>—</td>
</tr>
</tbody>
</table>

CPE, chlorpromazine equivalent dose; DF, antipsychotic drug free for at least 2 weeks (at least 6 weeks for aripiprazole); DN, antipsychotic drug naïve; F, female; L, left; M, male; PANSS, Positive and Negative Syndrome Scale; R, right; SANS, Scale for the Assessment of Negative Symptoms; SES, socioeconomic status.

*Age at diagnosis refers only to primary psychotic disorder. Data were available only for 20 (95%) of the unmedicated sample and 13 (43%) of the medicated sample.

*Current antipsychotic dose compares with 100 mg oral chlorpromazine, using 2 mg haloperidol, 2 mg risperidone, 7.5 mg aripiprazole, 20 mg lurasidone, 25 mg risperidone (depot), and 30 mg haloperidol (depot) (51). For depot paliperidone, we use the manufacturers’ recommended equivalent for the depot to oral conversion (234 mg paliperidone palmitate [depot] every 28 days = 12 mg oral paliperidone daily) and then converted to oral chlorpromazine equivalents.

Three patients were also taking a nonantipsychotic mood stabilizer at the time of participation, and 11 patients were taking an antidepressant.

Contrast values for overall activation were analyzed in a series of robust models (38); t tests for group comparisons or multiple regressions for testing effects of WM capacity and group were used as appropriate. These models evaluated 1) whether there were group differences in activation or inverted-U fit and 2) whether activation or inverted-U fit related to WM capacity in each group and whether there were group differences in this relationship (group by WM capacity interaction). See Supplemental Methods for multiple comparison corrections.

Region of Interest. Second-level analyses were first carried out in an anatomically and functionally defined a priori region of interest (ROI) of bilateral DLPFC (Supplemental Methods) and subsequently in an exploratory whole-brain analysis.

RESULTS

Task Performance

Accuracy, reaction times, and estimated WM capacity are shown in Figure 1. Healthy participants had a mean (SD) WM capacity of 5.63 (1.32), consistent with prior observations (35,36), whereas patients had a WM capacity of 3.89 (1.93), which differed significantly from control subjects (p < .00001). Unmedicated and medicated patients had WM capacities of 4.15 (1.88) and 3.72 (1.97), respectively (no significant difference; p = .43).

All groups performed above chance at every step (one-sample t tests, all p < .0001), and control subjects performed better than patients at all steps (two-sample t tests, all p < .0001). Unmedicated patients performed better than medicated patients at step 2 (p < .005) and showed a trend toward better performance at all other steps excluding step 7 (all p < .1). Control subjects responded significantly faster than patients at all steps (all p < .05) except step 2, at which a trend was observed (p = .06). Patient groups did not differ in reaction time (all p > .26).

fMRI Results

Activation to the SOT. Regions showing significant differences in activation between the SOT and control task are reported in Figure 2A and Supplemental Tables S1–S3. Patient subgroups are displayed for illustrative purposes, and between-group analyses are reported separately (see later). Consistent with our prior report (36), healthy control subjects showed robust activation of the classic WM network, including bilateral DLPFC, posterior parietal cortex, pre-supplementary motor area, and left dorsal anterior insula, as well as premotor areas and most of the lateral occipital lobe and fusiform gyrus. Control subjects also demonstrated substantial deactivations throughout the default mode network, including medial prefrontal cortex (mPFC), posterior dorsal cingulate, precuneus, and lateral temporal lobes, as well as the temporal parietal junction. Both patient groups showed patterns of activation and deactivation similar to the patterns observed in healthy control subjects.

Regions Exhibiting Inverted-U Activation Pattern. Regions that significantly fit an inverted-U activation pattern are shown in Figure 2B and Supplemental Tables S4–S6. These regions closely matched the regions in our prior work (36), including bilateral DLPFC, posterior parietal cortex, pre-supplementary motor area, premotor areas, lateral occipital lobe, fusiform gyrus, and medial temporal lobe in healthy control subjects, with a similar but less robust activation pattern observed in both patient groups.
Group Differences and Relationships to Performance in DLPFC. A region of left DLPFC (141 voxels; Montreal Neurological Institute (MNI) coordinates \(-48, 15, 28\); maximum \(t\) value 3.28) showed a poorer fit to an inverted-U in patients than in healthy control subjects (Figure 3A). Activation in this region did not appear to be “left shifted” in the patient group; rather, patients failed to show the clear rise and fall of activation in this region observed in healthy control subjects, leading to a flatter pattern of response. Moreover, we observed a positive relationship in both patient and control groups between inverted-U fit and WM capacity in left DLPFC, which overlapped with the region showing a group difference (Figure 3B; control subjects—109 voxels; MNI coordinates \(-51, 15, 31\); maximum \(t\) value 3.17; patients—71 and 54 voxels; MNI coordinates \(-45, 33, 16\) and \(-42, 9, 28\); maximum \(t\) values 3.24 and 3.42). Thus, the reduction in inverted-U fit in this region of left DLPFC can be considered a putative neurobiological marker of WM deficit in schizophrenia, as it is both deficient in patients and associated with WM capacity. No differences were observed within the DLPFC ROI between the two patient subgroups.

Regions within the DLPFC ROI showing differences in overall activation to the task (relative to the control task) are shown in Supplemental Figure S1. Briefly, inferior right prefrontal cortex showed greater activation in patients than in control subjects, whereas a more dorsal and anterior area showed a positive relationship between activation and WM capacity in patients but not control subjects.

Whole-Brain Group Differences and Relationships to Performance. The full set of regions showing significant group differences or relationships to performance in inverted-U fit or task activation are shown in Supplemental Figures S2 and S3 and Tables S7 and S8. We were primarily interested in identifying regions that exhibit both 1) a group difference and 2) a relationship to WM capacity in either inverted-U fit or task activation, as with the left DLPFC region identified in the earlier ROI analysis and consistent with a neurobiological substrate of WM deficit. Consequently, for both inverted-U fit and task activation, we produced conjunction maps of regions showing both of these effects (1 and 2) (Figure 4). This analysis recapitulated our ROI-based finding of a putative substrate of WM deficit in left DLPFC for inverted-U fit and further identified a region of mPFC that showed greater overall activation in patients and a negative relationship with performance in patient and control groups, demonstrating that failure by patients to adequately suppress activation in this region during task performance is associated with their deficit in WM. In addition, a region of visual cortex in the cuneus demonstrated increased activation in patients with schizophrenia, along with a positive relationship to WM capacity observed in healthy individuals (but not patients).

To tease apart the relative, unique contributions of each of these findings to individual differences in WM capacity, we extracted mean values (either inverted-U fit betas or task minus control contrast values, as appropriate) from each cluster (minimum 10 voxels) identified in the conjunction images shown in Figure 4. These were averaged within each cluster to produce a scalar value for each participant in each cluster, which was then related to WM capacity in a step-forward linear regression model selection framework.
The impact of symptoms (the three Positive and Negative Syndrome Scale subscales) on WM capacity was also evaluated in this framework. The resulting model demonstrated independent contributions to WM capacity from 1) the inverted-U fit in the smaller left prefrontal cortex region, which behaved very similarly to the larger DLPFC cluster (see later) and was positively associated with WM capacity; 2) cuneus, in which activation was positively associated with WM capacity; and 3) the suppression of activation in mPFC, where activation was negatively associated with WM capacity in patients (but not control subjects). No symptom variables were significant. In addition, diagnosis still had a significant impact on WM capacity in the model, and a trend was observed toward further WM deficit in medicated patients. Moreover, all variables retained in the regression model were also significant predictors in bivariate simple linear regression models. In all, the model accounted for 55.5% of the variance in WM capacity, whereas a model with diagnostic information removed accounted for 37.9% of the variance in WM capacity. Critically, inverted-U fit in the larger left DLPFC region was correlated with the smaller region that remained in the model ($r = .57$, $p < .00005$), and if we substituted it into the model in place of the smaller region, the model remained largely unchanged, although the $p$ value for this region was then only at trend level ($p = .071$). Taken together, these observations suggest that the contributions of the two left prefrontal regions in Figure 4 were largely indistinguishable, although slightly more robust in the smaller of the two regions.

**DISCUSSION**

These data identify two potential neurobiological mechanisms of WM deficits in patients with schizophrenia, one of which has not been previously identified in the literature. First,
patients with schizophrenia demonstrated a flattening of the inverted-U pattern of activation over increasing WM loads observed in the DLPFC of healthy individuals, a pattern that was associated with reduced WM capacity. This represents the first clear demonstration of an alteration in the long-hypothesized inverted-U relationship between WM load and DLPFC activation in patients with schizophrenia, although the alteration we observed does not take on the form of a “left shift,” as initially described (26). Rather, the flattening or blunting of the inverted-U observed here was proposed later, to explain findings of a reduced load-activation slope in patients relative to control subjects (30), although no inverted-U was observed directly in that study. Second, patients demonstrated a relative failure to deactivate mPFC during WM task performance, which was also associated with greater deficits in WM capacity among patients with schizophrenia. This failure to deactivate portions of the so-called default mode network by patients with schizophrenia has been widely reported (39–42), although we are aware of only one prior report linking deactivation of this region to WM performance in healthy individuals (but not patients) (43). Finally, activation in medial visual cortex (cuneus) was both significantly increased in schizophrenia and positively associated with WM capacity. Critically, multiple regression indicated an independent role for each of these three mechanisms in WM deficits. Moreover, these findings were obtained in an analysis using only task steps that were performed correctly, mitigating contamination of fMRI activation measures by trials on which participants were disengaged or otherwise unable to effectively use their WM.

Despite tremendous interest in DLPFC dysfunction as the (putative) primary neuropathologic substrate of WM deficits in schizophrenia, clear evidence for a functional abnormality in this region that is associated with individual differences in WM capacity has failed to emerge until this report, and confidence in our findings is enhanced by the relatively large sample employed here and by the inclusion of a substantial number of medication-free patients. Although the present results cannot speak directly to the molecular underpinnings of WM deficits in schizophrenia, and would certainly benefit from replication, we report here a direct connection between DLPFC dysfunction and WM deficits in schizophrenia in a clinical sample. Critically, this dysfunction does not come in the form of simply increased or decreased activation, but rather in a more subtle alteration of an activation pattern associated with strong WM capacity across diagnostic groups, which can (presumably) be elucidated only under conditions that allow for fine-grained manipulation of WM over a broad range of WM loads; namely, a failure to show a robust inverted-U relationship between WM load and activation in left DLPFC. This finding has important implications for future work, which will be needed to better understand how this functional alteration in inverted-U activation in DLPFC operates in clinical samples and animal models, and which could potentially identify new targets for treatment of cognitive deficits in schizophrenia. That is, the overwhelming majority of WM tasks that have been used to probe WM in both clinical and basic research employ at most two or three WM loads, which is likely insufficient to characterize the inverted-U activation pattern (or lack thereof) shown to be associated with WM capacity in the present study.

A critical unresolved question relates to the functional significance of the inverted-U observed in healthy control subjects, which we have discussed at length elsewhere (36). The initial formulation of the inverted-U hypothesis (26,27) speculated that it may occur as a result of task disengagement,
which is an unlikely explanation for the present findings given that we analyzed only correctly performed trials and that reaction times increase at higher loads even in poor performers (36). Moreover, the observed positive association between the inverted-U pattern and WM capacity also suggests that this activation pattern is adaptive. Although at the present time we are unable to definitively adjudicate between competing possibilities, in general terms it seems most likely that the inverted-U reflects an adaptive shift in cognitive strategy that patients (or at least many patients) fail to engage. For example, as we have argued elsewhere, participants may gradually shift from a WM-mediated to a long-term memory-mediated strategy that requires less reliance on active maintenance (36). In this case, the failure by patients to exhibit this neural response could reflect inefficient strategy use, direct impairment to the WM system that limits the extent of DLPFC activation (flattening the

Figure 4. Brain regions showing group differences and an association with working memory (WM) for either inverted-U fit or task activation. (A) Regions in a whole-brain analysis showing both a significant difference between patients and control subjects and an association with WM capacity in at least one group for the inverted-U fit. (B) Regions in a whole-brain analysis showing both a significant difference between patients and control subjects and an association with WM capacity in at least one group for activation to the self-ordered WM task. Scatterplots in (A) and (B) show the relationship between the circled region and WM capacity, after adjusting WM capacity for other predictors in the full model described in the text. (C) WM capacity regressions for a simple model including only diagnostic and medication grouping variables (left) and for a full model determined with step-forward model selection (right), including the four circled regions identified in (A) and (B).
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Finally, it is important to bear in mind that our two patient samples were identified more naturalistically than experimentally. Our unmedicated group consisted of psychiatrically stable outpatients who either refuse to take medications or were off medications for reasons unrelated to this study. Thus, they represent a population that is distinct from our medicated sample in ways that extend beyond medication status, and so any differences (or similarities) cannot necessarily be attributed to the medications per se. For example, the close correspondence in overall symptoms between the two groups (Table 1) strongly suggests that our unmedicated sample is more mildly psychotic than our medicated sample. Similarly, there was considerable suggestive (i.e., trend-level) evidence that the medicated patients may have performed more poorly on the SOT than the unmedicated patients. Although this poorer performance could plausibly be an effect of antipsychotic medications, it could also reflect more serious impairment in the medicated patients. Thus, although the lack of differences between patient groups in any of our neural outcome measures or in the observed relationships between neural outcomes and WM capacity suggests that the phenomena under consideration are not strongly impacted by antipsychotic medication, it is possible that these medications do exert important influences that have been missed in this study as a result of other systematic differences between these two groups.

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ARTICLE INFORMATION

From the Department of Psychiatry (JXVS, RRG, GH, EvdG, MS, NO, JJW, HM, JAL, AA-D), Columbia University College of Physicians and Surgeons; Divisions of Translational Imaging (JXVS, RRG, GH, EvdG, MS, NO, JJW, AA-D), Cognitive Neurosciences (JXVS, EES), and Integrative Neuroscience (HM), New York State Psychiatric Institute (JAL), New York, New York; Department of Nuclear Medicine (EvdG), University of Amsterdam, Amsterdam, The Netherlands; and Department of Psychology (DS, EES), Columbia University, New York, New York. Deceased (EES). EES was heavily involved throughout the preliminary and intermediate phases of the study reported in this manuscript, including task and experimental design.
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Address correspondence to Jared X. Van Snellenberg, Ph.D., 1051 Riverside Drive, Unit 31, New York, NY 10032; E-mail: jxv1@cumc.columbia.edu.

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