Amotivation in Schizophrenia: Integrated Assessment With Behavioral, Clinical, and Imaging Measures

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Motivational deficits play a central role in disability caused by schizophrenia and constitute a major unmet therapeutic need. Negative symptoms have previously been linked to hypofunction in ventral striatum (VS), a core component of brain motivation circuitry. However, it remains unclear to what extent this relationship holds for specific negative symptoms such as amotivation, and this question has not been addressed with integrated behavioral, clinical, and imaging measures. Here, 41 individuals with schizophrenia and 37 controls performed a brief, computerized progressive ratio task (PRT) that quantifies effort exerted in pursuit of monetary reward. Clinical amotivation was assessed using the recently validated Clinical Assessment Interview for Negative Symptoms (CAINS). VS function was probed during functional magnetic resonance imaging using a monetary guessing paradigm. We found that individuals with schizophrenia had diminished motivation as measured by the PRT, which significantly and selectively related to clinical amotivation as measured by the CAINS. Critically, lower PRT motivation in schizophrenia was also dimensionally related to VS hypofunction. Our results demonstrate robust dimensional associations between behavioral amotivation, clinical amotivation, and VS hypofunction in schizophrenia. Integrating behavioral measures such as the PRT will facilitate translational efforts to identify biomarkers of amotivation and to assess response to novel therapeutic interventions.

Key words: motivation/progressive ratio/ventral striatum/fMRI/negative symptoms

Introduction

Amotivation is one of the cardinal negative symptoms of schizophrenia, which as a group are disabling, poorly understood, and poorly responsive to current treatments. Increasing evidence suggests that amotivation represents a particularly important problem within the broader negative symptom domain.

Amotivation therefore constitutes a major unmet therapeutic need. However, there are important barriers to novel treatment development. One major barrier is limited knowledge regarding the pathophysiology of amotivation. Animal and human studies emphasize the critical role of the mesolimbic dopamine system, particularly the nucleus accumbens/ventral striatum (VS), in reward processing that generates motivation. Negative symptoms have previously been linked to VS hypofunction in functional magnetic resonance imaging (fMRI) studies. However, it remains unclear to what extent this relationship is selective for particular negative symptoms such as amotivation.

Limitations of existing measurement approaches pose another major barrier. While expressive negative symptoms such as flat affect and alogia are directly observable, amotivation is an inherently subjective psychological state. Understanding amotivation therefore requires careful assessment of both self-reported experience and objective behavior. New clinical interview measures informed by affective neuroscience findings represent an advance. However, even the best clinical interview measures have significant limitations for translational research, and the application of objective laboratory measures of motivation is essential. However, such work has been minimal until very recently, and development of laboratory motivation paradigms has lagged behind analogous work on anhedonia and emotion processing.

Here, we utilized a brief computerized progressive ratio task (PRT) to quantify behavioral motivation deficits in schizophrenia. A PRT identifies the maximum effort a subject is willing to exert for a reward by progressively increasing the number of responses required.
for the reward. PRTs have strong translational potential given their extensive use in animal research including models of negative symptoms, but to date, the only published work applying this method in schizophrenia consists of 2 very small studies examining smoking behavior. \(^{35,36}\)

We related motivation measured dimensionally with this novel PRT to clinical amotivation assessed with the recently validated Clinical Assessment Interview for Negative Symptoms (CAINS), which integrates experiential and behavioral information. We also related the PRT to VS activation in response to monetary rewards vs losses during fMRI, reasoning that such VS responses would index motivation-related processing of reward prediction errors. We hypothesized that people with schizophrenia would show reduced behavioral motivation on average and that the degree of behavioral amotivation would correlate with both clinical amotivation and VS hypofunction.

### Methods

#### Participants

The PRT was administered to 84 adults age 18–60 including 46 clinically stable individuals affected by schizophrenia \((n = 44)\) or schizoaffective disorder depressed type \((n = 2)\), and 38 controls without any personal or first-degree family history of psychosis. Behavioral analysis included data from 41 subjects with schizophrenia and 37 controls; fMRI analysis included 35 schizophrenia subjects and 36 controls (see supplementary materials for exclusions and examination of in-scanner motion). Schizophrenia and comparison groups did not differ on demographic variables except education and socioeconomic status (see table 1). After complete description of the study to the subjects, written informed consent was obtained. All study procedures were approved by the University of Pennsylvania’s Institutional Review Board.

### Table 1. Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls ((n = 37))</th>
<th>Patients ((n = 41))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>51%</td>
<td>46%</td>
<td>.82(^{ab})</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>89%</td>
<td>90%</td>
<td>.99</td>
</tr>
<tr>
<td>Smoke (% Y)</td>
<td>33%</td>
<td>45%</td>
<td>.36</td>
</tr>
<tr>
<td>Age (y)</td>
<td>39.2 (12.1)</td>
<td>41.7 (10.7)</td>
<td>.35(^c)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>14.8 (2.2)</td>
<td>13.5 (2.3)</td>
<td>.1</td>
</tr>
<tr>
<td>Parental education</td>
<td>14.2 (2.5)</td>
<td>13.3 (3.3)</td>
<td>.13</td>
</tr>
<tr>
<td>Socioeconomic status(^d)</td>
<td>39 (13)</td>
<td>27 (15)</td>
<td>.0004</td>
</tr>
<tr>
<td>CAINS amotivation(^e)</td>
<td>0.67 (0.57)</td>
<td>1.68 (0.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAINS anhedonia</td>
<td>0.63 (0.45)</td>
<td>1.20 (0.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAINS asociality</td>
<td>0.56 (0.54)</td>
<td>1.39 (0.78)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAINS expressivity</td>
<td>0.43 (0.48)</td>
<td>1.13 (0.87)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SANS global average(^f)</td>
<td>0.37 (0.64)</td>
<td>2.10 (0.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SAPS global average(^g)</td>
<td>0.09 (0.25)</td>
<td>1.18 (0.85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression symptoms(^h)</td>
<td>0.95 (1.88)</td>
<td>3.15 (3.09)</td>
<td>.0004</td>
</tr>
<tr>
<td>Cognitive performance(^i)</td>
<td>0.27 (0.57)</td>
<td>-0.24 (0.71)</td>
<td>.009</td>
</tr>
<tr>
<td>Nicotine dependence(^j)</td>
<td>0.9 (1.9)</td>
<td>2.1 (2.8)</td>
<td>.12</td>
</tr>
<tr>
<td>Antipsychotic dose(^k)</td>
<td>NA</td>
<td>493 (347)</td>
<td>NA</td>
</tr>
<tr>
<td>In-scanner motion(^l)</td>
<td>0.08 (0.04)</td>
<td>0.09 (0.04)</td>
<td>.11</td>
</tr>
</tbody>
</table>

**Note:** CAINS, Clinical Assessment Interview for Negative Symptoms; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms.

\(^{a}\)All \(P\) values in the table are 2 tailed, uncorrected.

\(^{b}\)Fisher’s exact test, 2 tailed, was used to compare proportions for categorical variables.

\(^{c}\)Student’s \(t\) test used for comparing group means.

\(^{d}\)Calculated using Hollingshead method.

\(^{e}\)CAINS scores are averages across items within each domain. See details in Supplementary materials.

\(^{f}\)SANS and SAPS scores reflect the average of global items (excluding SANS attention).

\(^{g}\)Calgary Depression Scale for Schizophrenia.

\(^{h}\)Calculated from Penn CNB as \(z\) scores across all subjects from both groups.

\(^{i}\)Fagerstrom Test for Nicotine Dependence; group comparison used nonparametric rank sum test, 2 tailed.

\(^{j}\)Antipsychotic treatment: none \((n = 1)\), 1st generation \((n = 5)\), 2nd generation \((n = 30)\), both \((n = 5)\).

\(^{k}\)Mean relative scan-to-scan displacement in millimeters, in sample retained for functional magnetic resonance imaging analysis.
Study Design and Assessment Procedures

Clinical diagnostic interview and cognitive testing were performed for all subjects on an initial study visit. On the second visit, motivation was comprehensively assessed using the CAINS interview (beta version),37 the PRT, and reward neuroimaging. The CAINS is a recently validated scale designed to assess negative symptoms of schizophrenia across multiple domains.19 Each item is measured on a 5-point scale (0–4) indexing increasing severity. CAINS scores reported here are averages of relevant items and hence lie on the same 0–4 scale. Given its prominence in prior literature, we also administered the Scale for Assessment of Negative Symptoms (SANS). Additional symptom scales allowed us to address questions of specificity, including positive symptoms (Scale for Assessment of Positive Symptoms [SAPS]), depression (Calgary Depression Scale for Schizophrenia [CDSS]), and nicotine dependence (Fagerstrom Test for Nicotine Dependence [FTND]). See supplementary materials for further assessment details.

Progressive Ratio Task

Participants performed a computerized PRT to earn money. Subjects received task instructions and a brief set of practice trials. The task included 7 sets of trials at each of 3 monetary reward levels ($0.50, $0.25, and $0.10). For each individual task trial, participants were required to view 2 numbers on the screen and identify the larger one by pressing one of 2 keys on a standard keyboard. Numbers were randomly selected between 0 and 1000. The effort (ie, number of correct responses) required to achieve a reward increased with each successive trial set within a given reward level (figure 1 and supplementary table S1).

Before each set, the number of trials required and the monetary value of the set was presented and the subject chose whether to perform the set or not; they also could choose to quit a set at any point. When a subject chose not to complete a set, the higher effort sets at that monetary value were not presented and the next set offered was the lowest effort set at the next (lower) monetary value. Subjects received their earnings at the end of the study; a maximum of $5.95 could be earned in the PRT by completing all 21 sets (1454 total correct trials). See supplementary materials for additional PRT details, instruction text, and rationale.

PRT Performance Analysis

The primary PRT outcome measure was the breakpoint. The breakpoint is the maximum effort a subject is willing to exert for a particular reward; higher breakpoints indicate greater motivation. We measured breakpoint in trials-per-cent (tpc). A single breakpoint was obtained for each subject by averaging across the breakpoints for each of 3 monetary amounts. Within each monetary level, the breakpoint was calculated as the mean of the log10(tpc) value of the last completed set and the first incomplete set; the log transformation was applied to normalize the distribution. If no sets were completed, the breakpoint was estimated as the log10(tpc) value for the first set; if all sets at a particular monetary amount were completed, then breakpoint was estimated as the log10(tpc) value for the last set. For some analyses (eg, figure 2A), breakpoints in the more intuitive units of trials/cent are shown, in which case nonparametric statistics were applied given nonnormal distributions. Overall, response time (RT) was also calculated for each subject as the average of the RTs at each monetary level.

Fig. 1. Progressive ratio task. Examples of the set choice screen (upper panel) and individual effort trial screen (lower panel) are shown in (A). The graph in (B) shows the task structure regarding monetary reward amounts and effort requirements. Sets were designed so that the number of responses (trials) required per cent earned was the same across reward levels (yielding parallel lines in the graph). Sets required more effort in increasingly large steps (note logarithmic scale) in order to be able to differentiate motivation levels across a broad range of breakpoints, from only being willing to make one response for 10 cents, to being willing to respond 10 times for 1 cent.
Within a monetary level, the RT was the median RT across trials within a set, averaged across all completed sets.

Group differences were examined using unpaired t-tests. The primary analysis relating PRT breakpoint to CAINS amotivation in schizophrenia used Pearson’s correlation. Secondary analyses in the schizophrenia group assessed specificity and potential confounds by relating PRT breakpoint to other clinical, demographic and performance measures using Pearson’s correlation, Spearman’s correlation, or linear regression as appropriate, depending on the distribution of the independent variable. As a further test of specificity, a stepwise multiple regression incorporating all variables into a single model was also performed (MATLAB function stepwisefit; entrance/exit criterion $P < .05/P > .10$).

fMRI Paradigm

VS activation to unpredictable reward outcomes was probed using a monetary card guessing task (figure 3A), adapted from Delgado et al. Although this task is not a motivation task per se, it elicits strong VS responses consistent with prediction errors implicated in generating learning and motivation and imposes minimal cognitive demands, thus reducing a potential impact of cognitive deficits in assessing motivation-related activity. In each trial, subjects viewed the back of a card and guessed whether the front of the card would be revealed to be red or black. Correct guesses gained $5.00, and incorrect guesses lost $4.75. A slightly greater amount was used for wins than losses to avoid potential task frustration while keeping 50/50 outcome probabilities. Subjects were instructed that outcomes depended on their guesses, but in fact outcome order was pseudorandomized so that each subject experienced equal numbers of wins and losses in a fixed order selected to maximize design efficiency. Nonresponses resulted in display of a nonresponse warning and a $4.75 loss; these missed trials were analyzed separately. Each individual trial contained 2 parts, a guessing phase (2 s) and an outcome phase (2 s), which were separated by a jittered intratrial delay (2–12 s, mean 5 s); intertrial intervals were jittered the same way. During these delays, the back of a card was displayed with a symbol for passive fixation. Responses and reaction times were recorded with a 2-button response pad. Two runs of this card task were performed; 2 runs using facial affective feedback were also performed (results to be presented elsewhere). Each card task run comprised 336 seconds (168 volumes) of analyzed data including 24 trials (12 win, 12 loss); the first 20 seconds of data including 2 “dummy” trials were discarded to allow for scanner equilibration. At the end of the study, all subjects received $6.50 for this task.

Image Analysis

3T BOLD data acquisition, preprocessing, and subject-level timeseries analyses were performed using FEAT (fMRI Expert Analysis Tool, www.fmrib.ox.ac.uk/fsl), as described in supplementary materials. Because of the robust and selective activation of VS to monetary rewards compared with monetary losses, our a priori contrast of interest was win > lose outcomes. Based on our strong a priori hypotheses regarding VS, we conducted a VS region of interest (ROI) analysis. VS was defined anatomically by generating two 10 mm spheres surrounding Montreal Neurological Institute (MNI) coordinates ($\pm 10, 10, -2$) selected from a prior study of VS activation to rewards and removing the dorsal striatum by excluding voxels with MNI coordinates $z > 0$ (ROI volume was 5808 mm$^3$). Significant effects within this ROI were defined as clusters with a voxel height $Z > 1.65$ (uncorrected $P < .05$) and cluster-corrected $P < .05$ (extent $\geq 62$ voxels; AlphaSim; R. W. Cox, National Institutes of Health). In addition to this ROI
analysis, exploratory whole brain analyses were conducted, using a voxel height threshold of \[ Z > 3.09 \] (uncorrected \[ P < .001 \]) and cluster-corrected \[ P < .01 \] (extent \( \geq 55 \) voxels).

For our strong directional a priori hypotheses relating diagnosis, clinical motivation, behavioral motivation, and VS activation (group comparison \( t \)-tests and within-group Pearson's correlations), we utilize 1-tailed \( P \) values; other statistical tests utilize 2-tailed \( P \) values.

**Results**

**Progressive Ratio Performance and Relationship to Clinical Amotivation**

Schizophrenia subjects exhibited significantly lower motivation as defined objectively by progressive ratio breakpoints (\( P = .024 \), figure 2A; supplementary table S2). As predicted, among individuals with schizophrenia, there was a statistically significant inverse correlation between PRT motivation and clinical amotivation severity as assessed by the CAINS (\( r = -.40, P = .005 \); figure 2B). A significant inverse correlation was also evident among controls (\( r = -.30, P = .038 \)). In the schizophrenia group, the relationships between PRT and other CAINS negative symptom domains were in the same direction, but none were as strong as the correlation between PRT and CAINS amotivation (figure 2C). The pattern of correlation strengths was not explained by domain differences in measurement reliability (supplementary table S3). Relationships between PRT and SANS negative symptom domains were also weaker and not statistically significant (all \( P \)'s > 0.1). The relationship between PRT and CAINS amotivation in the schizophrenia group...
remained significant (P < .05) after accounting for potential confounds including PRT response speed, age, gender, education, parental education, socioeconomic status, smoking status or nicotine dependence severity, cognitive ability, depression, positive symptoms, or antipsychotic dose (chlorpromazine equivalents) and type (first-generation antipsychotic present or absent), none of which correlated significantly with PRT (all P > 0.1). A stepwise regression predicting PRT breakpoint in schizophrenia and including all variables (CAINS domain scores and potential confounds) revealed that only CAINS amotivation was significant and retained in the final model (supplementary table S4).

**PRT Relationship to Ventral Striatum Activation**

Subjects demonstrated expected fMRI task behavior, without group differences (supplementary results). As expected, the contrast of win > loss outcomes in the monetary reward paradigm produced strong and selective VS activation (figure 3B); less robust effects were also found in additional regions including ventromedial prefrontal cortex, orbitofrontal cortex, and dorsal anterior cingulate (supplementary table S5). Within the a priori VS ROI, the schizophrenia group on average did not show significant reductions in VS response to wins vs losses relative to controls (control 0.14 ± 0.14%, schizophrenia 0.12±0.11%, P = .42). However, within the schizophrenia group, lower PRT motivation significantly correlated with impaired VS recruitment (figure 4). Because the fMRI task involves relatively large monetary gains and losses (~$5 each trial), we assessed whether the highest monetary level in the PRT (50 cents per set) would show the strongest correlations with VS activation in the fMRI task. This was indeed the case, and correlations in other regions including dorsolateral prefrontal cortex and visual cortex were also seen (supplementary figure S1 and tables S6 and S7). The correlation between CAINS amotivation and VS activation was in the expected (inverse) direction but was only a statistical trend (cluster P = .061 in VS ROI). Control group data did not reveal significant relationships between VS activation and either PRT or CAINS.

**Discussion**

Despite the importance of motivational deficits in schizophrenia, they have received relatively little focused empirical attention. Here, we sought to address this gap by applying a novel computerized PRT to quantify motivation deficits. As hypothesized, behavioral motivation deficits were found in the schizophrenia group and correlated with both clinical amotivation severity and hypofunction in brain motivation circuitry. This integrated set of behavioral, clinical, and brain imaging measures dimensionally captures motivation deficits in schizophrenia and can help us understand the phenomenology, pathophysiology, and ultimately the therapeutic sensitivity of motivation deficits.

**Relationship Between Behavioral and Clinical Amotivation**

The relationship of PRT motivation to different domains of negative symptoms was most robust for CAINS amotivation. While a larger study would be required to identify statistically significant differences in PRT correlations across CAINS domains that are themselves correlated, our results provide initial support for a selective
relationship between the PRT and clinical amotivation. This selectivity supports the construct validity of this brief behavioral measure, and encourages further use of quantitative laboratory paradigms to examine specific negative symptom domains.

PRTs are widely used to measure motivation in animal research, primarily in models of drug addiction. A few studies have applied PRTs in animal models of schizophrenia, identifying reduced PRT breakpoints. Use of PRTs in human studies has been more limited, again focused primarily on addiction, and PRTs have been applied in schizophrenia only to assess nicotine reward. Two very recent studies demonstrated reduced motivation in schizophrenia using choice effort tasks without a progressive ratio schedule. In the I study large enough to subdivide the schizophrenia sample based on negative symptoms, the high negative symptom group was less likely to choose the high-effort option and performed the required alternating button presses more slowly; effortful choices also correlated strongly with cognitive ability. Our results confirm the link between negative symptoms and reduced effortful behavior. In addition, we demonstrate this relationship is dimensional and especially robust for clinical amotivation, and is independent of global cognitive capacity, which was unrelated to performance on our task.

**Relationship Between Behavioral Motivation and Brain Reward Responses**

Our study is the first to establish a correlation between VS hypofunction in schizophrenia and impaired motivation on a PRT or other paradigm assessing the willingness to expend effort. Animal research identifies the mesolimbic dopamine system projecting from the midbrain ventral tegmental area to the VS as critical for motivated behaviors. Disruption of this system reduces effort for rewards even when preferences for rewards and basic motor functions remain intact. Our group and others have previously related negative symptom severity to reduced VS fMRI activation, as well as lower VS dopamine levels using PET imaging. These studies identified VS correlations using a variety of negative symptom measures including global severity, avolition-apathy, the combination of avolition-apathy and anhedonia-associality, and trait physical anhedonia. Here, behavioral amotivation significantly correlated with VS hypofunction, while clinical amotivation only showed a statistical trend. We speculate that this is because clinical amotivation measures are impacted by a broader array of factors (eg, environmental constraints) than laboratory tasks and may therefore provide less sensitivity in identifying neurobiological correlates of specific psychological constructs like willingness to exert effort for reward.

While we found a robust dimensional correlation between behavioral amotivation and VS hypofunction in schizophrenia, we did not find significant average reductions in VS response. This suggests that VS hypofunction should not be considered characteristic of schizophrenia per se, but rather a marker of important heterogeneity within the disorder. This interpretation is consistent with the complexities of prior literature: some studies have reported group differences in reward-related VS activation when comparing schizophrenia patients and controls, and many have related VS hypofunction to negative symptoms (see above) or to other individual differences including medication status and positive symptoms.

In addition to VS, our exploratory whole brain analysis identified significant correlations between PRT motivation and reward responses in left lateral occipital cortex, and for the highest PRT monetary level correlations were also seen in dorsolateral prefrontal cortex bilaterally. Thus, even in a simple guessing paradigm, more motivated subjects show stronger recruitment of visual regions involved in higher level sensory processing (including integration of sensory and reward information) and executive regions integrating reward information with goals and action plans. Lateral prefrontal activation has previously been related to global negative symptoms. Future research should investigate the role of VS-prefrontal interactions in both healthy motivation and its disruption in schizophrenia.

**Findings in Control Subjects**

In the control group, the correlation between behavioral motivation (PRT) and clinical motivation (CAINS) was also significant although somewhat less robust. The CAINS has not previously been applied in healthy subjects, and this finding supports the use of both PRT and CAINS in assessing individual differences in motivation across a variety of populations. However, the correlation between motivation and VS activity seen in schizophrenia was not present in controls. This indicates important complexity in the relationship between PRT motivation and VS responses to rewards. In particular, VS hypofunction appears to be more strongly related to motivation differences in schizophrenia, perhaps reflecting pathological VS function rather than normative variability in its engagement. Future work will need to further explore the extent to which neurobiological determinants of motivation variability in schizophrenia overlap or diverge with those found in other disorders and in nonclinical populations.

**Advantages of PRT and Other Laboratory Tests of Motivation**

The importance to psychiatry of developing behavioral tasks targeting specific psychological and symptom domains is increasingly recognized. Our PRT provides significant potential advantages over standard...
clinical or self-report measures. Computerized tasks are not dependent on the skill or subjectivity of an interviewer and hence should enhance reliability. They might also increase validity because they do not rely on the ability of subjects (or informants) to understand hypothetical or abstract questions, or to report their subjective emotional states with full insight and accuracy. Finally, a key advantage of the PRT is that it is directly translatable to animal models.\textsuperscript{54} Spurred by the National Institute of Mental Health Research Domain Criteria, translational psychiatric research is increasingly focused on specific psychological dimensions that can be related to variation at the level of neural circuits, as well as at cellular, molecular, and genetic levels.\textsuperscript{55} Quantitative behavioral measures of amotivation that can be applied across human and animal studies will be critical to this translational effort and will bolster confidence that findings in animal models can be related to human subjects. Of course, the advantages of laboratory behavioral tasks come with a price in terms of limits on ecological validity. The PRT cannot replace the clinical assessment of motivation but can provide a critical complement. Joint development and testing of behavioral and clinical scales should increase the validity and utility of both approaches.

\textbf{Limitations}

Several study limitations deserve discussion. Antipsychotic medications could potentially impact all of our key measures.\textsuperscript{17,36,57} However, here neither antipsychotic dose or type related to PRT motivation, clinical amotivation, or VS activation. While we did not include a clinical measure of extrapyramidal symptoms per se, response speed was unrelated to PRT breakpoint or CAINS amotivation (see supplementary results). Nonetheless, we cannot rule out an impact of antipsychotic medications on our findings, and future studies should examine drug-naive subjects.

We did not exclude subjects with depressive symptoms, which are of interest in a larger ongoing study. While our analysis indicates that depressive symptoms did not explain our within- or between-group results (see supplementary results and table S4), examination of samples free of depressive symptoms would allow more definitive conclusions.

The fMRI task used here provides a robust probe of VS activation and captures this activation in response to unpredictable vs loss outcomes. This corresponds to a reward prediction error, a crucial reward-processing signal known to be encoded by dopaminergic projections to striatum and identified as abnormal in prior schizophrenia studies.\textsuperscript{12,43,47,48,58,59} Failure to properly encode prediction errors in VS may constitute an important mechanism in amotivation. However, the current paradigm did not compare unpredictable vs predictable reward outcomes,\textsuperscript{12,14,59} nor distinguish between reward outcome prediction error and other important reward-processing constructs previously linked to VS activation, including expected action value,\textsuperscript{48,60,61} anticipatory (cue-evoked) responses,\textsuperscript{13,15,44,46} reinforcement learning,\textsuperscript{47,48,62} effort-cost computation,\textsuperscript{26} and salience detection.\textsuperscript{45,50} In addition, we did not assess conscious effort appraisals or defeatist beliefs\textsuperscript{63,64} that could impact individual and group differences in motivation and performance on our tasks. Determining the relative contribution of these interrelated constructs to VS dysfunction and amotivation in schizophrenia remains an important challenge.

The current fMRI paradigm also did not experimentally manipulate motivation or effort. Applying fMRI effort paradigms\textsuperscript{8,65} might yield stronger behavior-symptom-brain relationships, and bolster the statistical relationship we observe in the schizophrenia group by providing direct evidence for a causal relationship between VS hypofunction and reductions in effort.

Because of its variable duration across subjects and requirement for frequent movements, our PRT is not well suited for fMRI in its current form, and developing fMRI-suitable effort tasks tailored to subjects with neuropsychiatric disturbance is an important goal for future work.

\textbf{Conclusions}

We demonstrate that in schizophrenia, reduced effortful behavior in the laboratory relates dimensionally to clinical amotivation and to hypofunction of brain motivation circuitry. The strategy of integrating laboratory measures like the PRT together with clinical and imaging measures can provide multilevel dimensional assessment of amotivation. In assessing novel interventions, this approach could provide early evidence of physiological normalization of motivation circuitry and help identify subjects whose chronic symptoms and disability may respond to sustained intervention. As motivation deficits may present prior to frank schizophrenia and portend poor outcomes, this approach may also facilitate early identification of individuals at elevated risk for developing schizophrenia.

\textbf{Supplementary Material}

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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