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Publication Date

DOI

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ABSTRACT

Effortful motivation and reward valuation learning deficits are associated with negative symptoms and impaired cognition in schizophrenia (SZ) patients. Whereas clinical assessments of motivation and reward value typically rely upon clinician ratings or self-report scales, behavioral measures often confound these constructs. Simple reverse-translated behavioral tasks that independently quantify motivation and reward valuation—which could then be linked to cognition—may facilitate the development of pro-cognitive therapeutics by bridging the "preclinical-to-clinical" gap. This study determined whether novel behavioral measures of effortful motivation and reward valuation are associated with impaired cognition in SZ patients ($n = 36$). Patients completed the Progressive Ratio Breakpoint task (PRBT; physical effort motivation) and the Probabilistic Learning Task (PLT; reward learning/valuation) in conjunction with the MATRICS Consensus Cognitive Battery (MCCB). SZ patients exhibited statistically significant deficits in global cognition and all individual MCCB subdomains. Significant correlations were observed between PRBT and MCCB global cognition ($r = 0.52$), speed of processing ($r = 0.56$) and attention vigilance ($r = 0.48$) subdomains, but not with PLT or clinical symptoms. Results indicate that effort and reward learning deficits are dissociable targets that can improve our understanding of cognitive impairments associated among patients with SZ. More importantly, the results support the long-standing notion that the measurement of cognitive impairments in SZ is highly linked to a willingness to expend effort. The availability of a PRBT designed for use in both rodents and humans could improve our understanding of the nature of cognitive impairments in neuropsychiatric disorders and accelerate the development of novel pro-cognitive therapeutics.

Published by Elsevier B.V.

1. Introduction

Schizophrenia (SZ) is a neuropsychiatric disorder characterized by marked cognitive deficits and psychosocial disability, with limited responses to the currently available treatments. To date, the only treatments approved for SZ address positive symptoms but not negative symptoms or cognitive deficits, despite the latter two predicting outcome (Green et al., 2000; Thomas et al., 2017). The MATRICS Consensus Cognitive Battery (MCCB) was designed to provide researchers with a common set of standardized endpoints to be used in clinical trials targeting cognitive impairments associated with SZ. Unfortunately, no treatments have been approved that remediate cognitive deficits as measured by the MCCB, at least partially attributable to the widely recognized a "translational gap" between behaviorally informed animal models of pathology and human clinical ratings in patients (Hyman

and Fenton, 2003; Young and Geyer, 2015). The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) and the NIMH Research Domain Criteria (RDoC) initiatives have sought to bridge this gap via dimensional classification of mental disorders within functional domains and thereby enable greater cross-species translation of paradigms of relevance for therapeutic development (Young and Geyer, 2015; Cuthbert and Insel, 2013; Geyer et al., 2012; Markou et al., 2009).

The negative symptoms of SZ, and amotivation specifically, have been linked to poor cognition (Fervaha et al., 2014, Foussias et al., 2015, Lin et al., 2013), decreased functional outcome (Fervaha et al., 2015a, 2015b; Lin et al., 2013), and represent an unmet therapeutic target. Despite a growing literature demonstrating the centrality of motivational impairments in SZ, clinical assessment is predominantly reliant upon self-report measures or clinician ratings, with few performance-based tasks available (Fervaha et al., 2014, 2015a, b). To this end, animal work is beginning to drive effort-based clinical assessment tool development (Reddy et al., 2016; Horan et al., 2015; Green et al., 2015; Young and Markou, 2015) and leverage pre-clinical findings to

translate paradigms across species. Disentangling the contribution of motivational impairments to cognitive test performances in SZ is a challenging undertaking, given that many existing behavioral assays of motivation (e.g. Effort-Expenditure for Rewards Task [EEfRT], or Probabilistic Learning Tasks [PLTs]) impose additional cognitive task demands, e.g. reward learning, and/or working memory—domains impaired in SZ and significantly related to global cognitive performance (Markou et al., 2013; Lewandowski et al., 2016). Thus, decreased performance on tasks that conflate measures of cognitive and motivational functioning, and limit interpretive clarity necessary for understanding a patient's cognitive ability vs. observed performance. The potential impact of motivation on cognitive performance was raised previously by CNTRICS (Markou et al., 2013), but has only just begun to be assessed (Foussias et al., 2015).

PLTs are commonly used to assess the motivation to pursue rewards and have been used as a principle model for experimentally testing motivation in SZ (Waltz and Gold, 2007). PLTs use explicit trial-by-trial feedback learning to shape choice behavior to approximate implicit stimulus reward contingencies (reward learning). The ability to accurately choose stimuli with frequencies approximating the reward contingencies is based upon internal assignment of the value of the competing choices (reward valuation). Research has demonstrated intact implicit memory in SZ (Soler et al., 2015; Perry et al., 2000) while showing differential relationships between reward anticipation and reward enjoyment in SZ, such that patients show reduced responses during reward anticipation and responses similar to non-psychiatric controls once reward in received (Barch and Dowd, 2010, Dowd and Barch, 2012). However, recent research has shown that SZ patients have problems learning the differing values of rewarding choice alternatives (reward valuation) (Gold et al., 2013). This failure to associate differing reward values to choices may be due to impairments in reward associative learning or to deficits in higher-level cognitive processes such as attentional or working memory mechanisms (Collins et al., 2014; Gold et al., 2013). Therefore, observed decreased performance on commonly used PLTs may be due to motivational, reward valuation, or higher-order cognitive dysfunction, obscuring interpretations of specific deficits. This lack of interpretive clarity may be limiting the development of more domain-specific preclinical assays for screening novel therapeutics.

Other methods used to quantify motivation have focused on measuring the *effort* expended to achieve a task-relevant reward (Robbins, 2002; Kurniawan et al., 2010; McCarthy et al., 2016). A recent set of papers highlighted the psychometric properties of several of these new effort-based decision-making paradigms and their utility for assessing relationships between motivation, negative symptoms, and cognition in SZ (Reddy et al. 2015, Horan et al. 2015, Green et al., 2015, Markou et al., 2013). Unfortunately, SZ performance deficits in these paradigms may derive from a failure to accurately value future rewards (reward valuation) and bias the effort/cost calculation for pursuing that reward. To minimize reward-related contributions to motivation measurements, a paradigm commonly used in animal studies to quantify effort, the progressive ratio breakpoint task (PRBT), has been recently adapted for human testing (Wolf et al., 2014; Strauss et al., 2016). A PRBT identifies the maximum effort a person/animal is willing to expend to achieve a "reward" by progressively increasing the number of responses required to attain that reward. The 'breakpoint' is the highest level of reward achieved before the animal ceases to make further responses to achieve additional rewards and is thought to be a direct behavioral measure of motivation. Although widely used in animal studies, the PRBT also has great potential in clinical research for quantifying effortful motivation without the reliance on heavy cognitive load, self-reports, or clinical rating scales.

Studies utilizing cognitive effort tasks in SZ have indicated that patients display decreased effort compared to healthy individuals and neurological controls; with decreased cognitive effort predicting changes in cognitive test performance in SZ (Morra et al., 2015; Foussias et al.,

2015; Gorissen et al., 2005; van Beilen et al., 2005). Overlapping cognitive and motivational deficits in SZ highlight the growing concern that cognitive test performance in SZ may encapsulate both actual cognitive ability and the effort expended during assessment (Foussias et al., 2015). Although cognitive and physical effort tasks may share some overlap in quantifying motivation, the current PRBT was explicitly designed to measure physical effort and minimize cognitive contributions. Using paradigms with minimal cognitive load can more clearly disentangle effort/motivation as a contributor to the assessment of cognition in SZ.

The PRBT and modified PLT were reverse-translated directly from established animal paradigms to provide more specific metrics of their measured constructs and more independently assess the contribution of effort and reward valuation to marked cognitive impairments of SZ patients. Since motivation is quantified as the amount of effort (behavioral or cognitive) an individual is willing to expend to gain some reward, untangling the core deficits in effort and reward valuation in SZ and how they independently relate to cognitive test performance, is particularly important. If the behavioral measures of effortful motivation and/or reward valuation are related to global cognition, they may be sensitive to changes in cognition in response to treatments. Characterization of impaired behavioral performance of SZ patients in these cross-species tasks could therefore accelerate the development of pro-cognitive therapeutics that target motivational and reward related systems. As it is unclear the role that effort or reward valuation play in cognitive test performance, this study was designed to determine if behavioral measures of effortful motivation and reward valuation are dissociable and independently associated with cognitive test performance in SZ. Given their measurement of motivation and reward valuation respectively, we hypothesized that performance on the PRBT and PLT would be independently and significantly associated with global cognitive performance in people with SZ.

2. Methods

2.1. Participants

Thirty-six SZ patients between the ages of 18 and 61 years were recruited from a transitional care facility that primarily serves adults with diagnoses of SZ or schizoaffective disorder. Exclusion criteria for the study included: history of neurological disease, history of major head injury (LOC > 15 min), substance dependence within the last six months, severe systemic medical illness (e.g. Hepatitis C, HIV, insulin-dependent diabetes), IQ below 70, and difficulty with hearing, vision or English language comprehension that may interfere with the patient understanding consent, screening questions, and task directions. The Institutional Review Board of University of California, San Diego, has approved all experimental procedures (IRB#130874). All participants underwent an informed consent procedure, structured clinical diagnostic assessments including a modified Structured Clinical Interview for DSM-V Axis I disorders (SCID-I), and the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS; Andreason, 1983, 1984). All participants then underwent a cognitive assessment using the MCCB (the Mayer-Salovey-Caruso Emotional Intelligence Test was not administered due to concerns of fatigue and time limitations). The MCCB neurocognitive composite score was calculated using the mean of the domain T-scores as is consistent with prior publications (Lystad et al., 2014). All experimental tasks were completed after cognitive testing with PLT administered prior to the PRBT. Participant demographics and mean clinical ratings are reported in Table 1.

2.2. Progressive Ratio Breakpoint Task (PRBT)

Effortful motivation was quantified using the Progressive Ratio Breakpoint task (PRBT). This task required patients to rotate a digital 4-switch USB joystick handle in an indicated direction to receive a

Table 1
Participant demographics.

Demographics (± s.d., range) ($n = 36$)	
Mean age (yrs.)	36.7(± 12.5, 19–61)
Education	12.0(± 2.1, 8–18)
Sex (% male)	52.8%
Smoking	0%[a]
Right handedness	63.9%
Age of onset (yrs.)	19.0 (± 5.2, 4–30)
Illness duration (yrs.)	17.7 (± 13.5, 1–47)
SAPS total score	5.31 (± 4.7, 0–16)
SANS total score	6.42 (± 4.1, 0–16)

[a] The treatment facility is tobacco free, thus all participants were nicotine free for at least two months prior to study enrollment.

"reward" (50 points/level) on a progressive ratio schedule. Task instructions indicated that each participant was: 1. required to rotate the joystick in the indicated direction; 2. they would see a small white dot after 4 successful rotations as feedback for correctly completing the task; and 3. they were to earn as many points as possible, but that they could quit at any time. Participants were given no indication that "points" accumulated during the task held any value, explicit use, or were given otherwise encouraging words based on their point accumulation. Participants were given a short practice session to acclimate to the joystick rotations and task feedback. After completing the required number of rotations to complete each reward level, a screen appeared indicating they had earned 50 points, and the direction of the rotations alternated (i.e. clockwise to counter-clockwise). This alternation was meant to reduce perseverative motor effects. The task ended when patients completed all possible reward levels, verbally indicated they no longer wanted to continue the task, or failed to make a response for 5 min. The breakpoint was quantified as the largest number of levels completed before the subject chose to disengage with the task (i.e., "when the juice is no longer worth the squeeze"). The full task duration lasting approximately 10 min (Fig. 1).

2.3. Probabilistic Learning Task (PLT)

Reward value learning was quantified using a modified Probabilistic Learning Task (PLT) that requires adapting behavior in response to feedback after choosing between two stimuli with differing reward/punishment probabilities (e.g. 80/20%). Stimulus reward probabilities included (80/20%, 70/30%, 60/40%, and 50/50%) and were presented in block format. The participant was required to indicate, via directional joystick level-press, which stimulus they thought was the most rewarding (target stimulus). For each stimulus pair, the target stimulus presentation side was pseudorandomized. Prior to the start of the task, each participant was instructed to choose which stimulus was the "better option," and that they would receive feedback ("correct" vs. "incorrect") on their choices. No other instructions were provided. Each of the four blocks consisted of 50 trials and total task time was approximately 10 min. Accuracy for choosing the more rewarding stimulus at the 80/20, 70/30, and 60/40 probability reward levels was calculated separately, and then averaged to provide a task-level measure of accuracy. Behavioral metrics for the 50/50 reward probability block were not used in the current analysis. Task-level accuracy was the primary outcome measure of reward valuation (Fig. 2).

2.4. Statistics

Univariate and multivariate linear regression models (see Cohen et al., 2013) including PRBT breakpoint scores and PLT accuracy scores as predictors were used to determine the unique contribution of each behavioral measure to cognition (MCCB total score). Estimates of variance explained (R^2), standardized regression slopes (β) and Pearson correlations between predictors are reported. Correlations among PRBT breakpoint scores and PLT accuracy scores with MCCB scores and symptom ratings were examined for significance using a Bonferroni-corrected significance level of $\alpha = 0.0024$ to adjust for multiple comparisons (Blanchard and Cohen, 2006; Sayers et al., 1996). Single-sample t-tests were used to compare patients' MCCB scores against the standardization sample. All statistical analyses were conducting using SPSS (IBM Corp., Armonk, NY, USA).

3. Results

As shown in Fig. 3, patients with SZ exhibited significant deficits in MCCB global cognition composite score as well as each of the individual cognitive domains: MCCB composite ($t(35) = -11.9$, $p < 0.001$, d = 1.82), speed of processing: ($t(35) = -10.6$, $p < 0.001$, d = 1.90), attention and vigilance ($t(35) = -8.5$, $p < 0.001$, d = 1.6), visual learning ($t(35) = -11.9$, $p < 0.001$, d = 1.80), verbal learning ($t(35) = -16.1$, $p < 0.001$, d = 1.97), working memory ($t(35) = -7.9$, $p < 0.001$, d = 1.50), and reasoning and problem solving ($t(35) = -6.3$, $p < 0.001$, d = 0.94) (Fig. 3). Correlations among PRBT breakpoint scores, PLT accuracy scores, MCCB scores, and symptom ratings are reported in Table 2. There was a large significant positive correlation between PRBT breakpoint scores and MCCB composite scores. Bonferroni-corrected significance values for the correlations between
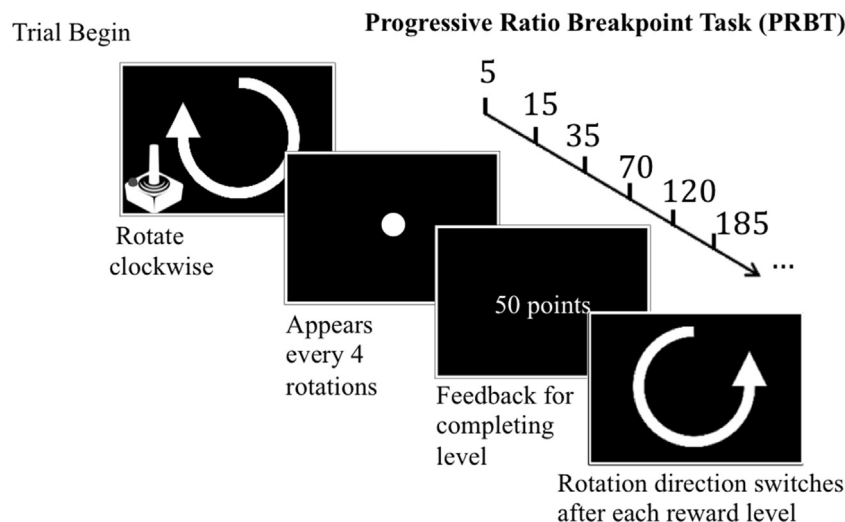

Fig. 1. Task structure of the Progressive Ratio Breakpoint Task (PRBT). Task began with instructions to rotate the joystick in direction indicated and that participants would earn points for completing levels. Participants were told to try to earn as many points as possible, but also explicitly told they could stop whenever they wanted.
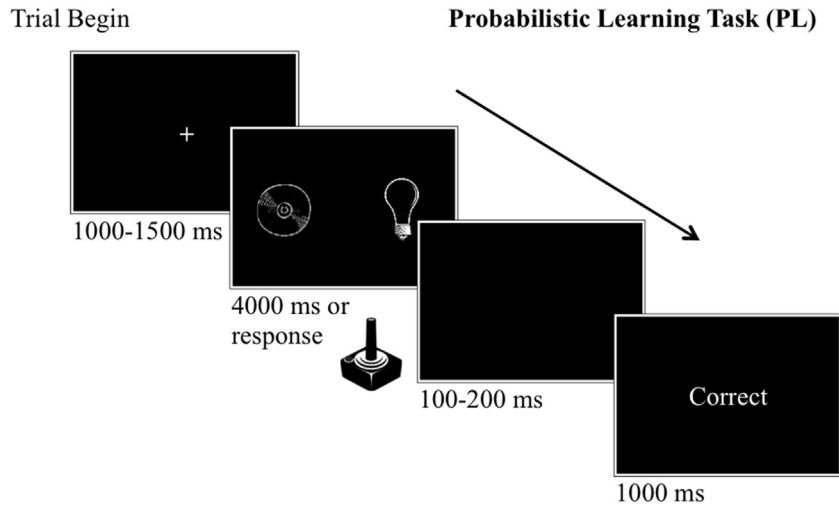
Trial Begin   **Probabilistic Learning Task (PL)**

1000–1500 ms

4000 ms or
response

100–200 ms

Correct

1000 ms

Fig. 2. Trial layout for the Probabilistic Learning Task (PLT). The task consisted of 200 trials (4 blocks of 50 trials each) with randomly assigned response size (L vs R).

the PRBT scores, PLT scores, and MCCB domain T-scores indicated the PRBT scores were positively and significantly correlated only with speed of processing (SOP; large effect) domain scores. A follow-up r-to-z comparison of correlations between the PBRT and PLT to the MCCB and all subtests yielded significantly higher intercorrelations between PRBT and MCCB composite and SoP compared to the PLT-cognition relationships (Supplementary Table 1). Additional correlations between PRBT and SoP subtests (Trials Making Test: Part A; Category Fluency: Animal Naming; and Symbol Coding) yielded significant correlations between PRBT and Trials A ($r = 0.52$, $p < 0.01$) and Symbol Coding ($r = 0.51$, $p < 0.01$), but no significant correlation with category fluency. PLT accuracy scores were not significantly correlated with PRBT scores or any of the MCCB measures. SANS and SAPS total scores were not significantly correlated with PRBT scores, but SAPS total scores were modestly and negatively correlated with PLT performance scores (but did not survive correction).

MCCB composite scores were next regressed onto PRBT breakpoint scores and PLT accuracy scores independently and in a combined model. The combined model accounted for 29.0% of the variance in MCCB composite scores ($F(2,33) = 6.734$, $p < 0.005$). PBRT scores uniquely accounted for 23.9% of the variance in MCCB composite scores ($b = 2.09$, $\beta = 0.488$, $p < 0.004$), while PLT accuracy scores uniquely

accounted for 3.2% ($b = 0.091$, $\beta = 0.156$, $p = 0.302$), with only 2.7% of the variance shared between PRBT scores, PLT scores, and MCCB composite scores (Fig. 4).

4. Discussion

Using reverse-translated tasks, the present study demonstrated that effortful motivation uniquely accounted for over a quarter of the variance in global cognition and was significantly associated with measures of processing speed and attention/vigilance in SZ patients. Significant correlations between SoP subtests (Trials A, Symbol Coding) indicate that PRBT is more heavily related to the physical effort components of SoP than the cognitive components (Category Fluency). Results further suggest that SZ patients' willingness to exert physical effort is globally linked to performance on MCCB cognitive scales. In contrast, reward valuation only explained 3.2% of the variance in cognition. Hence, these data additionally demonstrate the domains of physical effort and reward valuation are dissociable.

To date, studies have either quantified motivation through clinician/self-report ratings or behaviorally via effort-cost paradigms. Clinical ratings of motivation typically consist of single-items, or a small subset of
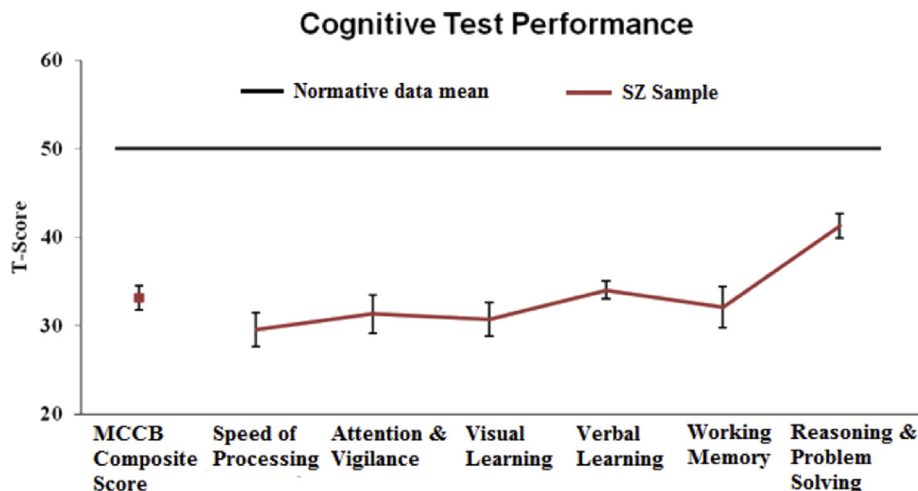
Cognitive Test Performance

Fig. 3. Figure represents T-score comparisons between SZ patients in the current sample and normative data for MCCB total and domain scores.

Table 2

Pearson correlations between behavioral tasks, MCCB composite, all subscale T-Scores, and SANS and SAPS total scores. Solid outlines indicate significant correlations with dashed outlines indicating trend level significance based on Bonferroni corrected p-values. Note: Relationships between behavioral task performance metrics, cognitive scores, and symptom ratings were the primary foci for the study. Although stronger inter-correlations between MCCB composite and subdomain scores are present, they have been highlighted in previous research and shown here merely for completeness.

	PRBT breakpoint	PLT accuracy	MCCB composite	Speed of processing	Attention and vigilance	Working memory	Verbal learning	Visual learning	Reasoning and problem solving	SAPS total score	SANS total score
PRBT breakpoint	1.00	0.18	0.52	0.56	0.48	0.34	0.35	0.35	0.32	-0.10	0.12
PLT accuracy	0.18	1.00	0.24	0.17	0.14	0.23	0.25	0.15	0.26	-0.38	-0.06
MCCB composite	0.52	0.24	1.00	0.80	0.86	0.86	0.64	0.71	0.73	-0.24	-0.28
Speed of processing	0.56	0.17	0.80	1.00	0.59	0.65	0.49	0.41	0.56	-0.19	-0.09
Attention and vigilance	0.48	0.14	0.86	0.59	1.00	0.71	0.39	0.59	0.57	-0.27	-0.24
Working memory	0.34	0.23	0.86	0.65	0.71	1.00	0.51	0.48	0.50	-0.19	-0.39
Verbal learning	0.35	0.25	0.64	0.49	0.39	0.51	1.00	0.39	0.51	-0.14	-0.15
Visual learning	0.35	0.15	0.71	0.41	0.59	0.48	0.39	1.00	0.39	-0.02	-0.27
Reasoning and problem solving	0.32	0.26	0.73	0.56	0.57	0.50	0.51	0.39	1.00	-0.33	-0.09
SAPS total score	-0.10	-0.38	-0.24	-0.19	-0.27	-0.19	-0.14	-0.02	-0.33	1.00	0.17
SANS total score	0.12	-0.06	-0.28	-0.09	-0.24	-0.39	-0.15	-0.27	-0.09	0.17	1.00

-1.00 -0.75 -0.50 -0.25 0.00 0.25 0.50 0.75 1.00

items drawn from other assessments. Although some studies have demonstrated inter-correlations within and across negative symptoms and motivation items (Fervaha et al., 2015a, b), follow-up correlations observed no significant correlations (all rs < 0.25, ps > 0.16) between PRBT and global or individual SANS items related to anhedonia or apathy scores were observed in the present study.
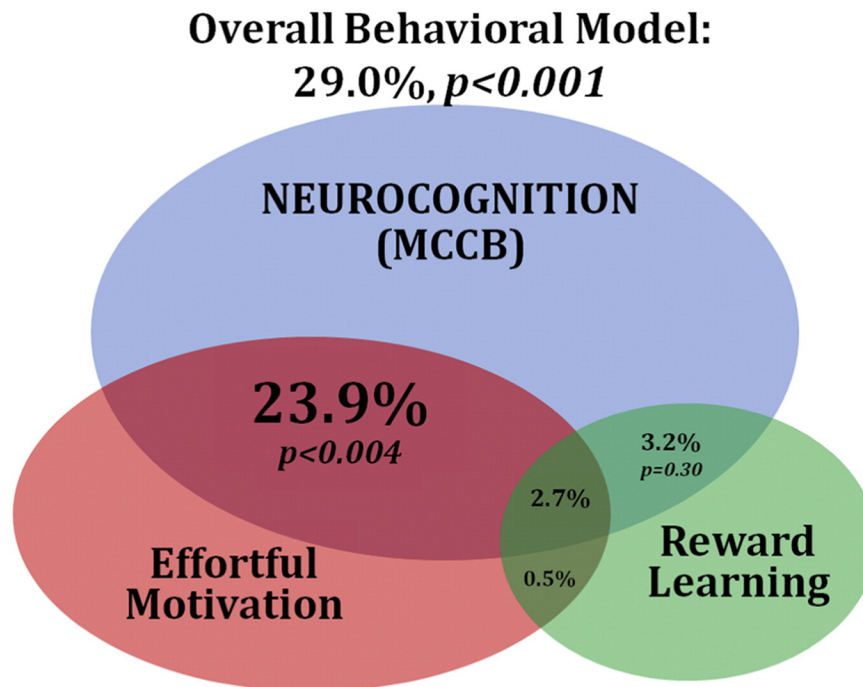

Fig. 4. Behavioral measure variance components predicting cognition. Total model variance in cognition (MCCB total score) accounted for was 29.0%. Overlapping areas depict the *unique* variance proportion for each predictor, PRBT 23.9%, PLT accuracy 3.2%, with the shared variance accounted for 2.7% of the variance in cognition. The PRBT and PLT share 0.5% of the variance with each other, independent of cognition.

To increase the validity of motivational assessment and bridge the pre-clinical to clinical gap, research has begun to translate animal effort-cost decision-making paradigms to quantify motivation in humans. Previous clinical decision-making research has shown effort-cost calculations to be important in assessing motivation and cognition in SZ (Fervaha et al., 2013, Reddy et al. 2015, Fervaha et al., 2015a, 2015b, Foussias et al., 2015). Recent studies indicate that SZ patients display deficits on cognitive effort tasks, and that decreased cognitive effort is related to higher negative symptoms and overall lower cognitive test performance (Morra et al., 2015, Gorissen et al., 2005). Reduced performance on existing cognitive effort tasks may however be due to motivational deficits, cognitive impairments, or potentially malingering. The use of reverse translated behavioral effort tasks with minimal cognitive demands may begin to disentangle these relationships between motivational effort and cognitive test performance in SZ. Two recent studies have used reverse-translated progressive ratio tasks to behaviorally quantify motivation in SZ patients (Wolf et al., 2014; Strauss et al., 2016). One study used trials comparing pairs of three- or four-digit numbers to assess which number was larger – potentially a *cognitive* effort task (Wolf et al., 2014), while the other involved trials where participants alternated button presses to inflate a balloon – a *physical* effort task (Strauss et al., 2016). Both tasks utilized progressive ratio schedules for monetary reinforcements but also explicitly told participants the number of trials required to reach the next reinforcement. The explicit notification of required effort for reinforcement is a key distinction from the current PRBT, and likely allowed subjects to make cognitive effort-cost appraisals but potentially weakening the direct translatability. Importantly, Strauss et al. (2016) found that although task performance was moderately related to clinician rated motivation and functional outcomes, performance did not distinguish SZ from controls or relate to global cognition. Thus, despite positive strides toward behavioral characterization of motivation in SZ, the reliance on self-reports, clinician ratings, or more explicit measures of cognitive effort tasks may still undermine translatability. The findings of robust relationships among behavioral measures of physical effort and measures of cognition, support the view that cognitive performance deficits observed in SZ do not purely reflect ability but may likely be confounded by deficits in intrinsic motivation, producing inaccurate measures of cognition. Thus, behavioral measures of effortful motivation with minimal or no cognitive task demands could: 1) maintain cross-species validity; 2) provide more specific metrics of motivation; and 3) provide a more valid basis for estimating the effects of motivation on cognitive performance in SZ.

This study used a reverse-translated progressive ratio task with primarily behavioral demands and little to no cognitive engagement. This quantification of effortful motivation refines its characterization by minimizing cognitive task demands, and so can theoretically leverage information from the animal literature. The current version of the PRBT has been used to evaluate aspects of motivation in healthy mice (Young et al., 2011; Young and Geyer, 2010) and amotivation in animal models of SZ (Cope et al., 2016; Young et al., 2015; Ward, 2015). Since the PRBT is reverse translated from animal work (where food is the primary reward for completing a level), this task was designed to balance participant engagement with cross-species validity. As prior studies using PRB tasks (Wolf et al., 2014; Strauss et al., 2016) explicitly utilize monetary rewards during task completion, this greatly increases the reward salience through explicit value of the rewards. By using "points," it is our hope that by decreasing the reward salience and explicit value of potentially rewarding feedback, that we can begin to separate the overlapping constructs of effort and reward. This is supported by the weak correlation between the PRBT and the PLT ($r = 0.18$), a task driven by rewarding feedback (correct vs incorrect). By using behavioral measures (such as the PRBT) to disentangle effortful motivation from highly interrelated constructs (e.g. reward valuation, working memory), we can more objectively quantify motivation and investigate how the willingness to exert effort may affect other measures. If objective and direct

behavioral measures of motivation - which are less prone to human self-report or clinical rating biases - can be reliably linked to measures of cognition, learning, or functional outcomes in SZ; motivational biomarkers can be used as targets for pharmacological interventions designed to improve cognitive test performance via motivational enhancement.

Cross-species findings have demonstrated similarities in dopaminergic activity that may underlie motivational deficits. Recent research has shown that striatal-specific increases in mouse dopamine D_2 receptors decreases breakpoints (Simpson et al., 2012), and the administration of the dopamine D_2 receptor antagonist haldoperidol, a commonly used antipsychotic, decreased breakpoints in mice during a progressive ratio choice task (Randall et al., 2012). Human imaging work has further demonstrated that changes in striatal dopamine transmission were related to individual differences of effort exertion (Treadway et al., 2012b). It is therefore necessary to develop/utilize cross-species tasks with clearly defined behavioral metrics of effortful motivation and reward valuation with *independent* links to dopaminergic signaling. By establishing biomarkers indexing underlying neurochemistry that are sensitive to cognitive performance, we can begin to clarify the relationships between dopaminergic function, motivation, and cognition in SZ. Targeted interventions at the underlying neurochemical dysfunction in SZ could then be developed. The current data also indicate that drugs that increase breakpoint across species (e.g., modafinil, Young and Geyer, 2010; Stip and Trudeau, 2005) may well improve global cognitive functioning in patients with SZ. Additionally, improving effortful motivation in patients with SZ could synergistically enhance behavioral therapy training (Swerdlow, 2012; Acheson et al., 2013). Likewise, we have shown that amphetamine potentiates the amount of perceptual learning during cognitive training exercises (Swerdlow et al., 2017). Future studies using Structural Equation Modeling (SEM) may also be used to disentangle causal pathways (Thomas et al., 2017) between effort and cognitive dysfunction in SZ. Therefore, the PRBT and PLT hold great utility for precision medicine by using simple laboratory based behavioral measures and help bridge the translational gap in the develop pro-cognitive therapeutics for cognitive impairments associated with SZ.

Several study limitation deserve discussion, most notably the lack of control comparison group. Although we have existing data for each of these tasks performed by healthy subjects, it comes from separate populations without similarly collected cognitive data and thus is unsuitable for direct comparison. Future studies will use these tests across both SZ and healthy subjects to ascertain specific behavioral relationships with cognition for between group comparisons. Whereas the current study evaluated negative symptoms using the SANS, a well-established measure used in previous effort-cost studies in SZ (Gold et al., 2013, Treadway et al., 2012, Foussias et al., 2015), the small number of anhedonia-specific items may limit the ability to detect relationships among symptoms and behavioral performance. Other more recently developed measures of negative symptoms such as the Clinical Assessment Interview for Negative Symptoms (CAINS) may provide more sensitivity to detecting symptom-behavior relationships (Kring et al., 2013). As in the vast majority of SZ studies, all patients were medicated at the time of testing, with most treated on a combination of typical and atypical antipsychotic mediation along with other psychotropics. While we did not include medication status/type as a factor in our analysis, behavioral measures were still sensitive to cognition with this medication-heterogeneous sample. Nonetheless, we cannot rule out the impact of antipsychotic medications on our findings; future randomized controlled trials are needed to disentangle potential medication effects (c.f. Light et al., 2015; Rissling et al., 2012). Fortunately, given the availability of this task in rodents the impact of chronic antipsychotic treatment on PRBT has begun to be examined (Heath et al., 2015; Randall et al., 2012; Wiley and Compton, 2004). Finally, it is possible that the seemingly innocuous "points earned" running tally on the PRBT was more motivationally salient as a "reward" than anticipated and

contributed to the effortful motivation relationships with cognition. Although it's possible that the inclusion of this "feedback" may introduce some slight reward valuation component to the task, the small overlap in variance between the PRBT and the PLT, a specific measure of reward valuation, suggests minimal contribution. We acknowledge the PRBT is not a "reward free" measure of effort, but by minimizing reward salience and value, we hope to minimize the reward related contributions to PRBT performance. Additionally, the non-significant relationship between reward valuation and cognitive performance also indicates the relationship of effortful motivation to cognition would in fact be higher in the absence of potential reward valuation contributions to the PRBT.

In conclusion, the strategy of using novel reverse-translated laboratory measures like the PRBT and PLT together with existing gold standard measures of cognition can provide more direct cross-species relationships to aid development of pro-cognitive therapeutics. This translational approach may provide further utility by identifying individuals likely to benefit from treatment and identify those who may benefit from additional targeted pharmacological or psychosocial pre-treatments to help boost treatment gains and long-term functional outcomes. These data support our contention that quantifying physical effort is a missing piece in the neurocognitive assessment toolkit. Lastly, as motivational deficits may be present prior to full disease onset and signal poor outcomes, this approach may also facilitate early identification of individuals at elevated risk for developing pathologies with prominent amotivational phenotypes.

Contributors

Dr. Bismark aided in data collection, analysis, and was the primary writer. Dr. Thomas aided in statistical analysis and manuscript preparation. Dr. Tarasenko aided in data collection. Ms. Shiluk and Rackelman aided in data collection. Dr. Young aided in study design, analysis, and manuscript preparation. Dr. Light oversaw all study design, data collection, statistical analysis, and manuscript preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.06.042.

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