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## Relationship between effortful motivation and neurocognition in schizophrenia

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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 “pre-clinical-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.

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### 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

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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 is 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; Andreasen, 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

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