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Effort, avolition and motivational experience in schizophrenia: Analysis of behavioral and neuroimaging data with relationships to daily motivational experience

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Abstract

Recent research suggests that schizophrenia is associated with reduced effort allocation. We examined willingness to expend effort, neural correlates of effort allocation, and the relationship of effort to daily motivational experience in schizophrenia. We recruited 28 individuals with schizophrenia and 30 controls to perform an effort task during fMRI. Individuals with schizophrenia also completed an ecological momentary assessment (EMA) protocol. Individuals with schizophrenia with high negative symptoms were less willing to expend effort for rewards. Daily EMA assessments of motivation were positively associated with effort allocation at a trend-level. Individuals with schizophrenia and controls displayed similar increases in BOLD activation in frontal, cingulate, parietal, and insular regions during effort-based decision-making. However, negative symptoms were associated with reduced BOLD activation in bilateral ventral striatum. These results replicate previous reports of reduced effort allocation in schizophrenia patients with severe negative symptoms, and provide evidence for the role of ventral striatum in effort impairments.

Introduction:

Many individuals with schizophrenia experience prominent negative symptoms, such as reductions in motivation, as well as decreased initiation and pursuit of goals. Such symptoms are associated with worse social and occupational functioning in those with schizophrenia, and thus motivational impairment represents an important target for treatment (Milev, Ho, Arndt, & Andreasen, 2005). However, current intervention strategies are, at best, marginally effective at treating these symptoms. Poor treatment efficacy may stem from inadequate

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mechanistic understanding of factors that give rise to motivational impairment in schizophrenia. While many potential contributory mechanisms have been proposed in the literature (Barch & Dowd, 2010; Gold, Waltz, Prentice, Morris, & Heerey, 2008; Kring & Moran, 2008), recent work has examined the possibility that motivational impairment in schizophrenia might arise due to aberrant effort-based decision-making (Barch, Treadway, & Schoen, 2014; Culbreth, Westbrook, & Barch, 2016; Docx et al., 2015; Fervaha et al., 2015; Fervaha et al., 2013; Gold et al., 2014; Gold et al., 2013; Hartmann et al., 2015; Horan et al., 2015; Huang et al., 2016; McCarthy, Treadway, Bennett, & Blanchard, 2016; Moran, Culbreth, & Barch, 2017; Park, Lee, Kim, Kim, & Koo, 2017; Reddy et al., 2015; Serper, Payne, Dill, Portillo, & Taliercio, 2017; Strauss et al., 2016; Treadway, Peterman, Zald, & Park, 2015; Wang et al., 2015; Wolf et al., 2014).

Effort-based decision-making refers to mental calculations that individuals perform to estimate the costs and benefits of engaging in a particular action. For example, a student might estimate the subjective cost of studying an additional hour in hopes of achieving a better grade on an upcoming exam. Importantly, there are individual differences in effort estimates (e.g., some students might find the extra study time worth the prospect of a higher grade and thus expend the effort while others may not). Recent clinical research has found that individuals with schizophrenia are less willing than healthy controls to exert effort to obtain monetary rewards on experimental tasks (Barch et al., 2014; Culbreth et al., 2016; Fervaha et al., 2013; Gold et al., 2013; Huang et al., 2016; McCarthy et al., 2016; Reddy et al., 2015; Treadway et al., 2015; Wang et al., 2015; Wolf et al., 2014). Many studies have also shown that this deficit in effort exertion is linked to clinician-rated (Barch et al., 2014; Culbreth et al., 2016; Gold et al., 2013; Hartmann et al., 2015; Horan et al., 2015; Moran et al., 2017; Strauss et al., 2016; Treadway, Bossaller, Shelton, & Zald, 2012; Wang et al., 2015; Wolf et al., 2014) and ambulatory assessments (Moran et al., 2017) of motivational impairment in those with schizophrenia, such that schizophrenia patients with prominent motivational impairment demonstrate the least willingness to exert effort. Taken together, previous literature has highlighted aberrant effort-based decision-making as a potential contributory mechanism for motivational impairment in people with schizophrenia.

Alongside clinical research, work in basic neuroscience has begun to delineate the neural circuits associated with effort-based decision-making. In the animal literature, there is consistent evidence that striatal dopamine is critically linked to effort allocation (Salamone, Wisniecki, Carlson, & Correa, 2001; Salamone, Koychev, Correa, & McGuire, 2015), such that rodents depleted of striatal dopamine show reduced willingness to perform effortful tasks for rewards. The anterior cingulate cortex (ACC) has also been implicated in the integration of reward and cost information in the context of decision-making (Floresco & Ghods-Sharifi, 2007; Floresco, Onge, Ghods-Sharifi, & Winstanley, 2008; Hosking, Cocker, & Winstanley, 2014), and specifically ablation of the ACC in rodents has been shown to reduce choice of high effort options. In humans, neuroimaging studies have found that blood oxygenation level dependent (BOLD) activation in the ventral striatum (a region highly innervated by dopaminergic signals) varies as a function of effort (Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009; Irma Triasih Kurniawan et al., 2010; Westbrook, Lamichhane, & Braver, 2019). Further, the dorsal ACC has been shown to integrate reward and cost information of potential actions (Croxson et al., 2009; Leotti & Delgado, 2011),

suggesting a central role for this region in selecting and maintaining effortful action. Finally, the ventral medial prefrontal cortex (VMPFC) has been shown to be critical to valuation of actions (Treadway, Buckholtz, et al., 2012). Taken together, cortico-limbic-striatal circuits appear critical to effective effort-based decision-making.

A limited number of studies have examined the neural correlates of effort-based decision-making deficits in schizophrenia. One study used a button-press paradigm where individuals decided between performing an easy button-pressing task for a small reward or a hard button-pressing task for large reward during neuroimaging (Huang et al., 2016). They found that individuals with schizophrenia showed lower BOLD activation of cingulate, ventral striatum, and medial frontal gyrus compared to healthy controls during decision-making. Similarly, although not a direct examination of the neural correlates of effort-based decision-making, Wolf et al., demonstrated that BOLD activation in ventral striatum and dorsolateral prefrontal cortex during reward processing positively correlated with behavioral measures of increased willingness to exert effort in those with schizophrenia (Wolf et al., 2014). Thus, plausible regions of interest for the neural correlates of effort-based decision-making deficits in schizophrenia may be lateral frontal cortex, cingulate cortex, and ventral striatum.

Although studies have consistently demonstrated reduced willingness of individuals with schizophrenia to exert effort for monetary rewards, with some exceptions (Docx et al., 2015; Strauss et al., 2016), several open questions remain in the literature. First, while diagnostic group differences are consistently reported, relationships between negative symptom severity in those with schizophrenia and effort allocation are less consistent. Thus, it is important to conduct additional studies to examine symptom relationships in order to provide replication of previous results. Second, while some work has been conducted examining cognitive effort in schizophrenia (Culbreth et al., 2016; Gold et al., 2014; Reddy et al., 2015), most studies have utilized physical effort-based decision-making tasks, and it is not currently known whether physical and cognitive effort-based decision-making are associated with similar or disparate psychological processes and neural circuits (Schmidt, Lebreton, Cléry-Melin, Daunizeau, & Pessiglione, 2012). Thus, it is important to examine non-physical tasks in order to observe whether symptom and diagnostic group effects generalize across effort modality. Third, only one study to date has examined whether effort deficits measured in the lab show relationships to more ecologically-valid assessments of motivation and emotionality (Moran et al., 2017), and tying experimental findings to daily motivational experience remains an important avenue for future research. Finally, while preliminary evidence suggests that patient deficits on effort-based decision-making tasks may be related to hypoactivation of striatum, cingulate, and lateral prefrontal cortex (Huang et al., 2016; Wolf et al., 2014), more research is needed examining the neural correlates of effort-based decision-making in people with schizophrenia.

In the current study, we collected neuroimaging data, recruiting both healthy controls and those with schizophrenia to complete a well-validated cognitive effort-based decision-making task, the cognitive effort-discounting task (COGED) (Westbrook, Kester, & Braver, 2013; Westbrook et al., 2019). Further, we collected ambulatory assessments of enjoyment and interest in daily activities of those with schizophrenia in order to observe whether willingness to expend effort and the neural correlates of effort-based decision-making were

associated with interest and enjoyment measured outside the lab. First, we examined whether individuals with schizophrenia were less willing than healthy individuals to exert effort for monetary rewards. Given previous literature on aberrant effort-based decision-making in those with psychosis (Culbreth, Moran, & Barch, 2017; Gold, Waltz, & Frank, 2015b; Green, Horan, Barch, & Gold, 2015), we hypothesized that individuals with schizophrenia would be less willing than healthy controls to exert cognitive effort for monetary rewards, even after controlling for task performance (Culbreth et al., 2016). Further, consistent with prior work, we proposed an individual differences relationship, such that those with schizophrenia with the greatest negative symptom severity would be the least willing to exert effort (Culbreth et al., 2017; Gold et al., 2015b; Green et al., 2015). In addition, we proposed that this reduced willingness to expend effort would be associated with measures of enjoyment and interest collected in daily life, such that those with schizophrenia who were least willing to engage with effort on experimental paradigms would also show the least interest and enjoyment in activities of daily life (Moran et al., 2017).

As a second aim, we also sought to gain preliminary evidence of the neural correlates of effort-based decision-making impairments in those with schizophrenia using functional magnetic resonance imaging (fMRI). Consistent with previous literature (Croxson et al., 2009; Leotti & Delgado, 2011; Treadway et al., 2012), we hypothesized that BOLD activation in cingulate cortex and frontal cortex would be enhanced across both healthy controls and those with schizophrenia during putatively difficult effort-based decision-making trials when compared to putatively easy trials. However, we hypothesized that individuals with schizophrenia would show less robust recruitment of striatum, cingulate, and frontal cortex during putatively difficult compared putatively easy effort-based decision-making trials and that activation in these regions would negatively correlate with motivational impairment.

Methods:

Participants

Study participants included 28 individuals meeting *Diagnostic and Statistical Manual of Mental Disorder*, fourth edition (*DSM-IV*) criteria for schizophrenia or schizoaffective disorder and 30 demographically matched healthy control participants with no personal or family history of psychosis (First, Spitzer, Gibbon, & Williams, 2001). Participants were recruited from the Saint Louis Community. Exclusion criteria for individuals with schizophrenia included the following: (a) *DSM-IV* diagnosis of substance abuse or dependence in the last year; (b) *DSM-IV* diagnosis of a current major depressive episode or bipolar disorder; (c) changes in medication dosage two weeks prior to consent; (d) past head injury with documented neurological sequelae and/or loss of consciousness; (e) *Wechsler Test of Adult Reading (WTAR) Estimated Full-Scale IQ* < 70 (Wechsler, 2001); (f) MRI contraindications. Exclusion criteria for healthy controls included the following: a) *DSM-IV* diagnosis of substance abuse or dependence in the last year; (b) *DSM-IV* diagnosis of a current major depressive episode or bipolar disorder; (c) changes in medication dosage two weeks prior to consent; (d) past head injury with documented neurological sequelae and/or

loss of consciousness; (e) *Wechsler Test of Adult Reading (WTAR) Estimated Full-Scale IQ* < 70 (Wechsler, 2001); (f) MRI contraindications; (g) *personal or family history of psychosis; (h) current prescription of psychotropic medications*. All participants were required to pass a urine drug screen prior to study participation. The Washington University Institutional Review Board approved the study, and participants provided written, informed consent in accordance with Washington University's Human Subject Committee's criteria.

Clinical Ratings

Diagnoses were determined by the Structured Clinical Interview for *DSM-IV-TR* (First et al., 2001). Negative symptoms were assessed using the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring, Gur, Blanchard, Horan, & Reise, 2013) conducted by either a Masters or Ph.D. level clinician. Converging structural analyses of the CAINS have identified two moderately correlated factors, one reflecting experiential impairments (anhedonia, asociality, avolition) and the other reflecting expressive impairments (alogia, blunted affect) (Horan, Kring, Gur, Reise, & Blanchard, 2011; Kring et al., 2013). These factors are now reflected in two subscales of the CAINS, Motivation and Pleasure Subscale (CAINS-MAP) and Expressive Subscale (CAINS-EXP) (Horan et al., 2011; Kring et al., 2013). Given the hypothesized relationship between effort allocation and motivational impairment, CAINS-MAP was the focus of the current report.

Ecological Momentary Assessment Protocol

Participants with schizophrenia were provided an Android-enabled smartphone during the EMA portion of the study. During the seven-day protocol, participants received four text messages per day between 10:00 a.m. and 8 p.m., approximately every two to three hours. Text messages contained hyperlinks to a Qualtrics online survey (Snow & Mann, 2013). Following the receipt of each text message, participants were given 15-minutes to begin each survey. Participants were paid $1.75 for each survey they completed within this 15-minute window. The protocol was identical to a previously published study by our group (Moran et al., 2017).

On each survey, participants were asked to indicate their current activities from a predetermined list of options (i.e., eating/drinking, TV/radio/computer/reading, entertainment away from home, socializing, exercising, work/school, sleeping, running an errand, cleaning/hygiene/chores, cooking, therapy/doctor's appointment, in transit, nothing in particular). Next, they indicated the (a) level of interest; (b) level of enjoyment they experienced from these activities on a 5-point point ranging from 1 (*not at all*) to 5 (*extremely*). Additionally, participants were asked to indicate their activities, level of interest, and level of enjoyment (a) since the last text message (i.e., in the last 2-3 hours) as well as (b) for what they expected to do in the upcoming 2-3 hours. Current, past, and future self-reports were averaged for each survey for interest and enjoyment, for all analyses creating a single EMA Enjoyment and Interest measure per time point (e.g., 28 potential data points per subject), EMA-EI. Averaging of the EMA survey questions was performed to closely mirror current experiential subscales of negative symptom interviews (e.g., CAINS-MAP), which assess interest and enjoyment with current, previous, and future activities. Overall, the EMA protocol was well tolerated (mean completion rate = 78%). Consistent

with previous EMA research (Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001), all participants completed at least 33% of surveys and thus were included in the present analyses. EMA adherence was not significantly related to CAINS-MAP (*r-value* = 0.04; *p-value* = 0.83).

Behavioral Cognitive Effort Discounting (COGED) Task

Participants completed a modified version of the Cognitive Effort Discounting Task (COGED) (Culbreth et al., 2016), originally developed by Westbrook and colleagues (Westbrook et al., 2013; Westbrook et al., 2019). In this task, participants first practice increasingly difficult versions of a cognitively demanding task (*N-Back: 1-4 back*). Participants completed two 64-trial runs of each N-back level; each run consists of 16 target trials and 48 non-targets. Next, individuals made a series of choices about repeating one task up to 10 more times for cash rewards. Specifically, each decision trial involved a two-alternative forced-choice between completing a more demanding level of the N-back (2-4 back) for a greater reward or a less demanding level (1-back) for a smaller reward. After each choice the reward amount for the 1-back was titrated until participants were putatively indifferent between the base offer for the harder task and the offer for the 1-back (Figure S1). This indifference point was then divided by the base offer amount for the hard task in order to quantify a subjective value for each hard task-base amount pair. Greater subjective value scores suggest greater willingness to exert effort. Critically, participants are instructed that they only need to perform as well on the N-back tasks as they performed during the practice phase to receive payment, helping to reduce any confounds associated with group or individual differences in performance levels. In the current study, three high-demand N-back levels (N = 2–4) and 2 base reward amounts ($2 and $4) were used. Each task amount pair was titrated over a series of five decision trials yielding a total of 30 decision-making trials and 6 indifference points across the task. Following scanning trials, one of the participant's choices was selected at random, to determine the task that they were required to repeat and the amount they were paid.

Neuroimaging Cognitive Effort Discounting Task

During fMRI scanning, participants made similar decisions between repeating a more cognitively demanding level of the N-back (2-4 back) for a greater reward ($2 or $4) or a less cognitively demanding (1-back) level for a smaller reward (Figure S2). First, one task-amount pair was presented in the center of the screen for three seconds (valuation phase). Participants were told to consider how they felt about performing the task for the amount offered. After a jittered inter-stimulus interval (zero, two, or four seconds), an additional task-amount pair appeared on the screen and the participant chose which task they would rather perform for the amounts provided using a button box (decision-making phase). Finally, a jittered inter-trial interval (two, four, six second) occurred prior to the onset of the next trial. Importantly, offers for the easy task were offered at various degrees above and below subject-specific indifference points (100% below, 20% below, 10% below, 40% above, 60% above, 100% above) calculated prior to scanning. This allowed for manipulation of choice difficulty, as trials that are presented closer to indifference points are putatively more difficult decisions. In total, the fMRI protocol consisted of 72 trials. These trials varied by hard task amount offer (i.e., $2 or $4), hard task N-back level (2-4 back), and proximity

to indifference point (100% below, 20% below, 10% below, 40% above, 60% above, 100% above). Specifically, two hard task load level trials were presented for each proximity level. Hard task amount offers were split such that $2 offers were presented during 10% below, 40% above, and 100% above indifference point levels and $4 offers were presented during 100% below, 20% below, and 60% above load levels. Thus, the design was not completely balanced across load level, proximity, and hard task amount. The main contrast of interest was between trials offered either 100% above/below indifferences points that are thought to be putatively easy trials and trials offered in between (e.g., 20% below, 10% below, 40% above, 60% above) which are thought to be more difficult (Figure S2).

Neuroimaging Preprocessing

Images were acquired on a 3T Siemens Skyra system with a 32-channel head coil, which was customized and used for the Human Connectome Project (HCP). Structural scans (0.8 mm isotropic) as well as 3 functional runs using a multiband echo-planar sequence (TR=720ms, TE=33.1ms, flip angle =52°, 2.4 mm isotropic voxels, with a multi-band acceleration factor of 8). Each run was approximately 5 minutes in length.

Imaging data was run through HCP minimal preprocessing pipelines (Glasser et al., 2013). Subsequently, data was analyzed using the Analysis of Functional NeuroImages software package (AFNI: Cox, Chen, Glen, Reynolds, & Taylor, 2017). Binary masking was applied to each image to remove voxels outside the brain. The EPI datasets for each participant were smoothed using an 8-mm FWHM Gaussian kernel to improve the signal-to-noise ratio. Six rigid body motion parameters were used as regressors to correct for motion.

Data Analysis

COGED Behavior—Subjective effort costs were quantified as the subjective value of discounted rewards. Specifically, the indifference point for a given task-amount pair was divided by the base amount to yield a subjective value. If, for example, a participant was indifferent between $1.43 for the 1-back and $2 for the 2-back, then the subjective value for the $2, 2-back pair would be $1.43/$2 = 0.715. Thus, greater subjective value estimates equal greater willingness to choose the high effort option. A hierarchical linear model was used to test for group differences in discounting, accounting for the hierarchical nesting of indifference points within participants. Specifically, subjective value was predicted by N-back level, diagnostic group, and their interaction. Hard task reward amount was not found to significantly predict subjective value and did not explain additional variance to justify added complexity to the HLM. Thus it was removed as a predictor in all analyses. To examine whether negative symptoms varied as a function of effort allocation, a second HLM was implemented using only the data from those with schizophrenia. In this model, subjective values were predicted by task level, CAINS-MAP, and their interaction.

Supplemental analyses were conducted in order to quantify whether task performance was driving diagnostic and negative symptom effects on effort allocation. In short, we wanted to assess whether individuals were less willing to engage in demanding task levels simply because they were worse at the task. Thus, we conducted two additional analyses that

included average N-back performance across task levels (d-prime) as an additional predictor of subjective value in the models described above.

Finally, we conducted analyses to determine whether effort allocation was related to interest and enjoyment in daily activities measured via EMA. For these analyses, subjective value estimates for each participant were averaged creating a summary score of COGED decision-making, area under the curve. Area under the discounting curve (AUC) connecting subjective values across all levels provides a summary measure of mean willingness to expend cognitive effort for reward. We conducted one hierarchical linear model predicting EMA-EI by AUC. Further, given strong evidence of group differences for 2-back subjective value (Figure 1), we conducted a supplemental analysis where EMA-EI was predicted by subjective value at the 2-back.

COGED Imaging—Each participant's fMRI data was analyzed with a general linear model (GLM) using AFNI software. Separate regressors including a single regressor for BOLD activity during the evaluation phase, as well as separate regressors for each trial type (easy vs. hard trial) during the decision-making phase were modeled using an assumed hemodynamic response (GAM function). Six absolute motion parameters were also included. A contrast comparing hard vs. easy decision trials was created. For this GLM, we conducted a region of interest (ROI) analysis in AFNI using an a priori mask including regions from a prior analysis of an identical contrast (Westbrook, Lamichhane, & Braver, 2018) (Table S3). Further, we included bilateral dorsal striatum defined from AFNI atlases, and bilateral ventral striatum ROIs were created using a 8-mm sphere placed at peak coordinates (+/−10,8,−4) based on a previous study examining the neural correlates of reward learning in schizophrenia patients (Schlagenhauf et al., 2014). Mean percent signal change for each participant for each ROI and condition (easy/hard decision-making trial conditions) were extracted using the AFNI 3dmaskave program. In addition to the primary ROI analyses, we conducted exploratory whole-brain analyses to examine task effects and group differences in the hard vs. easy decision-making trial contrast. Whole-brain statistical maps were corrected for multiple comparisons using AFNI ClustSim program to determine cluster and activation thresholds (Table S4) (Cox et al., 2017).

To examine whether negative symptoms or discounting behavior (AUC) varied as a function of BOLD activation, we conducted bivariate correlations between AUC, CAINS-MAP, and BOLD activation in ROIs for the hard vs. easy contrast in schizophrenia group only. False discovery rate (FDR) correction was utilized to control for multiple comparisons (Benjamini & Hochberg, 2000).

Power Analysis—For within group correlations between symptoms, BOLD activation, and effort-based decision-making task performance we had approximately 75% power to detect an effect of r = 0.4 or greater. For t-tests assessing group differences, we had approximately 73% power to detect a medium-sized effect (Cohen's d = 0.6). Finally, HLM analyses are most accurately calculated using simulations. These simulations revealed approximately 75% power to detect an effect size of r = 0.4 or greater when testing whether a single variable (e.g., BOLD activation in a particular ROI or COGED choice behavior) predicted EMA self-report.

Results

The groups did not significantly differ in age, gender, ethnicity, or parental education. The SZ group reported significantly less personal education than the HC group (Table 1). Medication information and negative symptom severity of SZ patients is also listed in Table 1.

COGED Behavioral Results

Both SZ and HC participants discounted reward offers for higher levels of the N-back task, and did so in a mostly monotonic fashion (Figure 1A). Thus, participant discounting was sensitive to task load, and subjective costs increased with objective demands, as expected. SZ participants discounted rewards more than HC participants (Table 2A), suggesting greater effort aversion in those with schizophrenia (Figure 1B). Diagnostic group differences appeared to be largely driven by steep discounting of rewards by individuals with SZ compared to HC at the 2-back (Figure 1A), though the interaction between diagnostic group and N-back level was not significant.

In order to determine whether the severity of experiential negative symptoms (CAINS-MAP) predicted discounting behavior, we conducted a second hierarchical linear model predicting subjective value for each task amount pair from N-back level, CAINS-MAP, and their interaction (Table 2B). Negative symptom severity negatively predicted subjective value, suggesting that willingness to expend effort was lowest in the high negative symptom patients. Scatterplots illustrating the relationship between negative symptoms and effort can be found in Figure 1B & 1C.

We wanted to assess whether individuals with schizophrenia were less willing to engage in demanding task levels at least in part because they are worse at the task. Thus, we conducted two analyses that included average N-back performance across task levels (d-prime) as a predictor of subjective value in the models described above. In these models, diagnostic group was a trend-level predictor of subjective value, suggesting that cognitive impairment is likely a partial contributor to the diagnostic group differences seen in effort allocation (Table 2C). In contrast, negative symptom severity remained a significant predictor of subjective value even when controlling for task performance (Table 2D).

Finally, levels of interest and enjoyment with daily activities measured via EMA were not significantly predicted by willingness to expend effort on COGED (COGED-AUC) (*beta* = 0.53, *standard error* = 0.45, *t-value* = 1.18, *p-value* = 0.24). However, prediction of interest and enjoyment in daily activities was trend-level significant for 2-back subjective value, where group differences are most robust (*beta* = 0.75, *standard error* = 0.40, *t-value* = 1.86, *p-value* = 0.08).

Neuroimaging Results

Behavioral Quality Control Analyses for Correct Identification of Indifference Points—Decision-making for neuroimaging task trials generally suggested valid identification of indifference points (Supplemental Materials S5 & S6). Specifically, when individuals were presented with 1-back offers below their subject-specific indifference

points they tended to choose the hard task and when presented 1-back offers above indifference they tended to choose the easy task (Supplemental Materials S5). Further, reaction time for easy trials, which putatively require less deliberation, was faster than hard trials across both groups (Supplemental Materials S6).

Main Effect of Task Across Groups—Neuroimaging analyses focused on a contrast of putatively hard (e.g., where participants find $2 for 3-back vs. $1 for 1-back to be close in subjective value) compared to putatively easy (e.g., $2 for 3-back vs. $0 or $2 for 1-back, where subjective offer values are far apart) decision-making trials. Across participants, BOLD activation in *a priori* ROIs located in cerebellar, frontal, cingulate, parietal, and insular cortices was greater during decision-making of difficult compared to easy trials (Table S7), consistent with a previous report using a similar design with an identical contrast (Westbrook et al., 2018). Striatal ROIs did not show significant effects in this contrast (Table S7).

Follow-up whole-brain analyses revealed significant effects in similar regions when compared to ROI analyses. Specifically, posterior parietal/occipital cortex, middle cingulate cortex, posterior cingulate cortex, left postcentral gyrus, and left precuneus showed increased BOLD activation during difficult compared to easy decisions (Table S8). Increased BOLD activation was found for dorsal striatum during putatively difficult compared to putatively easy decision-making trials, but this effect did not survive multiple comparison correction.

Diagnostic Group Differences—Diagnostic group differences in *a priori* ROIs were largely not significant when comparing putatively difficult to putatively easy decision-making trials (Table S9). While healthy controls showed greater BOLD activation on hard vs. easy trials compared to those with schizophrenia in the right inferior frontal gyrus, this effect was only marginally significant and did not survive multiple comparison correction. Follow-up whole brain analyses did not reveal significant differences between groups in the contrast of interest (hard vs. easy) when correcting for multiple comparisons.

Individual Differences—Negative symptoms severity in those with schizophrenia showed robust correlations with BOLD activation in both left ($r = -0.50$, *p-value* = 0.006) and right ($r = -0.54$, *p-value* = 0.004). ventral striatum during putatively difficult compared to putatively easy decisions (Figure 2; see Table S10 for correlations). Correlations remained significant after applying FDR correction. Specifically, high negative symptom patients showed decreases in BOLD activation for hard compared to easy decision trials, whereas low negative symptoms patients showed increases in BOLD activation. For the left ventral striatum, this effect was trend-level significant after an outlier was removed ($r = -0.37$, *p-value* = 0.06). No other significant correlations were found between BOLD activation in *a priori* ROIs and negative symptom severity.

Correlations between COGED discounting (area under the curve) and BOLD activation for the contrast of hard vs. easy trials in *a priori* ROIs was also examined. Here, a positive correlation was found between the left anterior insula and discounting behavior (Figure 2C, however this correlation did not survive multiple comparison correction (Table S10). No

other significant correlations were found between BOLD activation in a priori ROIs and negative symptom severity. No significant correlations were observed between EMA variables and BOLD activation in *a priori* ROIs.

EMA and task variables were not significantly associated with demographic variables. Further, correlations between BOLD activation in a priori ROIs and demographic variables were largely non-significant. For ROIs that showed significant associations with demographic variables, inclusion of demographic variables as a covariate did not alter the statistical significant of associations between BOLD activation and negative symptom severity (Table S11).

Discussion

The goal of the current study was to examine effort-based decision-making in those with schizophrenia. Behaviorally, we found that individuals with schizophrenia were less willing than healthy controls to exert effort to obtain monetary rewards. Further, we observed that willingness to expend effort was associated with negative symptom severity, such that high negative symptom patients were least willing to exert effort for monetary rewards, even when controlling for task performance. Regarding neural correlates, we observed increased BOLD activation of frontal, parietal, cingulate, and insular regions during hard compared to easy trials across participants. Contrary to our hypotheses, we observed similar patterns of BOLD activation in both SZ and HC groups during effort-based choice. However, negative symptom severity in those with schizophrenia was significantly associated with reduced BOLD activation in bilateral ventral striatum during decision-making, and greater discounting was associated with greater anterior insula activity, although this effect did not survive FDR correction. These findings are discussed in further detail below.

The findings of the current study are consistent with previous literature demonstrating decreased willingness of those with schizophrenia to expend effort for monetary rewards (Barch et al., 2014; Culbreth et al., 2016; Fervaha et al., 2013; Gold et al., 2013; Huang et al., 2016; McCarthy et al., 2016; Reddy et al., 2015; Treadway et al., 2015; Wang et al., 2015; Wolf et al., 2014). Also consistent with several previous reports (Barch et al., 2014; Culbreth et al., 2016; Gold et al., 2013; Hartmann et al., 2015; Horan et al., 2015; Moran et al., 2017; Strauss et al., 2016; Treadway, Bossaller, et al., 2012; Wang et al., 2015; Wolf et al., 2014), we found that negative symptoms were associated with effort exertion, such that greater negative symptom severity was associated with a decreased willingness to exert effort. In addition to measuring negative symptoms with traditional clinical interviews, we also measured negative symptoms using an ecological momentary assessment approach, asking individuals with schizophrenia to self-report their interest and enjoyment with daily activities using a smartphone. Using a similar approach, our lab previously (Moran et al., 2017) found that people with schizophrenia who demonstrated the least willingness to exert physical effort on an experimental task also reported the least interest and enjoyment with their daily activities. Although the associations between cognitive effort-based decision-making and EMA variables in the current report were not as robust as in our prior work, we did observe a trend-level positive association. Limited power due to lower sample size may have contributed to non-significant findings in the current report.

Similar to a previous report using a similar design (Westbrook et al., 2018), across participants, we observed increased BOLD activation in frontal, cingulate, parietal, and insular regions for hard compared to easy decision-making trials. Contrary to expectations, we did not observe significant effects in striatal regions for our overall contrast of hard compared to easy decisions. Several previous reports have found BOLD activation in ventral and/or dorsal striatum, which varies as a function of effort during valuation and decision-making (Croxson et al., 2009; Kurniawan, Guitart-Masip, Dayan, & Dolan, 2013; Kurniawan et al., 2010; Leotti & Delgado, 2011; Schmidt et al., 2012). Thus, the lack of robust BOLD activation in the striatum for the present contrast is surprising.

Contrary to our hypotheses, we observed similar patterns of BOLD activation for both HC and SZ groups for our contrast of hard compared to easy trials. These results are inconsistent with a recent report (Huang et al., 2016) that found blunted reward-related BOLD activation of dorsal and ventral striatum in schizophrenia participants as a group compared to healthy controls during effort-based decision-making. However, Park et al., found largely similar patterns of BOLD activation between individuals with schizophrenia and healthy controls during estimation of effortful options (Park et al., 2017). Aspects of the current experimental design may have limited our ability to observe strong group differences. Specifically, decision-making trials in our neuroimaging design were administered in a subject-specific manner, based on the individual participant's indifference points derived during the behavioral portion of COGED. Thus, each participant received different trials based on their own willingness to expend effort, resulting in different trial combinations in all participants. In future work, it will be important to include some standard trial types across participants to determine if more evidence of neural alterations emerge at the group level with comparisons well-suited to elicit group differences.

In regards to individual differences, we did observe robust correlations between negative symptom severity and BOLD activation in bilateral ventral striatum, as well as a positive association between willingness to expend effort and BOLD activation in the anterior insula, although at a nominal level of significance. The current striatal finding is consistent with previous work (Wolf et al., 2014) that demonstrated an association between willingness to expend effort and ventral striatal BOLD activation on a reward-processing task in those with schizophrenia. Further, the correlations observed in the current report are consistent with several previous reports that examined aspects of value-based decision-making and found blunting of VS BOLD activation related to increased negative symptom severity in those with schizophrenia (Simon et al., 2010; Waltz et al., 2013; Waltz et al., 2010). Interestingly, in these studies, while associations were found between VS BOLD activation and negative symptom severity, group differences in the VS between controls and those with schizophrenia were non-significant, similar to the current report.

Future work could extend the current findings in several directions. First, while multiple studies have examined effort-based decision-making in schizophrenia (Culbreth et al., 2017; Gold, Waltz, & Frank, 2015a; Green et al., 2015), work has been limited to medicated patients in the chronic phase of illness. An important direction for future research remains in assessing individuals in earlier phases of illness, as well as anti-psychotic naïve individuals. Research including such patient groups will help to establish the potentially confounding

role of anti-psychotic medications in effort-based decision-making deficits in schizophrenia, as well as help to determine whether effort-based decision-making impairments are present across illness course. Second, impairments in effort-based decision-making have also been found in other psychiatric disorders (e.g., major depressive disorder) (Cléry-Melin et al., 2011; Hershenberg et al., 2016; Sherdell, Waugh, & Gotlib, 2012; Treadway, Bossaller, et al., 2012; Yang et al., 2016; Yang et al., 2014). However, it remains unknown whether similar behavioral effort-based decision-making impairments across these disorders involve similar or disparate psychological and neural mechanisms (Culbreth et al., 2017). Transdiagnostic samples are necessary to determine such mechanistic questions, which could have important implications for development of novel intervention strategies to alleviate effort-based decision-making impairments. Finally, although effort-based decision-making impairments appear to be a robust deficit in those with schizophrenia, little work has suggested potential treatment approaches for improving effort expenditure. While future work is needed to better characterize the mechanisms that might give rise to aberrant effort-based decision-making in order to guide mechanistically-informed intervention, several promising interventions exist that could yield beneficial effects. For example, individuals with schizophrenia may show decreased willingness to expend effort, in part, due to negative beliefs about their ability to successfully perform actions (Grant & Beck, 2008; Reddy et al., 2017), and such beliefs can be successfully targeted with cognitive behavioral therapy (Grant & Beck, 2008).

The current study had several limitations. First, the sample size was modest and included individuals with schizophrenia primarily in the chronic phase of illness. Future work will be needed to replicate and extend the current findings in a larger sample. Second, we did not collect EMA measures in our healthy control group and this prohibits examination of more typical patterns of enjoyment/interest in daily activities. However, while such typical patterns are important, they were not necessary to the aims of the current analyses. Third, many of the participants with schizophrenia were taking anti-psychotic medications at the time of study completion, which may have influenced choice behavior due to influence on dopamine systems. Fourth, given the complexity of the EMA data, there are a multitude of potential alternatives for creating summary scores. In the current manuscript, we averaged together self-reported interest and enjoyment for current, past, and future daily activities within each EMA time point. Such an averaged approach has the benefit of assessing general hedonic and motivational experience, while limiting the number of statistical comparisons. However, it may be the case that specific questions, indexing particular aspects of hedonic and motivational experience, show stronger associations to task and biological variables. While we do not explore relationships between task variables and specific questions in the current manuscript, future research may benefit from attempting to relate task variables to more specific aspects of daily motivational experience. Further, future reports may benefit from examining daily motivational experience within particular behavioral contexts (e.g., social situations, during completion of effortful behaviors) in order to observe whether relationships. Finally, negative symptoms were partially assessed using the CAINS. Converging structural analyses of the CAINS have identified two moderately correlated factors, one reflecting experiential impairments (anhedonia, asociality, avolition) and the other reflecting expressive impairments (alogia, blunted affect) (Horan, Kring, Gur, Reise, &

Blanchard, 2011; Kring et al., 2013). Given the hypothesized relationship between effort allocation and experiential impairment, CAINS-MAP was the focus of the current report. A recent structural report has suggested a five-factor model of negative symptoms (i.e., anhedonia, avolition, asociality, alogia, and blunted affect; Strauss et al., 2018). While such a model was not utilized in the current report, future studies may benefit from examining relationships between willingness to expend effort and particular factors of this model (particularly avolition and anhedonia).

In conclusion, the current study provides replication of previous work suggesting decreased willingness of those with schizophrenia to exert effort to obtain monetary rewards. Further, we showed that this behavioral deficit varies as a function of negative symptom severity, and that negative symptom severity in patients is closely associated with hypoactivation of ventral striatum during effort-based choice. Future studies are needed to further examine the neural correlates of effort-based decision-making in schizophrenia in larger samples, as well as to assess patients at various phases of illness. In addition, it will be important to further examine the psychological and neural mechanisms of effort-based decision-making in order to guide development of novel interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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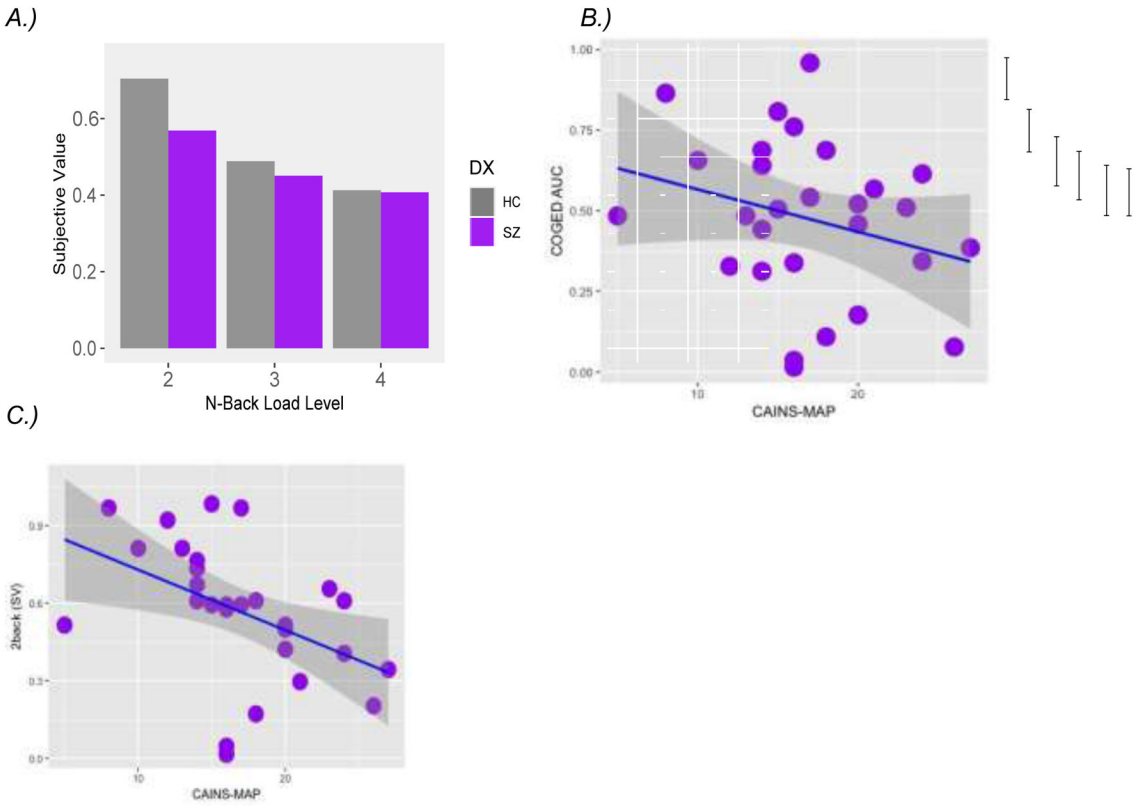

Figure 1:

Behavioral Results: (Top Left): Subjective value decreased as cogntive demand (n-back level) increased, suggesting that the n-back is cognitively demanding and participants required more money to perform harder load levels. Critically, those with schizophrenia showed steeper discounting. They required more money than controls to choose to engage with the harder task. (Top Right): Individuals with the greatest negative symptoms were the least willing to perform cogntively demanding tasks. (Bottom Left): Negative symptom effects were strongest during discounting of the 2-back, the load level with the most robust group differences.

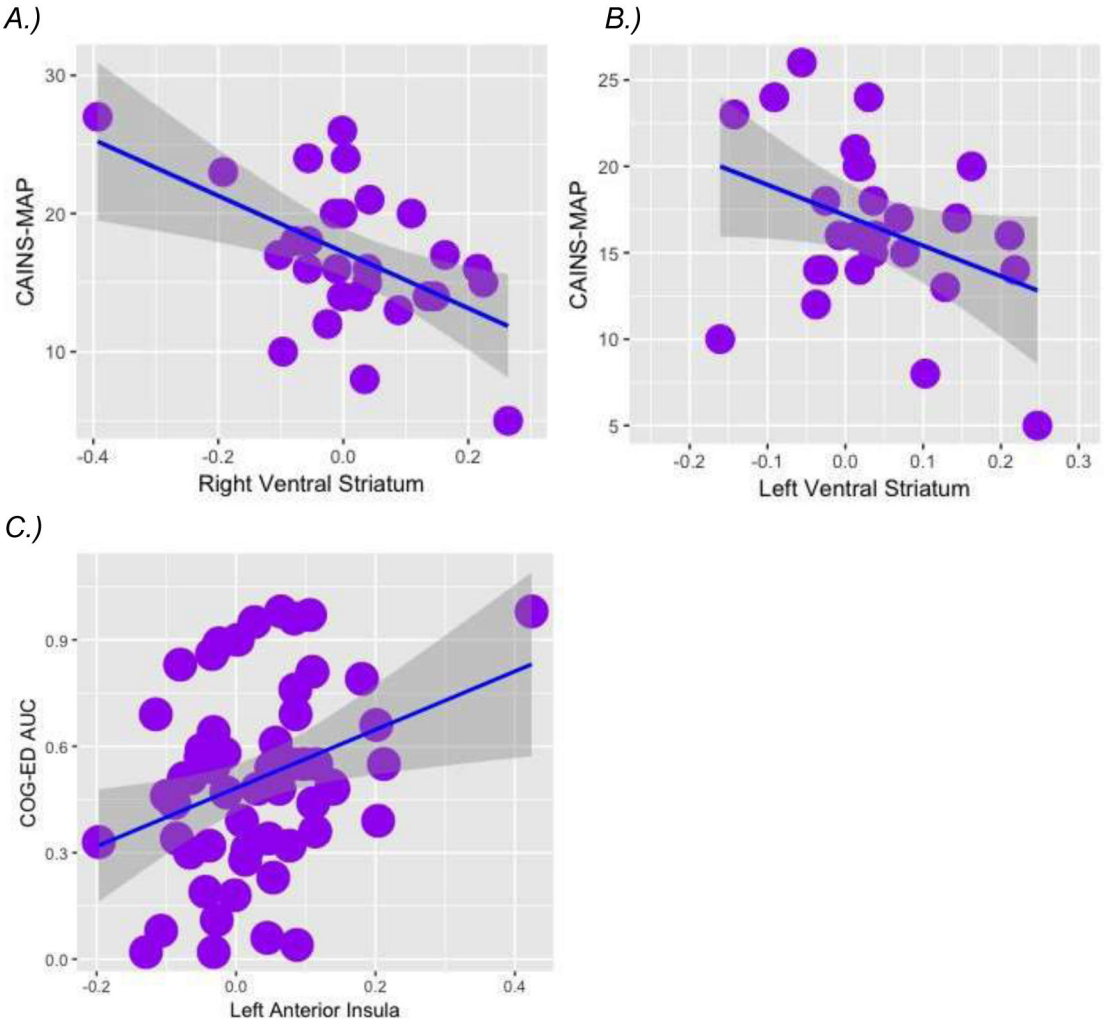

Figure 2:

Scatterplots of ROI, Negative Symptom, and Willingness to Expend Effort: Bold activation in *a priori* ROIs decreased as negative symptoms (CAINS-MAP) increased. Further, BOLD activation in the left anterior insula increased as willingness to expend effort (COGED-AUC) increased.

Table 1:

Demographic Information and Symptom Characterization

	Control (n = 30)		Schizophrenia (n = 28)			
	MEAN	**SD**	**MEAN**	**SD**	**test statistics**	**p-value**
Age (years)	35.2	10.63	37.18	12.25	$t = -0.66$	0.51
Sex (% Female)	23%		29%		$\mathbf{X}^2 = 0.207$	0.65
Ethnicity, (n)					$\mathbf{X}^2 = 1.95$	
African American	16	15				0.38
Asian	4		1			
Caucasian	10		12			
Education (years)	15.47	2.43	12.75	2.95	$t = 3.84$	<0.001
Parental Education (years)	13.92	2.34	14.48	3.76	$t = -0.69$	0.49
WTAR	95.58	18.06	93.25	20.48	$t = 0.69$	0.64
CAINS MAP	--		16.89	5.17		--
CAINS EXP	--		5.39	4.04		--
Medications (n)						
Unmedicated	--		5			
Atypical antipsychotics	--		18			--
Typical antipsychotics	--		5			
CPZ Equivalent	--		311.81	151.45		--

Table 2:

HLMs Predicting Subjective Value

A.)	**Parameter**	**Estimate**	**Standard Error**	**t-value**	**p-value**
	N-back Level	−0.21	0.07	−3.22	0.002
	Group	−0.19	0.09	−2.05	0.04
	N-back Level x Group	0.07	0.04	1.56	0.12
B.)					
	Parameter	**Estimate**	**Standard Error**	**t-value**	**p-value**
	N-back Level	−0.25	0.1	−2.62	0.01
	CAINS-MAP	−0.03	0.01	−2.92	0.007
	N-back Level x CAINS-MAP	0.01	0.01	1.87	0.7
C.)					
	Parameter	**Estimate**	**Standard Error**	**t-value**	**p-value**
	N-back Level	−0.21	0.07	−3.22	>0.002
	Group	−0.16	0.09	−1.71	0.09
	D-prime	0.04	0.04	1	0.32
	N-back Level x Group	0.07	0.04	1.56	0.12
D.)					
	Parameter	**Estimate**	**Standard Error**	**t-value**	**p-value**
	N-back Level	−0.25	0.1	−2.61	0.01
	CAINS-MAP	−0.03	0.01	−2.61	0.01
	D-prime	0.12	0.04	2.67	0.01
	N-back Level x CAINS-MAP	0.01	0.01	1.87	0.07