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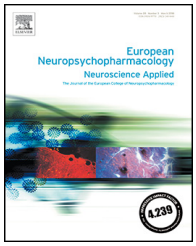

Effort-based decision-making impairment in patients with clinically-stabilized first-episode psychosis and its relationship with amotivation and psychosocial functioning

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Abstract
Effort-based decision-making has recently been proposed as a potential mechanism contributing to motivational deficits (amotivation) in psychotic disorder. Previous research has identified altered effort allocation in chronic schizophrenia, but produced mixed results regarding its relationship with amotivation. No study has investigated effort allocation in first-episode psychosis (FEP). We examined effort-based decision-making in 45 clinically-stabilized FEP patients and 45 demographically-matched controls, using Effort-Expenditure for Reward Task (EEfRT) which measures allocation of physical effort for monetary reward at varying magnitude and

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probability levels. Our results showed that FEP patients did not demonstrate overall reduction in effort expenditure but displayed reduced willingness to expend effort for high-value/high-probability reward as compared to controls. In particular, such selective effort-related impairment was most pronounced in patients with high levels of amotivation. Furthermore, reduced allocation of greater effort for higher probability reward was related to poorer psychosocial functioning. Decreased effort exertion was generally unrelated to other symptom dimensions, self-report anhedonia, antipsychotic dose and cognitive deficits. This study thus provides the first evidence of effort-based decision-making impairment in FEP, and indicates that first-episode patients were not generally effort-averse but exhibited inefficient effort allocation by failing to make high-effort choices to maximize reward receipt. Our findings affirm the critical role of amotivation on aberrant effort allocation, and support the link between laboratory-based effort-cost measures and real-world psychosocial functioning in medicated FEP. Further longitudinal research is required to clarify trajectory of suboptimal effort allocation and its potential utility in predicting amotivation and functional outcomes in the early course of illness.

1. Introduction

Reduced motivation and goal-directed behavior (i.e., amotivation) is a hallmark feature of negative symptoms in psychotic disorders (Foussias and Remington, 2010). Compared to diminished expression (DE), another core subdomain of negative symptoms (Messinger et al., 2011), amotivation has been found to be more prevalent and persistent over time in the early course of illness (Fervaha et al., 2015a; Norman et al., 2015). Recent studies have further demonstrated that amotivation is a significant predictor of functional outcome in chronic schizophrenia (Strauss et al., 2013; Fervaha et al., 2014) and first-episode psychosis (FEP) (Faerden et al., 2013; Chang et al., 2016a, 2017), above and beyond the contributions of cognitive deficits, DE and other symptom dimensions (Fervaha et al., 2015a; Chang et al., 2016a, 2017). Given that a significant proportion of FEP patients experience pronounced functional impairment even after clinical stabilization (Chang et al., 2012, 2018; Verma et al., 2012), amotivation thus represents an important treatment target for promotion of early functional recovery.

It is, however, widely recognized that amotivation constitutes an unmet treatment need, with limited response to pharmacotherapy (Fusar-Poli et al., 2015). In an attempt to facilitate development of targeted treatments, there has been increased interest in clarifying mechanisms that underlie motivational impairment in psychotic disorders. Previous research has revealed that negative symptoms, in particular amotivation, are related to impairment in various components of reward processing including reward anticipation, reinforcement learning and representation of reward values (Kring and Barch, 2014; Strauss et al., 2014; Waltz and Gold, 2016) in schizophrenia patients, who are otherwise found to have preserved hedonic capacity (Cohen and Minor, 2010). Recently, effort-based decision-making paradigms have been put forward as a promising translational research target linking well-studied preclinical models of effort-cost computation to investigation of motivational deficits in schizophrenia (Young and Markou, 2015). These paradigms provide quantitative, performance-based measures of motivation by evaluating a participant's willingness to expend effort for a given reward. The fact that dopamine system and corticostriatal circuits, especially anterior cingulate cortex, are both critically involved in effort-cost computation (Corxson et al., 2009; Kurniawan et al., 2011; Salamone et al., 2016) and implicated in the pathophysiology of psychotic disorders (Minzenberg et al., 2009; Howes et al., 2012; Brugger and Howes, 2017) suggests that effort-based decision-making is likely impaired in patients with the disorder.

In fact, a growing body of research has recently been conducted to examine effort-based decision-making in schizophrenia, with the majority focusing on physical effort allocation (Gold et al., 2015; Green et al., 2015; Culbreth et al., 2018). Most (Fervaha et al., 2013; Gold et al., 2013; Barch et al., 2014; Hartmann et al., 2015; Reddy et al., 2015; Treadway et al., 2015; Wang et al., 2015; Huang et al., 2016; McCarthy et al., 2016), though not all (Docx et al., 2015; Strauss et al., 2016), of these studies revealed altered effort allocation in schizophrenia. Specifically, patients did not show general reduction of effort expenditure but displayed suboptimal effort allocation in pursuit of reward by making significantly fewer high-effort choices than healthy participants at high levels of reward magnitude and probability of reward receipt (Gold et al., 2015; Green et al., 2015; Culbreth et al., 2018). A recent study, using ecological momentary assessment (EMA), also demonstrated that schizophrenia patients engaged in fewer effortful activities, set fewer effortful goals and had compromised estimation of effort involved in goal attainment (Gard et al., 2014). Less consistent findings, however, were observed regarding the relationship between diminished effort allocation and amotivaiton. Some prior studies showed that decreased willingness to expend effort for monetary reward was significantly related to higher clinician-rated amotivation scores (Fervaha et al., 2013; Barch et al., 2014; Hartmann et al., 2015; Strauss et al., 2016; Horan et al., 2015; Serper et al., 2017), while others failed to find such an association (Gold et al., 2013; Docx et al., 2015; Treadway et al., 2015; Huang et al., 2016; McCarthy et al., 2016; Moran et al., 2017; Bismark et al., 2018). Several reports further indicated that patients with high levels of negative symptoms or amotivation exhibited the greatest impairment in effort allocation relative to controls and patients with low symptom

severity (Gold et al., 2013; Hartmann et al., 2015; Wang et al., 2015; Fervaha et al., 2015a,b; Serper et al., 2017). Alternatively, relatively few studies (Barch et al., 2014; Horan et al., 2015; McCarthy et al., 2016; Strauss et al., 2016) have examined whether effort-based decision-making is associated with functional outcome, and existing findings are mixed.

Of note, despite the clinical significance and prognostic implication of amotivation in early psychosis, all previous studies investigating effort-based decision-making have focused on patients with chronic schizophrenia which is confounded by illness chronicity and prolonged exposure to antipsychotic treatment. There is evidence suggesting that antipsychotic treatment, especially first-generation antipsychotic, might impair patients' motivation via dopamine-receptor blockade (Gründer et al., 2016; Juckel, 2016; Kirschner et al., 2017). Thus far, there has been no published report examining effort-based decision-making in a FEP sample. Whether deficits in effort allocation have already emerged in the initial stage of psychotic illness remain to be clarified. In the current study, we sought to examine effort-based decision-making in a cohort of Chinese patients with clinically-stabilized FEP, using the Effort-Expenditure for Reward Task (EEfRT) (Treadway et al., 2009) which is a computerized button-pressing task assessing physical effort allocation in response to varying levels of reward magnitude and probability. Specifically, we aimed to clarify the relationships of effort allocation performance with amotivation and functional status of FEP patients. EEfRT has been well-studied in healthy populations (Treadway et al., 2009, 2012) and is the most frequently used performance-based paradigm in investigating effort-cost computation in schizophrenia (Green et al., 2015; Culbreth et al., 2018). A recent study, which systematically evaluated psychometric properties across multiple effort-based decision-making tasks (Horan et al., 2015; Reddy et al., 2015), has suggested EEfRT as a potentially useful effort allocation paradigms to objectively quantify amotivation for clinical trial use in psychotic disorders. Based on prior studies (Green et al., 2015; Culbreth et al., 2018), we hypothesized that, overall, clinically-stabilized FEP patients would display altered physical effort allocation with reduced willingness to exert effort for high-value/high-probability reward as compared to healthy controls. Furthermore, we predicted that patients with high levels of amotivation would select fewer effortful choices at the highest levels of reward magnitude and probability of reward receipt than controls and patients with low levels of amotivation. We also predicted that diminished effort expenditure for reward would be associated with poorer psychosocial functioning.

2. Experimental procedures

2.1. Participants and setting

Forty-five patients in their first psychotic episode, aged 15–40 years, were recruited from the outpatient unit of a specialized early intervention service for FEP in Hong Kong. Diagnosis was ascertained using the Chinese-bilingual Structured Clinical Interview for DSM-IV (CB-SCID-I/P) (So et al., 2003) (27 received a DSM-IV (American Psychiatric Association, 1994) diagnosis of schizophrenia, 6 with schizophreniform disorder, 2 with schizoaffective disorder, 7 with brief psychotic disorder, and 3 with psychotic disorder not otherwise specified). First-episode status, age at onset of psychosis and duration of untreated psychosis (DUP) were verified using the Interview for Retrospective Assessment of the Onset of Schizophrenia (IRAOS) (Hafner et al., 1992). Study assessments were administered to patients within 7 months following antipsychotic initiation (mean:141days; SD:54), at which point all patients had been on stable antipsychotic regimens for at least four weeks.

Forty-five healthy controls were recruited from the community via advertisements and word-of-mouth among recruited participants. Patients and controls were matched for age, gender, and educational level. Controls were screened to confirm that they had no current psychiatric diagnosis (by CB-SCID-I/P), family history of psychotic disorder, and were not taking any psychotropic medications.

The study was approved by the local institutional review boards, and all participants provided written informed consent. For those aged under 18 years, parental consent was also obtained. Any individual showing evidence of substance abuse (according to the Alcohol Use Scale and the Drug Use Scale) (Drake et al., 1996), intellectual disability or neurological disease was excluded from participation. Patients who had clinically-significant antipsychotic-induced Parkinsonism as ascertained by having 2 or more item ratings $>$ 2 on the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) were also excluded.

2.2. Clinical and cognitive assessments

Positive and disorganization symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Negative symptoms were measured by the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1984). As the negative symptom construct has consistently demonstrated two distinct subdomains of amotivation and DE (Messinger et al., 2011), we derived amotivation and DE scores based on the method applied by previous research (Chang et al., 2016a, 2017): Amotivation consisted of items of Avolition-apathy and Anhedonia-asociality subscales (excluding global items) on the SANS; and DE comprised items of Affective flattening subscale (excluding global item) and the poverty of speech item from the Alogia subscale. Depression was evaluated using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992). Psychosocial functioning was assessed by the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992). The Snaith-Hamilton Pleasure Scale-Chinese version (C-SHAPS) (Liu et al., 2012) was administered to both patients and controls as a self-reported measure of anhedonia. Cognitive assessments included letter-number span (Gold et al., 1997), digit symbol subtest from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Hong Kong Psychological Society, 1989a), letter cancellation test (Diller et al., 1974), Trail making test (Reitan, 1955), and logical memory subtest from the Wechsler Memory Scale-Revised (WMS-R) (Hong Kong Psychological Society, 1989b). Additionally, participants completed three 10-s trials of measuring finger-tapping speed using their non-dominant pinky finger prior to EEfRT administration. The average number of presses over three trials was used as a quantitative measure of motor function to evaluate potential group differences in motor speed as a confound.

2.3. Effort-based decision-making task

The Effort-Expenditure for Reward Task (EEfRT) (Treadway et al., 2009) is a computerized, multi-trial button-pressing experiment

that assesses a participant's willingness to expend physical effort for monetary reward. On each trial, participants were asked to choose between a "high-effort" (hard) and "low-effort" (easy) task. Low-effort trials required participants to make 30 button presses within 7 s using their dominant index finger, and high-effort trials required participants to make 100 button presses within 21 s using their non-dominant pinky finger. The reward value for the low-effort choice was fixed at $1, while that of the high-effort choice ranged from $1.24 to $4.12. Receipt of reward following successful completion of a trial was contingent upon three probability levels (12%, 50% or 88%), regardless of high- or low-effort choice. There were an equal number of three probability-level trials associated with each level of reward value. All participants received trials presented in the same pre-randomized sequence. Information regarding the probability of receiving reward and the reward value associated with high-effort choice was provided at the beginning of each trial. Following trial completion, participants were provided with feedback about whether the trial was successfully completed, and if so, whether they had won monetary reward for that trial. Task duration was modified to last for 15 min to minimize potential fatigue effect on task performance. Participants were provided with standardized task instructions and underwent four practice trials under the supervision of a trained research assistant. Participants were told that they would receive a bonus at the end of the study based on their task performance, in addition to the base-compensation of HK$100 (US$13) for their participation. In actuality, all participants were compensated HK$200 (US$26). After study completion, participants were asked to rate on an 11-point Likert scale of how difficult they perceived the high-effort trials to be and how engaged they were during the task.

2.4. Statistical analysis

To examine the effects of group, probability and reward magnitude on effort allocation, we performed a 2 group (patients vs. controls) $\times$ 3 probability (12%, 50%, 88%) $\times$ 3 reward (values for high-effort option were binned into: low=$1.24-$2.00, medium=$2.01-$3.00, and high=$3.01- $4.12) repeated-measures analysis of variance (ANOVA), with proportion of high-effort choices as the dependent variable. A Huynh-Feldt correction was applied when the sphericity assumption was not met. Significant effects were further explored using a series of post-hoc t-tests. To investigate the relationships between effort expenditure and negative symptoms, two approaches were adopted in the current study. First, as evidence suggested that amotivation subdomain of negative symptoms may be specifically linked to impaired effort allocation, we pursued a categorical approach by classifying FEP patients into high (HIGH-AMO) and low (LOW-AMO) amotivation subgroups, based on a median split on SANS amotivation score (split score=10), for comparison analyses on EEfRT performance. Second, following the method employed by previous studies (Barch et al., 2014; Horan et al., 2015), we examined correlations of negative symptom measures (SANS total and SANS amotivation scores) with four recommended EEfRT performance indices, namely (1) percentage of high-effort choices in 88% probability condition; (2) percentage of high-effort choices at high reward condition; (3) difference in percentage of high-effort choices between 12% and 88% probability conditions (probability difference score); and (4) difference in percentage of high-effort choices between low and high reward conditions (reward difference score). Evaluating the effects of negative symptoms both categorically and dimensionally is important because the construct is not purely continuous, but rather of a hybrid categorical-dimensional nature (Ahmed et al., 2015). As we did not observe any participant who only selected high-effort trials across all reward levels (i.e., all-hard inflexible responder) in either patient or control groups, the entire study sample was included for difference-score analyses (Horan et al., 2015). Relationships between EEfRT performance indices and psychosocial functioning, as measured by SOFAS score, were also examined. Additionally, we assessed correlations of EEfRT performance with other symptom dimensions, self-reported anhedonia, antipsychotic dose and cognitive functions. We did not apply multiple-comparison correction to correlations that were hypothesis-driven (i.e., EEfRT measures with overall negative symptom severity, amotivation levels, and functional outcome), but did so in the case of correlations that were not hypothesis-driven.

3. Results

3.1. Characteristics of the sample

Demographics, cognitive functions and clinical characteristics of the participants are summarized in Table 1. There were no significant differences among control, HIGH-AMO and LOW-AMO groups in age, gender or educational levels. Controls had significantly lower levels of self-reported anhedonia and better performance in all individual cognitive tests than the two patient groups. Controls had faster finger-tapping rate than patient groups ($F_{2,87}$=3.1, p = 0.05), but there was no significant correlation between finger-tapping speed and the proportion of selecting high-effort trials in control (r = 0.02, p = 0.91) and patient groups (r=−0.04, p = 0.84). The three groups did not differ in post-experiment perception of task difficulty ($F_{2,71}$=0.70, p = 0.50) or engagement ($F_{2,71}$=1.50, p = 0.23). Among FEP patients, HIGH-AMO group had significantly higher SANS amotivation score as expected and lower SOFAS score than LOW-AMO group. No other significant differences were observed between the two patient groups in demographics, self-report anhedonia, finger-tapping rate, cognitive functions, clinical and treatment characteristics.

3.2. Effort task performance in the FEP sample

There were no significant differences between patients and controls in total number of trials attempted (t_{88}=0.25, p = 0.81), the proportion of high-effort trials chosen (t_{88}=0.37, p = 0.71) and reaction time (t_{88}=1.62, p = 0.11). Patients completed fewer trials (FEP: 43.5; HC: 48.2; t_{88}=2.89, p = 0.01) than controls, but the proportion of completed trials did not significantly correlate with the percentage of high-effort trials selected in both patient (p = 0.23) and control (p = 0.16) groups. The repeated-measures ANOVA revealed significant main effects of probability ($F_{1.8,157.8}$ = 110.2, p<0.01) and reward magnitude ($F_{2,176}$=71.3, p<0.01), indicating that overall, participants were more likely to choose high-effort trials when the probability of receiving reward and the reward value was higher. Consistent with prior studies using the EEfRT, there was no significant main effect of group ($F_{1,88}$=0.02, p = 0.89). We observed significant group x probability ($F_{1.8,159.8}$ = 7.2, p=<0.01), group x reward ($F_{2,176}$=4.2, p = 0.02), probability $\times$ reward ($F_{4,352}$=22.7, p<0.001), as well as three-way interactions ($F_{4,352}$=3.6, p<0.01). Given that group difference on educational levels approached significance (p = 0.09) and patients had significantly worse cognitive performance than controls, repeated-measures ANCOVAs with years of education and cognitive composite score as a covariate, respectively, were also conducted. Results of the additional

Table 1 Demographics, cognitive functions and clinical characteristics of patients and controls.

Variables[a]	Patients[b] ($N=45$)	Controls ($N=45$)	Statistic[c] (t/χ^2)	P	HIGH-AMO ($N=21$)	LOW-AMO ($N=24$)	Statistic[d] ($F/t/\chi^2$)	P
Demographics								
Age in years	24.9 (7.0)	25.0 (6.7)	0.09	0.93	24.3 (7.0)	25.4 (7.1)	0.13	0.88
Male gender, *N* (%)	24 (53.3)	18 (40.0)	1.61	0.21	12 (57.1)	12 (50.0)	1.84	0.40
Years of education	12.6 (3.0)	13.7 (2.6)	1.74	0.09	12.2 (3.3)	13.0 (2.6)	1.93	0.15
Cognitive function								
Letter number span	14.3 (3.0)	17.8 (3.7)	4.84	<0.001	14.4 (2.9)	14.2 (3.2)	11.58	<0.01
Digit symbol coding	10.4 (3.4)	14.4 (3.0)	5.76	<0.001	10.4 (3.9)	10.5 (3.0)	16.39	<0.01
Logical memory	7.7 (3.4)	11.7 (3.0)	5.90	<0.001	7.2 (3.4)	8.0 (3.5)	17.69	<0.01
Letter cancellation[e]	4.3 (3.6)	2.7 (3.2)	2.20	0.03	5.1 (3.9)	3.5 (3.2)	3.40	0.03
Trail making A	29.5 (10.0)	22.9 (7.2)	3.60	<0.01	29.2 (9.1)	29.9 (11.0)	6.43	<0.01
Trail making B	73.1 (33.7)	49.9 (21.9)	3.78	<0.001	80.7 (40.2)	67.6 (30.9)	8.30	<0.01
Cognitive composite score[f]	−1.1 (1.0)	0.0 (0.7)	6.27	<0.001	−1.1 (0.9)	−1.1 (1.0)	19.42	<0.01
Self-report anhedonia, SHAPS-C score	45.1 (5.6)	48.8 (5.4)	3.03	<0.01	43.8 (6.0)	46.6 (4.9)	5.88	<0.01
Clinical characteristics								
Age at onset, years	24.0 (7.1)	-	-	-	23.8 (6.9)	24.2 (7.4)	0.19	0.85
DUP in days (median)	72	-	-	-	82	63	-	-
Log DUP[g]	1.9 (0.6)	-	-	-	2.0 (0.4)	1.9 (0.8)	0.55	0.58
PANSS positive symptom score[h]	9.0 (2.7)	-	-	-	9.4 (4.4)	8.2 (1.8)	1.19	0.24
PANSS disorganization score[h]	7.8 (1.3)	-	-	-	8.1 (1.5)	7.6 (1.1)	1.29	0.20
SANS total score	18.4 (11.0)	-	-	-	25.5 (11.2)	12.2 (6.1)	4.86	<0.01
SANS amotivation score	11.6 (6.6)	-	-	-	17.1 (5.3)	6.6 (2.6)	8.33	<0.01
SANS diminished expression score	6.9 (6.4)	-	-	-	8.4 (7.6)	5.6 (5.1)	1.41	0.17
CDSS total score	1.6 (2.6)	-	-	-	1.8 (3.4)	1.3 (1.7)	0.61	0.55
SOFAS score	53.0 (11.7)	-	-	-	47.5 (9.8)	57.8 (11.3)	3.26	<0.01
Chlorpromazine equivalents[i], mg/day	219.7 (196.0)	-	-	-	226.9 (254.2)	213.5 (131.3)	0.23	0.82

AMO = Amotivation; CDSS = Calgary Depression Scale for Schizophrenia; DUP = Duration of untreated psychosis; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for Assessment of Negative Symptoms; SHAPS-*C* = Snaith-Hamilton Pleasure Scale - Chinese version; SOFAS = Social and Occupational Functional Assessment Scale.

[a] Data are presented in mean and standard deviations, except gender and DUP.

[b] All patients were receiving antipsychotic medication: 33 on second-generation antipsychotic (SGA) monotherapy, 2 on first-generation antipsychotic (FGA) monotherapy, 8 on two SGAs, and 2 on combined FGA and SGA treatment.

[c] Potential group differences were examined using independent-samples t tests and chi-square tests for continuous and categorical variables, respectively.

[d] Test statistic and *p* values reflect three-group analyses in demographic, cognitive and self-report anhedonia data, conducted on HIGH-AMO (patients with high amotivation), LOW-AMO (patients with low amotivation) and control groups. Patient group comparisons on clinical characteristics were examined using independent-samples *t* tests and chi-square tests for continuous and categorical variables, respectively.

[e] Letter cancellation test performance was measured by the number of omission error committed, with higher number of omission errors indicating poorer performance.

[f] Cognitive composite score for each participant was calculated by averaging the *z*-scores of individual cognitive tests. Standardized *z*-score of each of the cognitive tests were computed based on performance of healthy controls.

[g] DUP was log-transformed for analysis due to its skewed distribution.

[h] PANSS positive symptom and disorganization scores were derived on the basis of a previous factor-analytic study on first-episode psychosis patients (Emsley et al., 2003).

[i] Chlorpromazine equivalents were computed according to Gardner et al. (2010).

analyses were consistent with our original unadjusted analysis, with group × probability (education as covariate: $p<0.01$; cognition as covariate: $p=0.01$) and group × reward (education as covariate: $p=0.03$; cognition as covariate: $p=0.04$) interactions remained statistically significant. A series of post-hoc contrasts were conducted to further clarify these significant interactions. Results showed significant group differences at 88% ($t_{88}=2.5$, $p=0.02$) and 12% ($t_{88}=2.8$, $p=0.01$) probability conditions (Fig. 1A), and a trend approaching significance between patients and controls for high reward condition ($t_{88}=1.9$; $p=0.06$; Fig. 1B). As shown in Fig. 2C, patients selected high-effort trials significantly less frequently than controls for the 88% probability condition. Conversely, patients chose high-effort trials more often than controls at 12% probability condition ($t_{88}=2.6$, $p=0.01$; Fig. 2A).

3.3. Effort task performance in high and low amotivation patient groups

There were no significant differences between the two patient groups in total number of trials attempted ($t_{43}=0.80$, $p=0.43$) and completed ($t_{43}=0.54$, $p=0.59$), the proportion of high-effort trials chosen ($t_{43}=0.99$, $p=0.33$) as well as reaction time ($t_{43}=0.16$, $p=0.87$). A 3 group (controls, HIGH-AMO patients, LOW-AMO patients) × 3 probability (12%, 50%, 88%) × 3 reward (low, medium, high value) repeated-measures ANOVA indicated significant main effects of probability ($F_{1.8,160.1}=82.90$, $p<0.001$) and reward magnitude ($F_{2,174}=54.51$, $p<0.001$), as well as significant interactions for group × probability ($F_{3.7,160.1}=5.31$, $p=0.001$) and probability x reward ($F_{4,348}=16.34$, $p<0.001$). Main effect of group, group × reward interaction, and three-way interaction were non-significant. Repeated-measures ANCOVAs with years of education and cognitive composite score as a covariate, respectively, were also performed. Results of the additional analyses were consistent with our original unadjusted analysis, and in particular, group x probability interaction remained statistically significant (education as covariate: $p=0.001$; cognition as covariate: $p=0.04$). The significant group × probability interaction was followed-up by post-hoc one-way ANOVAs, which showed significant group differences at 12% ($F_{2,87}=4.14$, $p=0.02$) and 88% ($F_{2,87}=5.49$, $p=0.01$) probability conditions (Fig. 1C). Post-hoc pairwise comparisons revealed that HIGH-AMO patients chose significantly fewer high-effort trials than controls ($p=0.001$) and LOW-AMO patients ($p=0.02$) at high reward options for the 88% probability condition (Fig. 3C). HIGH-AMO patients were also found to select high-effort trials of medium reward magnitude significantly more often than controls ($p=0.02$) at the 12% probability condition (Fig. 3A) (see Table S1 for detailed statistics of three-group comparison across different task conditions). Additional analyses comparing EEfRT performance indices among three groups further revealed that HIGH-AMO patients selected significantly fewer high-effort trials at the 88% probability condition across reward levels, and displayed significantly smaller increase in the proportion of high-effort trials chosen from 12% to 88% probability condition (i.e., smaller probability difference score) than both LOW-AMO patients and controls (Table S2). No significant differences were observed between LOW-AMO patients and controls in any of the EEfRT performance indices.

Relationships of effort task measures with clinical, functional and cognitive variables. As seen in Table 2, we observed a significant positive correlation between SOFAS scores and the probability difference score. EEfRT performance indices did not correlate with SANS total score or SANS amotivation score, as well as ratings on DE, positive symptoms, depressive symptoms and self-reported anhedonia. Significant correlations between EEfRT performance indices and PANSS disorganization symptoms and antipsychotic dose did not survive correction for multiple-comparisons. Several significant correlations were observed between task performance indices and scores on letter-number span, logical memory, letter cancellation and Trail making tests in the patient group, but none survived Bonferroni correction (note: some survived less stringent FDR correction, Table S3). Likewise, there were no significant correlations between EEfRT performance indices and any of the individual cognitive measures or cognitive composite score in controls after correction for multiple-comparisons was applied (Table S4).

4. Discussion

The aim of the current study was to examine effort-based decision-making and its relationship with amotivation and psychosocial functioning in clinically-stabilized FEP patients, using a physical effort allocation paradigm. Three major findings emerged from our analysis. First, FEP patients exhibited altered effort allocation with decreased willingness to expend effort for reward at the highest magnitude and likelihood of reward receipt as compared to healthy participants. Second, such reduction in effort expenditure for reward was most pronounced in patients with high levels of amotivation. Third, diminished effort exertion was related to poorer psychosocial functioning.

To the best of our knowledge, this is the first study to demonstrate evidence of aberrant effort allocation in medicated, clinically-stabilized FEP sample. Thus, our results indicate that effort-based decision-making impairment is already present even in the early stage of psychotic illness. In line with most previous studies on chronic schizophrenia (Gold et al., 2013; Green et al., 2015; Culbreth et al., 2018), our findings revealed that first-episode patients did not differ from controls in the overall proportion of high-effort trials selected, but were significantly less willing to exert physical effort for high-value/high-probability reward. Additionally, we found that patients chose effortful options more often than controls at low-probability condition (especially for medium-value/low-probability reward). Our adoption of the EEfRT with three-probability levels enabled us to detect an excessive effort exertion at the lowest probability condition in FEP, which would otherwise be masked in studies using a modified EEfRT version (Barch et al., 2014; Reddy et al., 2015) or a similar button-pressing paradigm (Gold et al., 2013; Serper et al., 2017) with two probability-levels. Some prior studies administering the EEfRT with three-probability levels also reported similar findings that schizophrenia patients showed increased willingness to expend effort for reward

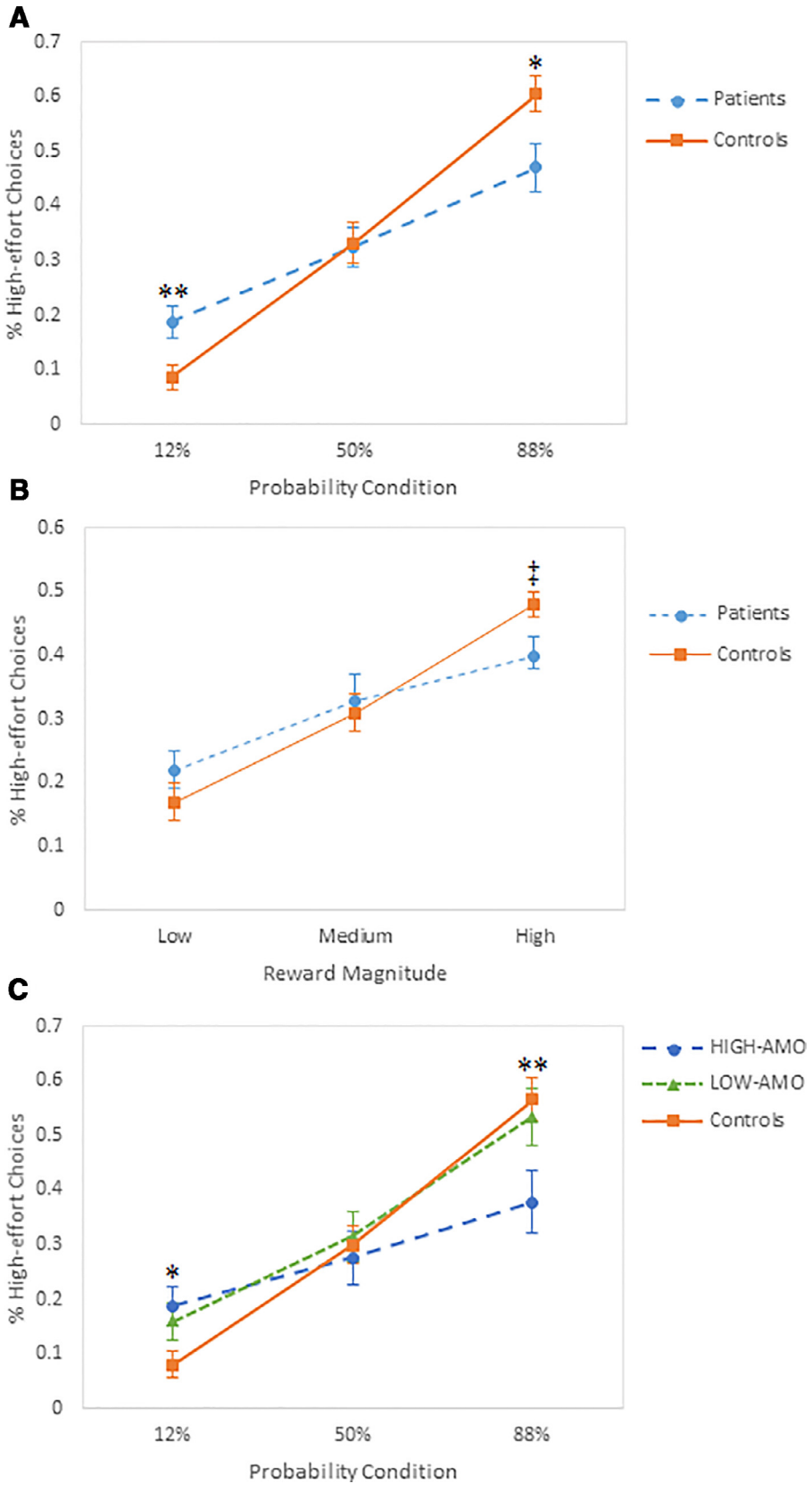

Fig. 1 Proportion of high-effort trials selected by patients and healthy controls. (A) Percentage of high-effort choices across probability conditions in the overall patient group and in controls. (B) Percentage of high-effort choices across reward magnitudes in the overall patient group and in controls. (C) Percentage of high-effort choices across probability conditions in high (HIGH-AMO) and low (LOW-AMO) amotivation patient groups, and controls.
†$p<0.10$, *$p<0.05$, **$p<0.01$.

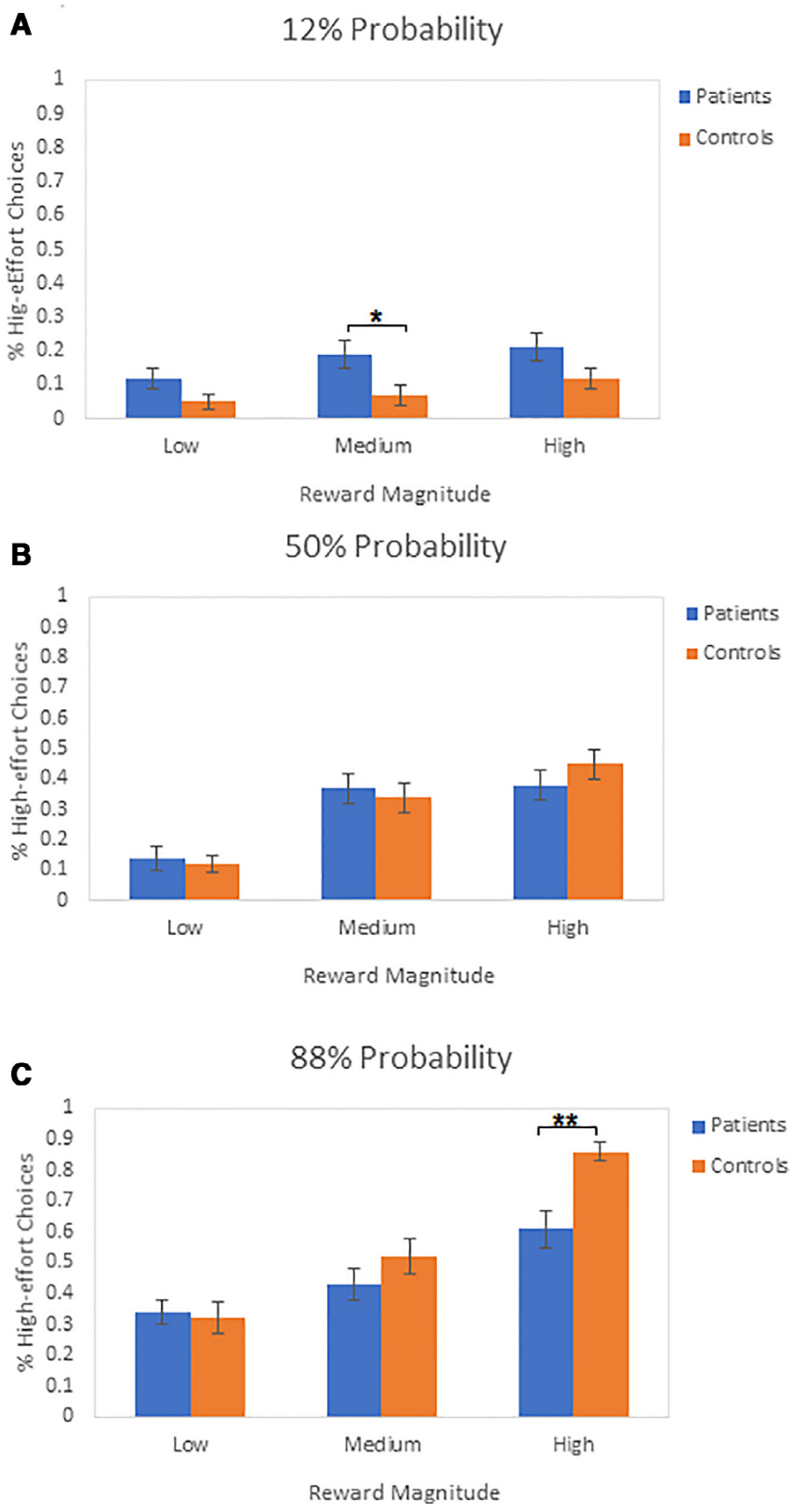

Fig. 2 Proportion of high-effort trials selected by the overall patient group and controls as a function of reward magnitude. (A, B, C) Percentage of high-effort choices in 12%, 50% and 88% probability conditions, respectively. $^{*}p<0.05$, $^{**}p<0.01$.

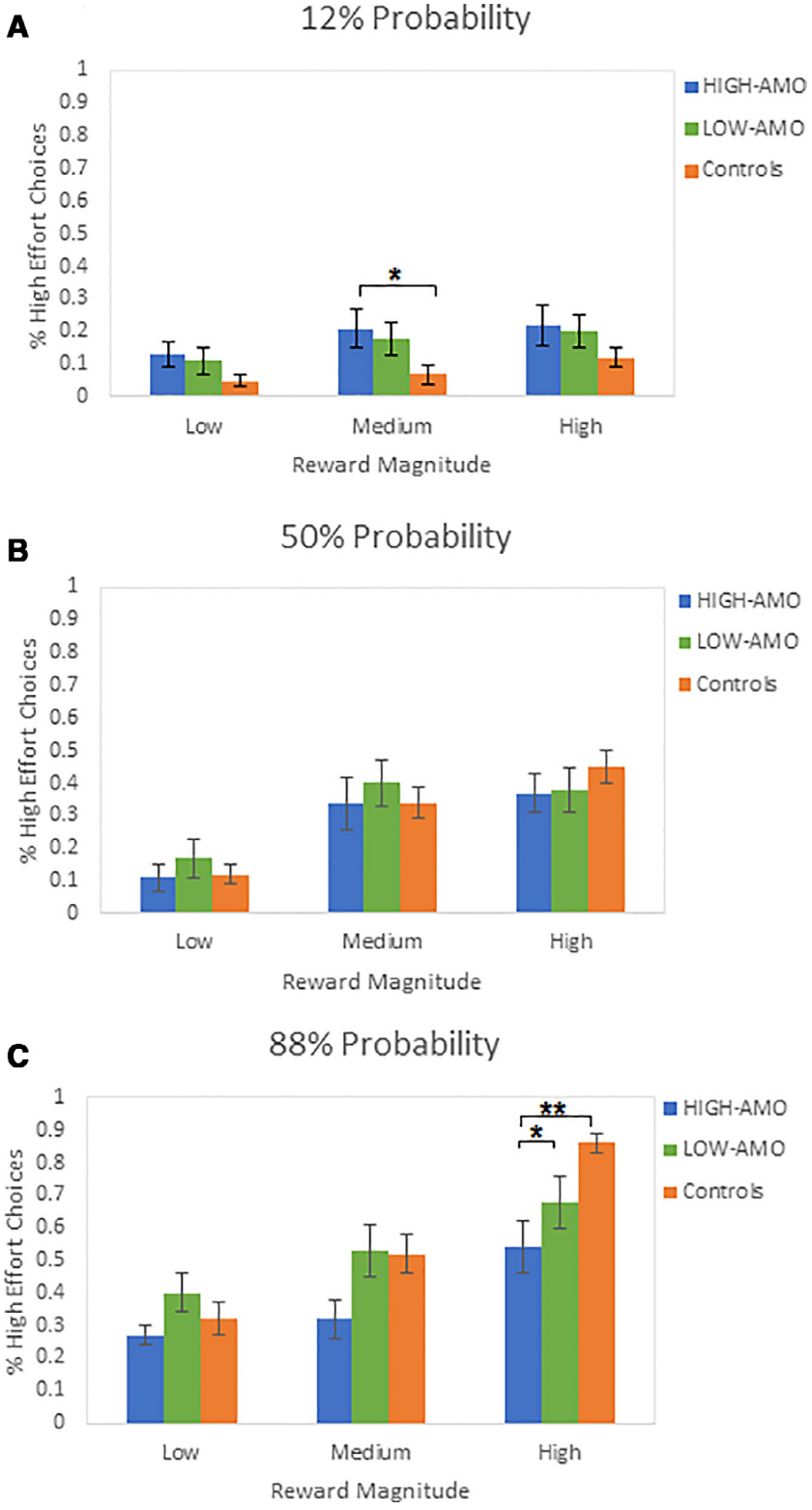

Fig. 3 Proportion of high-effort trials selected by high (HIGH-AMO) and low (LOW-AMO) amotivation patient groups and controls as a function of reward magnitude. (A, B, C) Percentage of high-effort choices in 12%, 50% and 88% probability conditions, respectively. $^{*}p<0.05$, $^{**}p<0.01$.

Table 2 Correlations between percentage of high-effort choices and clinical variables[a].

Variables[b]	88% Probability	High reward	Change from 12% to 88% probability	Change from low to high reward
SANS total score[d]	−0.09	−0.04	0.05	−0.01
SANS amotivation score[d]	−0.23	−0.03	−0.25	0.08
SANS diminished expression score	0.10	0.02	0.26	−0.06
PANSS positive symptom score	−0.07	−0.15	−0.06	−0.20
PANSS disorganization score	−0.41**[,e]	−0.41**[,f]	−0.13	−0.11
CDSS total score	−0.04	−0.03	0.03	−0.04
SHAPS-C score[c]	0.16	0.15	0.15	0.21
SOFAS score[c,d]	0.23	0.11	**0.34***	0.02
Chlorpromazine equivalents	−0.24	−0.29	−0.06	−0.34*[,g]

CDSS = Calgary Depression Scale for Schizophrenia; DUP = Duration of untreated psychosis; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for Assessment of Negative Symptoms; SHAPS-*C* = Snaith-Hamilton Pleasure.
Scale - Chinese version; SOFAS = Social and Occupational Functional Assessment Scale.
Bold value indicates statistical significance for hypothesized relationship.

[a] Spearman-rank correlation analyses were performed and *p* values were presented.

[b] Bonferroni correction was applied for the correlations that were not hypothesis-driven ($p = 0.00139$). We also applied less stringent FRD (false discovery rate) correction for multiple-comparisons and the results remained unchanged (i.e., none survived correction).

[c] Pearson product-mean correlation analyses were performed and r values were presented as Shapiro-Wilk test of normality was not significant.

[d] Hypothesized relationship, $p<0.05$.

[e] $p = 0.006$ (statistically non-significant after Bonferroni correction).

[f] $p = 0.005$ (statistically non-significant after Bonferroni correction).

[g] $p = 0.021$ (statistically non-significant after Bonferroni correction).

* $p<0.05$.

** $p<0.01$.

at low-probability and/or low-reward conditions (Fervaha et al., 2013; Treadway et al., 2015; McCarthy et al., 2016). This further supports the notion that patients are not generally effort-averse, but displayed inefficient effort allocation by failing to make high-effort choices to maximize reward. In fact, our interpretation of suboptimal effort allocation with selective rather than general reduction in willingness for effort expenditure in FEP is consistent with dopaminergic abnormalities observed in psychotic disorders which are associated with increased instead of attenuated striatal dopamine release (Howes et al., 2012). Critically, adaptive effort-based decision-making depends on both an optimal level and appropriate time-course of dopaminergic activities in response to stimuli (Schultz, 2007; Floresco et al., 2008). An excessive and dysregulated burst firing of dopamine neurons would lead to blunting of phasic dopamine responses for relevant rewarding-cues, in particular high-value/high-probability reward, and therefore results in an impaired ability to optimally allocate effort for reward maximization (Maia and Frank, 2017).

In an attempt to clarify the impact of amotivation on effort-based decision-making in FEP, we categorized patients into those with high versus low levels of amotivation for comparison. Our results showed that high-amotivation patients exhibited the lowest degrees of willingness to expend effort for reward at the highest magnitude and probability. Furthermore, there was no significant difference in effort expenditure across any of the reward/probability conditions between low-amotivation patients and healthy participants. This is in agreement with several prior studies which demonstrated that schizophrenia patients with high levels of negative symptoms or amotivation were the least willing to increase physical effort for reward of higher value and likelihood of reward receipt (Gold et al., 2013; Hartmann et al., 2015; Wang et al., 2015). Two recent studies without control comparison also revealed that patients with high negative symptoms chose significantly fewer high-effort trials than those with low negative symptoms (Fervaha et al., 2015b; Serper et al., 2017). We thus extend previous findings of effort-based decision-making in chronic schizophrenia to FEP, and affirm the critical role of amotivation on suboptimal allocation of physical effort to pursue reward. Of note, we failed to demonstrate significant association between effort task performance and ratings of amotivation or negative symptoms using correlation analyses. However, as negative symptoms are characterized by a hybrid dimensional-categorical structure (Ahmed et al., 2015), which distorts observations made using a purely dimensional correlational approach. Failure to evaluate negative symptoms from both a categorical and dimensional approach may explain inconsistencies within the literature. Indeed, several other studies have only found significant negative symptom effects via categorical, but not continuous correlational approaches (Gold et al., 2013; Fervaha et al., 2015b; Wang et al., 2015). Alternatively, null findings in our correlation analyses might partly be attributable to the choice of symptom assessment. In the current study, amotivation was measured by ratings derived from the relevant subscales in SANS. On the other hand, the use of next-generation negative symptom scales (e.g. BNSS and CAINS) (Kirkpatrick et al., 2011; Kring et al., 2013), which were developed on the basis of modern conceptualization

of negative symptoms and have addressed the limitations of existing rating instruments by including items measuring anticipatory pleasure and distinguishing internal experience from behavior for avolition and asociality, enables more refined and accurate assessment of amotivation. There is also emerging evidence suggesting that multiple momentary symptom assessment in daily life using EMA methodology might represent a more sensitive measurement of amotivation than clinician-rated symptom scales, which are based primarily on retrospective evaluation that could be significantly affected by patients' cognitive impairment. In fact, one recent study has demonstrated that amotivation assessed via EMA but not by clinician-administered symptom scale was correlated with EEfRT performance in schizophrenia patients (Gard et al., 2014). More research is thus required to verify whether EMA-measured amotivation aligns consistently better than clinician-rated symptoms with effort allocation.

Until now, few studies have examined the relationship between effort-based decision-making and functional status in schizophrenia patients, and none has focused on FEP samples. Our result that greater increase in effortful options from low to high probability levels (i.e., probability difference score) was related to better psychosocial functioning in FEP replicates the findings of a recent large-scale psychometric study on effort tasks which demonstrated that EEfRT probability difference scores were positively correlated with independent living and work functioning in chronic schizophrenia patients (Horan et al., 2015). This also generally accords with some past studies showing that schizophrenia patients who were more willing to expend effort for reward had better functioning (Barch et al., 2014; Strauss et al., 2016), and therefore provides evidence supporting the link between real-world functional outcome and effort allocation in the early phase of illness. Importantly, our finding thus suggests that abnormal effort-based decision-making may be a potential therapeutic target for functional enhancement in FEP patients. Alternatively, there is evidence suggesting that cognitive deficits is related to aberrant effort-based decision-making in schizophrenia, with some (Fervaha et al., 2013; Gold et al., 2013; Horan et al., 2015; Serper et al., 2017; Bismark et al., 2018), but not all previous studies (Docx et al., 2015; Fervaha et al., 2015b; Hartmann et al., 2015; McCarthy et al., 2016; Strauss et al., 2016) indicating that better cognitive performance was associated with increased willingness to exert physical effort for reward in schizophrenia patients. The current analysis revealed several significant correlations between cognitive variables and effort allocation performance, mostly in the patient sample. Although none survived Bonferroni correction, some remained significant after less stringent correction was applied for multiple-comparisons. Our results are thus partially in keeping with some prior studies and suggest that cognitive impairment might be related to suboptimal effort-based decision-making.

Several study limitations should be acknowledged. First, as longer duration is required to complete high-effort trials relative to low-effort trials, effort allocation performance might be confounded by temporal discounting. Second, subjective reward valuation was not examined in this study. Deficits in representation of expected value is observed in patients with chronic schizophrenia and has been postulated as one of the potential mechanisms contributing to altered effort allocation and motivational impairment (Gold et al., 2015; Waltz and Gold, 2016). Our earlier study suggested relatively preserved ability of value-guided decision-making in clinically-stabilized FEP patients (Chang et al., 2016b). However, owing to the paucity of existing data, further research is warranted to clarify the potential independent contributions of reward-value representation and effort-cost estimation to impaired effort allocation in FEP. Third, all patients in the current study were receiving antipsychotics at the time of assessment. Although our analyses revealed no significant correlations between antipsychotic dose and effort ask performance, we cannot rule out an effect of dopamine D2-receptor antagonist on effort allocation. In fact, previous studies have shown that antipsychotic treatment might contribute to motivational deficits in patients with psychotic disorders (Gründer et al., 2016; Kirschner et al., 2017). Prospective investigation of effort allocation prior to and following antipsychotic treatment in FEP patients is required to differentiate the impacts of illness and medication on effort-based decision-making.

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Contributors

Authors W.C.C designed the study. Authors W.C.C, A.O.K.C, M.T.T and G.P.S conceptualized the analysis approach. Authors A.O.K.C and W.C.C conducted statistical analysis and did literature search. Author W.C.C and A.O.K.C wrote the first draft of the manuscript. Authors M.T.T and G.P.S provided critical feedback and helped the revision of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Author M.T.T. has served as a paid consultant to NeuroCog Trials, Avanir Pharmaceuticals, and Blackthorn Therapeutics in the past three years. M.T.T. is a co-inventor of the EEfRT, which was used in this study. Emory University and Vanderbilt University licensed this software to BlackThorn Therapeutics. Under the IP Policies of both universities, M.T.T receives licensing fees and royalties from BlackThorn Therapeutics. Additionally, M.T.T. has a paid consulting relationship with BlackThorn. The terms of these arrangements have been reviewed and approved by Emory University in

accordance with its conflict of interest policies, and no funding from these entities was used to support the current work. Author E.Y.H.C. has participated in the paid advisory board for Otsuka, has received educational grant support from Janssen-Cilag, and has received research funding from Astra-Zeneca, Janssen-Cilag, Eli Lilly, Sanofi-Aventis and Otsuka. Author E.H.M.L has been a member of the paid advisory boards for Eli Lilly and AstraZeneca. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.03.006.

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