Title Page

Title: Effort-Based Decision-Making in Schizophrenia

Adam J. Culbreth, M.A.[1], Erin K. Moran Ph.D.[2], & Deanna M. Barch Ph.D.[1,2,3]

1. Department of Psychological and Brain Sciences, Washington University in Saint Louis
2. Department of Psychiatry, Washington University in Saint Louis
3. Department of Radiology, Washington University in Saint Louis

Number of words in abstract: 106
Number of words in text: 1999
Number of figures: 1
Number of tables: 0
Number of boxes: 1

Corresponding author:

Adam J. Culbreth
Washington University in St. Louis Box 1125
One Brookings Drive
St. Louis, MO 63130
Phone: 314-935-8547
Email: aculbreth@wustl.edu

Abstract:

Motivational impairment has long been associated with schizophrenia but the underlying mechanisms are not clearly understood. Recently, a small but growing literature has suggested that aberrant effort-based decision-making may be a potential contributory mechanism for motivational impairments in psychosis. Specifically, multiple studies have consistently shown that individuals with schizophrenia are less willing than healthy controls to expend effort to obtain rewards. Further, this effort-based decision-making deficit has been shown to correlate with severity of negative symptoms and level of functioning, in many but not all studies. In the current review, we summarize this literature and discuss several factors that may underlie aberrant effort-based decision-making in schizophrenia.

Introduction

Many individuals with schizophrenia experience reductions in motivation and goal-directed behavior [1]. These deficits are strongly associated with social and occupational functioning, but treatments are not sufficiently effective at alleviating such symptoms [2], potentially due to a poor mechanistic understanding of the causes of impaired motivation in schizophrenia. Recently, research has suggested that motivational deficits in schizophrenia might arise, in part, due to aberrant effort-based decision-making [3,4].

Effort-based decision-making refers to mental computations individuals perform to estimate the amount of work required to obtain an outcome (see Box 1 for example). Recent work has suggested that individuals with schizophrenia are less willing than healthy controls to exert effort to obtain monetary rewards on experimental tasks [5-15], and that this deficit in effort allocation is related to negative symptoms [5,6,8,9,13-19]. In the current review, we summarize this literature, discuss interpretative challenges, and provide ideas for future directions.

Physical Effort-Based Decision-Making

Many recent studies have been published suggesting a reduced willingness of individuals with schizophrenia compared to healthy controls to exert physical effort for monetary rewards [5,7-14]. Broadly, these studies involve participants making repeated decisions between completing a hard or easy physical task for high or low monetary reward. For example, studies have used button-pressing tasks where individuals select between completing an easy task (i.e., a minimal number of button presses) for a small reward or a hard task (i.e., a large number of button presses) for a larger reward [8,20]. These studies find that individuals with schizophrenia are less likely than controls to select the harder task [5,7-14], although some studies have reported null results [19,21]. Further, these studies typically find that this group difference is largest when the reward amount for completing the hard task is highest and the probability of reward receipt is most certain [5,7,8,11-14].

In regards to relationships with individual differences, many studies have shown that individuals with schizophrenia with the most severe negative symptoms are those least willing to exert effort [5,8,9,13,14,16-19]. Further, work by our group has shown patient behavior on effort-based decision-making tasks is a reliable predictor of motivation and pleasure ratings in daily life (i.e., individuals more willing to exert effort also report more interest and enjoyment with their daily activities) [18]. However, not all studies have observed significant associations between physical effort-based decision-making tasks and negative symptoms [7,10,21,22]. In part, this inconsistency may be due to differences in the methods used to assess negative symptoms with most of the significant associations using newly developed measures of negative symptoms (i.e., the CAINS [23] or BNSS [24]). Indeed, these new measures better reflect the field's current conceptualization of negative symptoms, differentiating the experience (i.e., motivation and pleasure) from the expression of negative symptoms (i.e., flat affect, alogia). Recent studies using these measures have found that impairments in effort-based decision-making are more robustly related to experiential negative symptoms [6,15,17,19].

Cognitive Effort-Based Decision-Making

Similar to physical effort-based decision-making, multiple studies have been published reporting decreased cognitive effort-based decision-making [6,12,15]. For example, our group utilized a cognitive effort-discounting task [25] where individuals first experienced increasingly difficult levels of a cognitively demanding task and subsequently made decisions about repeating an easy or hard level for small or large monetary rewards. We found that individuals with schizophrenia were less willing than healthy controls to select the hard task [6]. Several other studies have reported similar results, using a variety of paradigms [6,12,15], though one study reported null results potentially due to patients' difficulty detecting effort demands [26]. Further, studies observed that individuals with the greatest negative symptom severity showed the least willingness to exert effort [6,15], although some studies have reported null results [17,26].

Neural Correlates of Effort-Based Decision-Making

While a comprehensive review is beyond the scope of the current manuscript [27-29], work in the basic human and animal sciences has begun to detail aspects of the neural circuitry underlying effort-based decision-making including the anterior cingulate cortex, the ventral striatum, and dopamine systems. Specifically, human functional neuroimaging studies have shown that ventral striatum [10,30,31] and anterior cingulate [30,32] BOLD activation tracks the subjective value of actions, increasing with reward value and decreasing with effort. Further, rodent work has shown that ablation of the anterior cingulate cortex [33] or depletion of ventral striatal dopamine [34] in mice leads to decreases in effort exertion.

In regards to schizophrenia, only a few studies have examined the neural correlates of aberrant effort-based decision-making. In one study, Huang and colleagues found that greater BOLD activation in the ventral striatum during effort-based choice was associated with greater willingness to exert effort across patients and controls [10]. Further, they found that individuals with schizophrenia showed reduced BOLD activation in the ventral striatum, the posterior cingulate gyrus, and the left medial frontal gyrus as a function of reward value and reward probability compared to healthy controls [10]. In a related study, Wolf and colleagues found that increased BOLD activation of the ventral striatum and the dorsolateral prefrontal cortex during reward processing was significantly related to increased willingness to exert effort on a behavioral task [15]. Finally, Park and colleagues showed greater activation of the caudate for individuals with schizophrenia compared to healthy controls as a function of effort [35]. However, this task did not include a choice, but rather required individuals to perform either a hard or easy option. Thus, it is difficult to generalize the results of the Park study to the larger effort-based decision-making literature [35]. In summary, while still preliminary, results suggest roles for the ventral striatum, cingulate gyrus, and the dorsolateral prefrontal cortex in effort-based decision-making deficits in schizophrenia.

Factors That Might Drive Reduced Effort

Although several papers have been published establishing reduced effort expenditure in schizophrenia [3,4], few studies have been conducted to determine the types of factors that might drive this deficit. In Box 1 we provide an example of factors that may increase or decrease the willingness of individuals to expend effort. In the sections below we discuss these factors and the likelihood of their contribution to aberrant effort-based decision-making in schizophrenia.

Reward Responsivity

One explanation for reduced effort expenditure is reduced reward responsivity. Put simply, if individuals with schizophrenia do not like rewards as much as healthy individuals they may be less likely to exert effort to obtain them. While reduced liking of rewards was a prominent explanation for motivational impairment in schizophrenia for many years [36,37], a large body of recent work has suggested that individuals with schizophrenia self-report levels of pleasure similar to controls when experiencing pleasurable activities in daily life or in the laboratory [38]. Further, behavioral tasks [39,40], electrophysiological indices [41,42], and neuroimaging markers [43-45] of reward responsivity consistently show similar patterns between controls and those with schizophrenia, suggesting intact reward responsivity. Finally, one study by our group [6] assessed the contribution of reward responsivity to effort-based decision-making by asking patients and controls to self-report factors that influenced decision-making. Specifically, we asked “To what degree were your choices based on the amount of money that you could win?” We found similar responses across groups, and further that group differences in effort allocation remained significant when controlling for responses. Thus, reduced reward responsivity appears to be an unlikely mechanism for impaired effort allocation in schizophrenia.

Anticipatory Pleasure

While individuals with schizophrenia report similar levels of pleasure “in the moment”, a large literature suggests reduced anticipatory pleasure in schizophrenia compared to healthy controls [46,47]. Anticipatory pleasure is thought to be an integral aspect of motivated behavior

and effort allocation. For example, individuals who self-report greater trait levels of anticipatory pleasure demonstrate increased willingness to expend effort to obtain rewards [48-50], although not in all studies. In schizophrenia, patients self-reporting higher trait levels of anticipatory pleasure demonstrate increased willingness to expend effort [16], although results are inconsistent. Future work will need to replicate and extend such findings to better understand how state anticipatory pleasure may influence effort allocation in those with schizophrenia.

Cognitive Control

Effort-based decision-making requires a variety of functions highly reliant on cognitive control including the integration of decision information and the utilization of internal representations of cost and reward information to drive choice behavior. Schizophrenia is associated with a robust cognitive control deficit [51]. No study has directly assessed the contributions of cognitive control processes to effort expenditure in schizophrenia. However, several studies have found that patients with greater cognitive impairment are less willing to exert effort to obtain rewards [8,16,17,26]. One recent study, also found that increased working memory was related to increased effort expenditure in schizophrenia [16]. However, several studies have also reported non-significant associations between cognition and effort expenditure in schizophrenia [7,9,11,15,19,21,22]. Thus, further research is needed in this area. In particular, studies may benefit from using cutting-edge cognitive control paradigms developed in the basic science literature to discern clear associations between control processes and effort allocation.

Defeatist Performance Beliefs

Individuals with schizophrenia may also be less willing to exert effort compared to healthy controls due negative beliefs they may have about their ability to successfully complete actions [52]. Studies have found elevated defeatist performance beliefs in those with schizophrenia compared to healthy controls and linked such beliefs to negative symptoms, cognition, and functioning [52,53]. Granholm and colleagues [54] collected data from individuals

with schizophrenia and healthy controls on a digit span task. They found that effort allocation, as measured through pupillary response, increased in healthy controls and patients with low levels of defeatist performance beliefs as the cognitive demands of the task increased. However, individuals with schizophrenia with high levels of defeatist performance beliefs failed to increase effort allocation as task demands increased, suggesting a potential link between effort allocation and defeatist performance beliefs [54]. While this finding is intriguing further research is needed to replicate this finding using effort-based decision-making tasks.

Medications Effects

One limitation to previous work regarding effort-based decision-making in schizophrenia is antipsychotic medication. As stated above, effort-based decision-making has been linked to striatal dopamine [34] and antipsychotics are proposed to work by blocking D2 receptor sites [55]. Thus, antipsychotics may modulate aspects of the effort-based decision-making circuitry. While studies consistently find insignificant correlations between antipsychotic dose equivalents and effort-based decision-making, the utility of such equivalency measures is widely debated [56]. A recent study used an alternative approach, classifying the antipsychotics by D2 receptor affinity, and found that patients prescribed antipsychotics with greater D2 affinity were less willing to expend effort [3]. While this result is intriguing, the sample was small and the patients prescribed antipsychotics with high D2 affinity also had the greatest negative symptom severity, limiting clear interpretations of medication effects. Future research would also benefit from collecting data in unmedicated samples and those at-risk for developing schizophrenia in order to more carefully examine medication effects.

Summary and Future Directions

Recent literature has suggested that impaired effort-based decision-making may be a potential contributory mechanism for motivational impairment in schizophrenia. This work includes primarily behavioral studies, but recent studies suggest preliminary neural correlates to this deficit including reduced striatal, cingulate, and dorsolateral prefrontal cortex activation

[10,15]. While recent work has consistently shown reduced effort allocation in schizophrenia, the factors that may give rise to this reduction are less clearly understood and remain important avenues for future research. An understanding of such factors is critical to discerning potential targets for intervention strategies. For example, cognitive-behavioral therapy targeting defeatist performance beliefs [52] may be particularly effective if future research determines contributions of defeatist performance beliefs to effort deficits in schizophrenia. Finally, although not discussed in the current review, studies have suggested that impaired effort allocation is associated with several other psychiatric disorders including major depressive [49,50,57-60] and bipolar disorder [58]. Future work will need to examine whether the mechanisms underlying effort deficits are transdiagnostic or disorder-specific in order to guide targeted treatment of novel intervention strategies across patient groups. In summary, impaired effort-based decision-making appears to be an attractive contributory mechanism for motivational impairment in schizophrenia. Future work examining neural correlates, unmedicated patients, potential psychological mechanisms, and transdiagnostic samples is needed to better characterize these initial findings.

References:

1. Bleuler E: **Dementia praecox or the group of schizophrenias**. 1950.
2. Milev P, Ho B-C, Arndt S, Andreasen NC: **Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up**. *American Journal of Psychiatry* 2005, **162**:495-506.
3. Gold JM, Waltz JA, Frank MJ: **Effort cost computation in schizophrenia: A commentary on the recent literature**. *Biological psychiatry* 2015, **78**:747-753.
4. Green MF, Horan WP, Barch DM, Gold JM: **Effort-Based Decision Making: A Novel Approach for Assessing Motivation in Schizophrenia**. *Schizophrenia bulletin* 2015:sbv071.

5. Barch DM, Treadway MT, Schoen N: **Effort, anhedonia, and function in schizophrenia: Reduced effort allocation predicts amotivation and functional impairment**. *Journal of abnormal psychology* 2014, **123**:387.
6. Culbreth A, Westbrook A, Barch D: **Negative symptoms are associated with an increased subjective cost of cognitive effort**. *Journal of abnormal psychology* 2016, **125**:528.
7. Fervaha G, Graff-Guerrero A, Zakzanis KK, Foussias G, Agid O, Remington G: **Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making**. *Journal of psychiatric research* 2013, **47**:1590-1596.
8. Gold JM, Strauss GP, Waltz JA, Robinson BM, Brown JK, Frank MJ: **Negative symptoms of schizophrenia are associated with abnormal effort-cost computations**. *Biological psychiatry* 2013, **74**:130-136.
** Gold et al., 2013: The first study to examine effort-based decision-making in those with schizophrenia. Results showed decreased willingness of patients compared to healthy controls to increase effort as reward value and probability increased. This effect was most robust in the high negative symptom patients.
9. Hartmann MN, Hager OM, Reimann AV, Chumbley JR, Kirschner M, Seifritz E, Tobler PN, Kaiser S: **Apathy but not diminished expression in schizophrenia is associated with discounting of monetary rewards by physical effort**. *Schizophrenia bulletin* 2015, **41**:503-512.
10. Huang J, Yang X-h, Lan Y, Zhu C-y, Liu X-q, Wang Y-f, Cheung EF, Xie G-r, Chan RC: **Neural substrates of the impaired effort expenditure decision making in schizophrenia**. *Neuropsychology* 2016, **30**:685.
* Huang et al., et al., 2016: This study collected data from individuals with schizophrenia and healthy controls using a button-pressing task in the scanner. They found that activation in the ventral striatum significantly predicted choice behavior and further that this activation was significantly blunted in those with schizophrenia compared to healthy controls.
11. McCarthy JM, Treadway MT, Bennett ME, Blanchard JJ: **Inefficient effort allocation and negative symptoms in individuals with schizophrenia**. *Schizophrenia research* 2016, **170**:278-284.
12. Reddy LF, Horan WP, Barch DM, Buchanan RW, Dunayevich E, Gold JM, Lyons N, Marder SR, Treadway MT, Wynn JK: **Effort-Based Decision-Making Paradigms for Clinical Trials in Schizophrenia: Part 1—Psychometric Characteristics of 5 Paradigms**. *Schizophrenia bulletin* 2015:sbv089.
** Reddy et al., 2015: First large sample study to show decreased effort allocation in those with schizophrenia across several commonly used paradigms. Psychometric characteristics of these paradigms and use in patient samples are examined.
13. Treadway MT, Peterman JS, Zald DH, Park S: **Impaired effort allocation in patients with schizophrenia**. *Schizophrenia research* 2015, **161**:382-385.
14. Wang J, Huang J, Yang X-h, Lui SS, Cheung EF, Chan RC: **Anhedonia in schizophrenia: Deficits in both motivation and hedonic capacity**. *Schizophrenia research* 2015, **168**:465-474.
15. Wolf DH, Satterthwaite TD, Kantrowitz JJ, Katchmar N, Vandekar L, Elliott MA, Ruparel K: **Amotivation in schizophrenia: integrated assessment with behavioral, clinical, and imaging measures**. *Schizophrenia bulletin* 2014, **40**:1328-1337.

** Wolf et al., 2014: This study examined willingness to expend effort in those with those with schizophrenia and healthy controls. They found decreased willingness to expend cognitive effort in the patients. Further, they found that, during neuroimaging, BOLD activation of the dorsolateral prefrontal cortex and the ventral striatum during a reward-processing task was related to willingness to expend effort behaviorally.

16. Serper M, Payne E, Dill C, Portillo C, Taliercio J: **Allocating effort in schizophrenia: Relation to negative symptoms, working memory, reward anticipation and real world functioning**. *European Psychiatry* 2017.
17. Horan WP, Reddy LF, Barch DM, Buchanan RW, Dunayevich E, Gold JM, Marder SR, Wynn JK, Young JW, Green MF: **Effort-Based Decision-Making Paradigms for Clinical Trials in Schizophrenia: Part 2—External Validity and Correlates**. *Schizophrenia bulletin* 2015:sbv090.
18. Moran EK, Culbreth AJ, Barch DM: **Ecological momentary assessment of negative symptoms in schizophrenia: Relationships to effort-based decision making and reinforcement learning**. *Journal of Abnormal Psychology* 2017, **126**:96.

** Moran et al., 2017: This study showed that willingness to expend effort on an experimental task was associated with self-reports of enjoyment and interest with daily activities measured outside of the laboratory using ecological momentary assessment techniques

19. Strauss GP, Whearty KM, Morra LF, Sullivan SK, Ossenfort KL, Frost KH: **Avolition in schizophrenia is associated with reduced willingness to expend effort for reward on a Progressive Ratio task**. *Schizophrenia research* 2016, **170**:198-204.
20. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH: **Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia**. *PloS one* 2009, **4**:e6598.

* Treadway et al., 2009: This was the initial study that used the Effort Expenditure for Rewards Task, the most commonly utilized task for assessing individual and diagnostic group differences.

21. Docx L, de la Asuncion J, Sabbe B, Hoste L, Baeten R, Warnaerts N, Morrens M: **Effort discounting and its association with negative symptoms in schizophrenia**. *Cognitive neuropsychiatry* 2015, **20**:172-185.
22. Fervaha G, Duncan M, Foussias G, Agid O, Faulkner GE, Remington G: **Effort-based decision making as an objective paradigm for the assessment of motivational deficits in schizophrenia**. *Schizophrenia research* 2015, **168**:483-490.
23. Horan WP, Kring AM, Gur RE, Reise SP, Blanchard JJ: **Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS)**. *Schizophrenia research* 2011, **132**:140-145.
24. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, Marder SR: **The brief negative symptom scale: psychometric properties**. *Schizophrenia bulletin* 2010, **37**:300-305.
25. Westbrook A, Kester D, Braver TS: **What is the subjective cost of cognitive effort? Load, trait, and aging effects revealed by economic preference**. *PLoS One* 2013, **8**:e68210.
26. Gold JM, Kool W, Botvinick MM, Hubzin L, August S, Waltz JA: **Cognitive effort avoidance and detection in people with schizophrenia**. *Cognitive, Affective, & Behavioral Neuroscience* 2014, **15**:145-154.
27. Salamone JD, Koychev I, Correa M, McGuire P: **Neurobiological basis of motivational deficits in psychopathology**. *European Neuropsychopharmacology* 2015, **25**:1225-1238.

* Salamone et al., 2015: Exceptional review paper that summarizes findings regarding the neurobiological processes underlying motivation in the basic and animal sciences. The review also describes how such processes might come to be disturbed in psychopathology.
28. Westbrook A, Braver TS: **Dopamine does double duty in motivating cognitive effort**. *Neuron* 2016, **89**:695-710.
29. Young JW, Zhou X, Geyer MA: **Animal models of schizophrenia**. In *Behavioral neurobiology of schizophrenia and its treatment*. Edited by: Springer Berlin Heidelberg; 2010:391-433.
30. Croxson PL, Walton ME, O'Reilly JX, Behrens TE, Rushworth MF: **Effort-based cost–benefit valuation and the human brain**. *The Journal of Neuroscience* 2009, **29**:4531-4541.
31. Schmidt L, Lebreton M, Cléry-Melin M-L, Daunizeau J, Pessiglione M: **Neural mechanisms underlying motivation of mental versus physical effort**. 2012.
32. Prévost C, Pessiglione M, Météreau E, Cléry-Melin M-L, Dreher J-C: **Separate valuation subsystems for delay and effort decision costs**. *Journal of Neuroscience* 2010, **30**:14080-14090.
33. Hosking JG, Cocker PJ, Winstanley CA: **Dissociable contributions of anterior cingulate cortex and basolateral amygdala on a rodent cost/benefit decision-making task of cognitive effort**. *Neuropsychopharmacology* 2014, **39**:1558-1567.
34. Salamone JD, Correa M, Farrar A, Mingote SM: **Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits**. *Psychopharmacology* 2007, **191**:461-482.
35. Park IH, Lee BC, Kim J-J, Kim JI, Koo M-S: **Effort-based reinforcement processing and functional connectivity underlying amotivation in medicated patients with depression and schizophrenia**. *Journal of Neuroscience* 2017, **37**:4370-4380.
36. Meehl PE: **Schizotaxia, schizotypy, schizophrenia**. *American psychologist* 1962, **17**:827.
37. Rado S: **Dynamics and classification of disordered behavior**. *American Journal of Psychiatry* 1953, **110**:406-416.
38. Cohen AS, Minor KS: **Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies**. *Schizophrenia bulletin* 2008, **36**:143-150.
39. Barch D, Carter C, Gold J, Johnson S, Kring A, MacDonald A, Pizzagalli D, Ragland J, Silverstein S, Strauss M: **Explicit and Implicit Reinforcement Learning Across the Psychosis Spectrum**. *Journal of abnormal psychology* 2017.
40. Heerey EA, Bell-Warren KR, Gold JM: **Decision-making impairments in the context of intact reward sensitivity in schizophrenia**. *Biological psychiatry* 2008, **64**:62-69.
41. Horan WP, Foti D, Hajcak G, Wynn JK, Green MF: **Impaired neural response to internal but not external feedback in schizophrenia**. *Psychological medicine* 2012, **42**:1637-1647.
42. Llerena K, Wynn JK, Hajcak G, Green MF, Horan WP: **Patterns and reliability of EEG during error monitoring for internal versus external feedback in schizophrenia**. *International Journal of Psychophysiology* 2016, **105**:39-46.
43. Dowd EC, Barch DM: **Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia**. *PloS one* 2012, **7**:e35622.

44. Simon JJ, Biller A, Walther S, Roesch-Ely D, Stippich C, Weisbrod M, Kaiser S: **Neural correlates of reward processing in schizophrenia—relationship to apathy and depression**. *Schizophrenia research* 2010, **118**:154-161.
45. Waltz JA, Schweitzer JB, Ross TJ, Kurup PK, Salmeron BJ, Rose EJ, Gold JM, Stein EA: **Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia**. *Neuropsychopharmacology* 2010, **35**:2427-2439.
46. Kring AM, Moran EK: **Emotional response deficits in schizophrenia: insights from affective science**. *Schizophrenia bulletin* 2008, **34**:819-834.
47. Strauss GP, Gold JM: **A new perspective on anhedonia in schizophrenia**. *American Journal of Psychiatry* 2014.
48. Geaney JT, Treadway MT, Smillie LD: **Trait anticipatory pleasure predicts effort expenditure for reward**. *PloS one* 2015, **10**:e0131357.
49. Sherdell L, Waugh CE, Gotlib IH: **Anticipatory pleasure predicts motivation for reward in major depression**. *Journal of abnormal psychology* 2012, **121**:51.
50. Yang X-h, Huang J, Zhu C-y, Wang Y-f, Cheung EF, Chan RC, Xie G-r: **Motivational deficits in effort-based decision making in individuals with subsyndromal depression, first-episode and remitted depression patients**. *Psychiatry research* 2014, **220**:874-882.
51. Barch DM, Sheffield JM: **Cognitive Control in Schizophrenia**. *The Wiley Handbook of Cognitive Control* 2017:556-580.
52. Grant PM, Beck AT: **Defeatist beliefs as a mediator of cognitive impairment, negative symptoms, and functioning in schizophrenia**. *Schizophrenia bulletin* 2008, **35**:798-806.
53. Campellone TR, Sanchez AH, Kring AM: **Defeatist performance beliefs, negative symptoms, and functional outcome in schizophrenia: a meta-analytic review**. *Schizophrenia bulletin* 2016, **42**:1343-1352.
54. Granholm E, Ruiz I, Gallegos-Rodriguez Y, Holden J, Link PC: **Pupillary responses as a biomarker of diminished effort associated with defeatist attitudes and negative symptoms in schizophrenia**. *Biological Psychiatry* 2015.
55. Seeman P: **Atypical antipsychotics: mechanism of action**. *The Canadian Journal of Psychiatry* 2002, **47**:29-40.
56. Danivas V, Venkatasubramanian G: **Current perspectives on chlorpromazine equivalents: Comparing apples and oranges!** *Indian journal of psychiatry* 2013, **55**:207.
57. Cléry-Melin M-L, Schmidt L, Lafargue G, Baup N, Fossati P, Pessiglione M: **Why don't you try harder? An investigation of effort production in major depression**. *PloS one* 2011, **6**:e23178.
58. Hershenberg R, Satterthwaite TD, Daldal A, Katchmar N, Moore TM, Kable JW, Wolf DH: **Diminished effort on a progressive ratio task in both unipolar and bipolar depression**. *Journal of affective disorders* 2016, **196**:97-100.
59. Treadway MT, Bossaller NA, Shelton RC, Zald DH: **Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia**. *Journal of abnormal psychology* 2012, **121**:553.
60. Yang X-h, Huang J, Lan Y, Zhu C-y, Liu X-q, Wang Y-f, Cheung EF, Xie G-r, Chan RC: **Diminished caudate and superior temporal gyrus responses to effort-based**

decision making in patients with first-episode major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2016, **64**:52-59.

Box 1: Factors that may influence effort-based decision-making: A real-world example

Below, we provide a real-world situation to better contextualize the decision-making components individuals utilize to perform effort-based decision-making. We also discuss factors that may influence effort exertion.

Situation:

Nicholas is debating whether he should recreate the delicious chocolate-chip cookie that he ate last weekend. In weighing his decision, he considers the reward (i.e., that delicious cookie). Further, he considers the probability of reward receipt (e.g., what if he accidentally burns the whole batch). Next, he considers the effort necessary to bake the cookie, including going to the store and time spent in the kitchen. He also considers the precision of his estimation of effort (e.g., the cookies might be easier or harder to bake than anticipated). Finally, he considers his motivational state (e.g., is he hungry right now?).

Factors That Modulate Effort Exertion:

1. *Reward Responsivity:* If Nicholas does not enjoy cookies, he may be less likely to make them. Alternatively, if Nicholas' favorite dessert is a cookie he may be more likely to make them.

2. *Anticipatory Pleasure:* Nicholas may think about how good the cookie will taste prior to baking it. If this anticipatory pleasure is strong, Nicholas may use such a representation to drive behavior and expend effort in baking the cookies.

3. *Defeatist Performance Beliefs:* Nicholas may be less likely to attempt to recreate the recipe if he views himself as being a bad cook unable to successfully make complex receipes.

4. *Impaired Cognitive Control:* There are a number of different components of decision information (e.g., reward, cost, and probability information) that Nicholas must integrate to determine whether he is willing to expend effort to bake the cookies. If such information is poorly represented or ineffectively integrated Nicholas may be less likely to bake the cookies.

Figure 1: Model of Factors That Influence Effort-Based Decision-Making and Subsequent Symptoms