Donders Graduate School for Cognitive Neuroscience
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MSc Thesis

Pharmacological and Behavioral Interventions for Focus: The Comparison of Reversal Learning Under the Influence of Lysergic Acid Diethylmide (LSD), Methylphenidate (MPH) and Mindfulness Based Cognitive Therapy

by

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Abstract

The ability to learn and flexibly adapt behavior in response to salient changes in the surrounding environment is a fundamental skill for survival. Cognitive rigidity is characteristic of many mental disorders such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression and drug addiction. Psychoactive medications and cognitive therapies have attempted to treat cognitive rigidity by altering learning and feedback processing.

The aim of this study is to assess if pharmacological and behavioral interventions differently alter the ability to learn and unlearn stimulus-outcome contingencies and feedback sensitivity. Specifically, we will assess how small doses of methylphenidate (MPH) (n=102), lysergic acid diethylmide (LSD) (n=19) and mindfulness based cognitive therapy (MBCT) (n=110) affect reversal learning. All participants completed a Probabilistic Reversal Learning (PRL) task which requires them to learn the different probabilities of receiving rewards and punishment for each of the three cues. Midway through the task, the probabilities are reversed and participants must now update the values associated with these cues. The PRL tasks provide a window on adaptive behavior, as it allows us to assess two crucial components: (1) the (in)ability to reverse well-learnt responses ('perseverative behavior'), and (2) immediate behavioral adaptation following motivational outcomes ('feedback sensitivity').

A single dose of catecholamine transporter blocker MPH (20 mg) improved acquisition learning and reduced sensitivity to negative feedback in healthy controls as a function baseline individual variability and trait impulsivity, respectively. In contrast, a single dose of LSD (75 µg), a predominantly serotonergic receptor partial agonist, did not affect reversal learning but significantly reduced outcome sensitivity in healthy controls. The difference between the MPH and LSD highlights the dissociable effects of dopaminergic and serotonergic interventions on learning stimulus-outcome contingencies and feedback sensitivity. The PRL task was an effective diagnostic tool for assessing perseverative behavior but not abnormal feedback sensitivity in an adult ADHD population. MBCT did not differ from the wait-list control group in terms of reversal learning or feedback sensitivity. Further, baseline cognitive flexibility did not affect the change in ADHD symptom severity. These findings suggest that pharmacological interventions target differential aspects of reversal learning, however, MBCT was not more effective than alternative ADHD treatments for shifting learning or feedback sensitivity.

Keywords: Methylphenidate, LSD, Mindfulness, ADHD, reward, punishment, reversal learning, probabilistic reversal learning

Abbreviations

5-HT: Serotonin

ADHD: Attention Deficit Hyperactivity Disorder

DA: Dopamine

NE: Norepinephrine

MBCT: Mindfulness Based Cognitive Therapy

MPH: Methylphenidate

LSD: Lysergic Acid Diethylamide

TAU: Treatment As Usual

Introduction

Cognitive flexibility requires a process of detecting, learning and relearning salient changes in the environment (Cañas, Fajardo, & Salmerón, 2006). Standardized tests of reversal learning are used to measure how humans can efficiently and swiftly adapt to new situations. Successful reversal learning demands effective monitoring and modulating of attention to overcome prepotent impulsive responses and to adjust performance when necessary. Poor performance is a consistent observation associated with Attention Deficit Hyperactivity Disorder (ADHD)(Wixted & Sue, 2016), Obsessive Compulsive Disorder (OCD) (Chamberlain et al., 2006), drug addiction (Jentsch, Olausson, De La Garza, & Taylor, 2002) and mood disorders (Piguet et al., 2016). Cognitive flexibility is a therapeutic target for medical and psychological interventions.

The non-medical and medical use of prescription stimulants such as MPH (Smith & Farah, 2011) and the illicit use of recreational drugs for cognitive enhancement has risen in popularity among young adults (Winstock, Barratt, Ferris, & Maier, 2017). A main concern with pharmaceutical interventions are the potential adverse side effects, such as anxiety, loss of appetite and insomnia, dependency (Morton & Stockton, 2000). Further, pharmacological interventions at times are only as useful as their half-life and maintenance is required. Therefore, there is a demand for an effective alternative non-pharmacological treatment, such as meditation, to improve attentional function and cognitive flexibility.

This study investigated the effects of two pharmacological interventions: methylphenidate (MPH), lysergic acid diethylamide (LSD) and one behavioral intervention Mindfulness Based Cognitive Therapy (MBCT), on reversal learning. We used a three-cue PRL paradigm to assess two aspects of learning, perseverative behavior and outcome sensitivity. The Probabilistic Reversal Learning (PRL) paradigm assesses a subject's ability to learn, unlearn and relearn the positive and negative contingencies in the face of irrelevant stimuli (Lawrence, Sahakian, Rogers, Hodges, & Robbins, 1999). Perseverative behavior is indicative of an inability to update stimulus-outcome contingencies and is reflected through the continued selection of a no longer rewarded stimulus. Outcome sensitivity refers to the behavioral adaptation to immediate positive and negative feedback.

INTERVENTIONS & HYPOTHESES

LYSERGIC ACID DIETHYLAMIDE (LSD)

LSD is a serotonergic hallucinogen (or "psychedelic") that profoundly alters perceptual, cognitive and psychological states (Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008). Ingestion of LSD can lead to increased sensory perception, pronounced affectivity, synesthesia and enhanced mental imagery (Grof, 1975; Hintzen & Passie, 2010). The degree to which LSD alters consciousness is dose-dependent. At 40-80 µg of LSD, individuals under the influence of LSD are more susceptible to suggestibility (Carhart-Harris et al., 2015). At 75-100 µg of LSD,

attention, concentration and intellectual functions are reduced (Abramson et al., 1955). From a behavioral perspective, given LSD's propensity to increase susceptibility toward suggestibility (Carhart-Harris et al., 2015) and enhance more creative states (Janiger & de Rios, 1989), we postulated that subjects would be more sensitive toward detecting more probabilistic and relevant feedback and could more readily update their internal representation of the stimulus-outcome contingencies. In other words, LSD would allow for better reversal learning and greater outcome sensitivity.

LSD's pleiotropic mechanism of action is mediated by the serotonergic system in the dorsal raphe nucleus (DRN) and, at large doses, the dopaminergic system at the VTA (De Gregorio, Comai, Posa, & Gobbi, 2016) . Serotonin (5-HT) is implicated in the etiology of decision-making (Dayan & Huys, 2008), impulsivity (Faulkner, 2014; Schweighofer et al., 2008) and reward and punishment processing (Rogers 1999b, Eshel and Roiser 2010). The enhancement of creativity, conceptual thinking and perception may be a result of the 5-HT2A stimulation (Glennon, Titeler, & McKenney, 1984). 5-HT2A stimulation promotes learning (Frokjaer et al., 2008; Harvey, 2003; Harvey, Quinn, Liu, Aloyo, & Romano, 2004; Üçok et al., 2007) and cognitive flexibility (Boulougouris, Glennon, & Robbins, 2008) in humans. Further, genetic research has illustrated that subjects with higher 5-HT transporter density showed greater sensitivity to aversive stimuli compared to their short allele counterparts (den Ouden et al., 2013; Finger et al., 2007). This suggests that 5-HT modulates immediate behavioral adaptation to punishment based learning (den Ouden et al., 2013). In rats, there are distinct temporal phases of LSD reflecting early serotonergic and later dopaminergic action. The latter temporal phase of discriminative stimulus effects of LSD is mediated by D2 receptor stimulus (Marona-Lewicka, Thisted, & Nichols, 2005). Given that the rats were administered with doses far higher than that of their human counterparts (rats: 0.16 mg/kg; humans: 0.0018 mg/kg), it is not evident if these dopaminergic induced behavioral effects would be also seen in humans. We hypothesized that due to the agonistic activity on the 5-HT receptors, LSD would promote cognitive flexibility and increase sensitivity toward immediate punishment. In addition, we did not contemplate that subjects would exhibit DA mediated decision-making behavioral as the serotonergic effects would be more pronounced.

METHYLPHENIDATE (MPH)

MPH is a catecholamine reuptake inhibitor that directly increases extracellular DA and norepinephrine (NE) in the brain (Hannestad et al., 2010; Kuczenski & Segal, 1997; Volkow et al., 2001). MPH is a commonly prescribed medication for ADHD and acts as a central nervous system stimulant (Farah et al., 2004; Markowitz et al., 2003). MPH promotes task accuracy, prolonged focus attention and decreased impulsivity in patients with ADHD (Brumaghim and Klorman, 1998; Douglas et al., 1995; Tannock et al., 1995). MPH also enhances attention as well as decreases distractibility in healthy subjects (Tomasi et al., 2011). However, there is large variability in MPH-induced effects in healthy adults (Smith & Farah, 2011).

Polymorphisms of the DAT1 and DARPP-32 have been implicated in learning on a longer timescale (den Ouden et al., 2013; Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). The dose dependent effects of DA gene variants determine the strength of the reliance of previous experiences and the inability to update stimulus-outcome contingencies (den Ouden et al., 2013). Baseline dopamine synthesis and release will affect the catecholamine dependent function of MPH as reuptake is dependent on catecholamine release. Given the importance of baseline dependency of the effects of catecholamine manipulation, differential effects are likely to arise within and between subjects. We've included two neuropsychological measures: working memory span and trait impulsivity to predict baseline DA function. PET scans have revealed that working memory span and trait impulsivity are predictive of DA synthesis capacity (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008; Landau, Lal, O'Neil, Baker, & Jagust, 2009) and D2 autoreceptor availability, respectively (Buckholtz et al., 2010; Costa et al., 2013; Tournier et al., 2013). At a neurobiological level, we hypothesized that MPH would affect learning and feedback sensitivity as a function of baseline dopamine levels. To build on the current literature, we postulated that MPH with improve learning in subjects with a larger working memory capacity (van der Schaaf, Fallon, Ter Huurne, Buitelaar, & Cools, 2013) and higher trait impulsivity (Smith & Farah, 2011).

MINDFULNESS BASED COGNITIVE THERAPY (MBCT)

We used the PRL task to explore the effects of MBCT on cognitive flexibility in an adult ADHD population compared to a wait-list treatment group. First, we assessed if PRL performance is affected by the severity of ADHD symptoms, replicating previous studies (Sokolova et al., 2017). Second, we explored whether changes in PRL performance are predictive of improvement in ADHD symptoms at two time points, independent of intervention. Third, we investigated whether an MBCT intervention improved performance on the PRL. Finally, we examined if the efficacy of the MBCT intervention in the improving ADHD symptoms could be predicted from baseline PRL performance. This final step is crucial for clinical usefulness of cognitive lab-based tasks for treatment prediction in patients.

Impaired self-regulation and the inability to direct attention are core deficits found in adults with ADHD (Marchetta, Hurks, Krabbendam, & Jolles, 2008; Nigg, 2001). Adults with ADHD show poorer performance in mental flexibility (the Trail Making Test) (Gansler et al., 1998) as well as interference control (Stroop Color Word Test) (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005) .The inability to respond with flexibility in the reversal learning task is correlated with impulsive behavior (Franken, van Strien, Nijs, & Muris, 2008; Romer et al., 2009) and deficits in reward processing (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Luman, Oosterlaan, & Sergeant, 2005; Luman, Van Meel, Oosterlaan, & Geurts, 2011); we would expect that performance on the PRL task is indicative of ADHD symptom severity.

Mindfulness is defined as the intentional cultivation of attention to the present moment without any judgement of the unfolding experience (Kabat-Zinn, 2006). MBCT has been shown to strengthen attention regulation (Jha, Krompinger & Baime, 2007), cognitive inhibition

(Zylowska, et al., 2008), expand working memory (Heeren & Philippot, 2011; Jha, Stanley, Kiyonaga, Wong, & Gelfand, 2010; Semple, 2010) and reduce automatic responses (Teasdale, Segal, & Williams, 1995). Further, the implementation of MBCT in ADHD adolescents has engendered improvement in attentional impairments (van de Weijer-Bergsma, Formsma, de Bruin, & Bögels, 2012), self-regulation of emotional functioning (Mitchell, Zylowska, & Kollins, 2015) and reduction in depressive and anxiety symptoms (Zylowska, et al., 2008). Patients with a history of MBCT interventions have demonstrated greater cognitive reappraisal ability than their no-therapy counterparts (Troy, Shallcross, Davis, & Mauss, 2013), reduced cognitive rigidity (Greenberg, Reiner, & Meiran, 2010) and reduced trait impulsivity (Reza, Haghighat, & Hosseinaiy, 2014). Based on the current literature, we postulated that the MBCT would allow for greater ease to update existing stimulus-outcome contingencies and therefore reduce perseverative behavior and immediate behavioral adaptation to probabilistic feedback.

Cognitive flexibility and attentional performance are positively correlated with mindfulness practice (Greenberg et al., 2010; Moore & Malinowski, 2009). Hence, we further hypothesized that greater baseline cognitive flexibility prior to mindfulness training may therefore be an indicator of treatment success of mindfulness practice in alleviating ADHD symptoms (Van De Weijer-Bergsma, Formsma, De Bruin, & Bögels, 2011).

METHODS

EXPERIMENTAL PARADIGM

We utilized the Probabilistic Reversal Learning (PRL) task to assess cognitive flexibility (Cools, Clark, Owen, & Robbins, 2002; Lawrence et al., 1999). Prior to the task, subjects were informed that on each trial they should select the stimulus they believed had the highest probability of reward and that these probabilities may change during the task. In each trial, participants were presented with three cues (colored, abstract fractals) rather than the traditional implementation of this paradigm using two cues (Fig 1a). The correct cue had a 75% probability of reward (and 25% punishment), the incorrect cue had a 25% probability of reward (and 75% punishment), and the neutral cue had a 50% chance of reward or punishment. At reversal, the correct and incorrect cues reversed contingencies, while the third cue remained stable. This neutral cue thus dissociated an inability to stop selecting the previously rewarded cue after reversal, from an inability (or unwillingness) to start selecting a previously punished cue. The former would be characterized by increased selection of the initially rewarded cue during reversal, while the latter would be characterized by increased selection of cue 3. Location for each cue was pseudo-randomized across 4 locations on each trial. After the subject selected the cue for each trial (self-paced), they were then shown either positive (green smiley face) or negative feedback (red sad face). Hence, the three cues require the subjects to remember the value of multiple alternative choices.

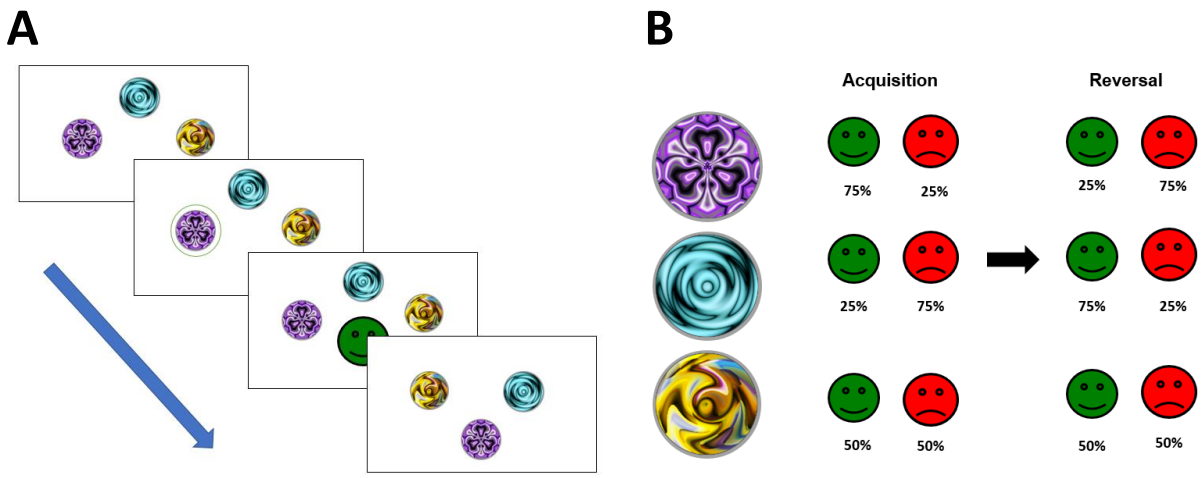

Figure 1. **Probabilistic Reversal Learning Task Design**

A) Within trial task design. The subjects must select the cue with the highest probability of reward. After selecting a cue, they will either receive a green smiley face (for reward) or a red sad face (for punishment). Shortly after the new trail will start (location of the cues are randomized).
B) Probabilistic feedback of each cue. The probability of receiving a reward or punishment is probabilistic and differs per cue. The probabilistic feedback of the mostly rewarded and mostly punished cues reverse after 40 trials.

BEHAVIORAL MEASURES

Successful performance during the acquisition phase requires the subjects to learn to select the 75% rewarded cue (the correct cue) and to ignore the probabilistic negative outcomes. During the reversal phase, subjects must update their internal representation so that the once correct, as the mostly rewarded stimulus now leads to mostly punishment, and the once mostly punished (incorrect) stimulus now leads to reward. Hence, to successfully learn, subjects will need to be attentive to the frequency in which the negative outcome occurs in both the acquisition and in the reversal phase.

Performance on the PRL task will be assessed by examining perseverative behavior and outcome sensitivity. To evaluate perseverative behavior, we calculated the probability of selecting the correct and incorrect cues in both the acquisition and reversal phase. Perseverative behavior would be reflected by either an increased selection of the incorrect cue (which was previously correct), or by decreased selection of the correct (but previously punished) cue, or both. Feedback sensitivity was assessed by measuring behavioral adaptation immediately following reward and punishment. We examined the probability of a subject reselecting the same cue following a reward (win-stay) and the probability of shifting to a different cue following a punishment (lose-shift), independent of task phase or which cue they had selected.

LYSERGIC ACID DIETHYLAMIDE

METHODS:

SUBJECTS

19 healthy volunteers were recruited for this subject (4 females, 21-35 years of age). Exclusion criteria were: under 21 years of age, personal history or familial history of psychiatric disorders, history of substance abuse, absence of a previous experience with psychedelic drugs, adverse responses to hallucinogenic drugs, claustrophobia, needle or blood phobia. Subjects were recruited through word of mouth.

STUDY DESIGN

This was a placebo-controlled, subject-blind, balance ordered study. Subjects attended both study days (with at least 14 days of separation). All subjects were injected intravenously with either 10 ml saline solution or 75 µg of LSD via a 10-ml saline solution that was infused over a two-minute period. This was followed by a saline infusion. Subjects acclimatized for approximately 60 minutes. The study was approved by the National Health Service research committee. The physical examination included a routine blood and urine test for drug abuse or pregnancy.

STATISTICAL ANALYSES

Learning:

To explore the effects of LSD on the probability of selecting the correct and incorrect cues in the acquisition and reversal phase, we employed a repeated measures ANOVA with the following within-subject factors: drug (LSD, PLB), phase (acquisition, reversal) and valence (correct and incorrect). The Greenhouse-Geisser corrections were used when the assumptions of sphericity were validated. No covariates were considered due to the limited sample size. For the control analysis, we included test day. (Logistic regression mixed model analysis methods and analysis discussed in supplementary materials.)

Feedback Sensitivity:

Win-stay and lose-shift (both were corrected for chance) were the dependent variables of a repeated measures ANOVA. Here, note that *a priori* probability of making a 'stay' response is $^1/_3$, while the *a priori* probability of making a 'shift' response is $^2/_3$, because the task had 3 choice options. Thus, for this analysis, we corrected for these prior probabilities using subtraction, to assess win-stay/lose-shift w.r.t. chance levels. The within-subject factors included were the drug conditions and valence (win-stay or lose-shift). The Greenhouse-Geisser corrections were used when the assumptions of sphericity were validated. No covariates were considered due to the limited sample size.

As we investigated both the learning behavioral and feedback sensitivity, we used a Bonferroni corrected alpha of $p < 0.025$.

RESULTS

LSD DOES NOT AFFECT LEARNING

Subjects selected the correct rewarded cue significantly more than the incorrect punished cue across both drug sessions [Valence: F(1,18)=34.98, p=.000]. However there was evidence of perseveration as subjects performed significantly better in the acquisition phase than in the reversal phase [Valence x Phase: F(1,18)=32.93, p=.01] (Fig 2a).

There was no effect of the drug on learning behavior [Drug: F(1,18)=.44,p=.5]. LSD did not alter the probability of selecting the correct or incorrect cue [Drug x Valence: F(1,18)=2.4, p=.1] in either phase [Drug x Phase x Valence: F(1,18)=.1,p=.7] (Fig 2b).

Table 1. **Choice Probabilities.** Mean accuracy scores (standard deviation) per trial type in the acquisition and reversal phase under each drug condition (N=19).

Phase	Choice	PLB	LSD
Acquisition	Correct	0.63(0.22)	0.681(0.21)
	Incorrect	0.18(0.13)	0.130(0.08)
Reversal	Correct	0.44(0.20)	0.453(0.20)
	Incorrect	0.33(0.17)	0.29(0.13)

LSD REDUCES FEEDBACK SENSITIVITY

Across conditions, win-stay behavioral was more prevalent than lose-shift behavior [Valence: F(1,18)=33.52, p=.000]. There was a tendency to win-stay above chance [Intercept: F(1,18)=54.44,p=.000] and lose-shift significantly below chance [Intercept: F(1,18)=12.91,p=.002]. LSD significantly affected feedback sensitivity [Drug: F(1,18)=22.18,p=.000]. Lose-shift behavior was reduced significantly [Drug x Lose-Shift: F(1,18)=8.94,p=0.008]. Reduction in win-stay behavior was a robust trend [Drug x Win-Stay: F(1,18)=5.24,p=0.03].

In summary, we found that LSD has no significant effect on learning or perseverative behavior. However, under the influence of LSD, subjects were significantly less likely to lose-shift (and an overall trend towards reducing win-stay behavior).

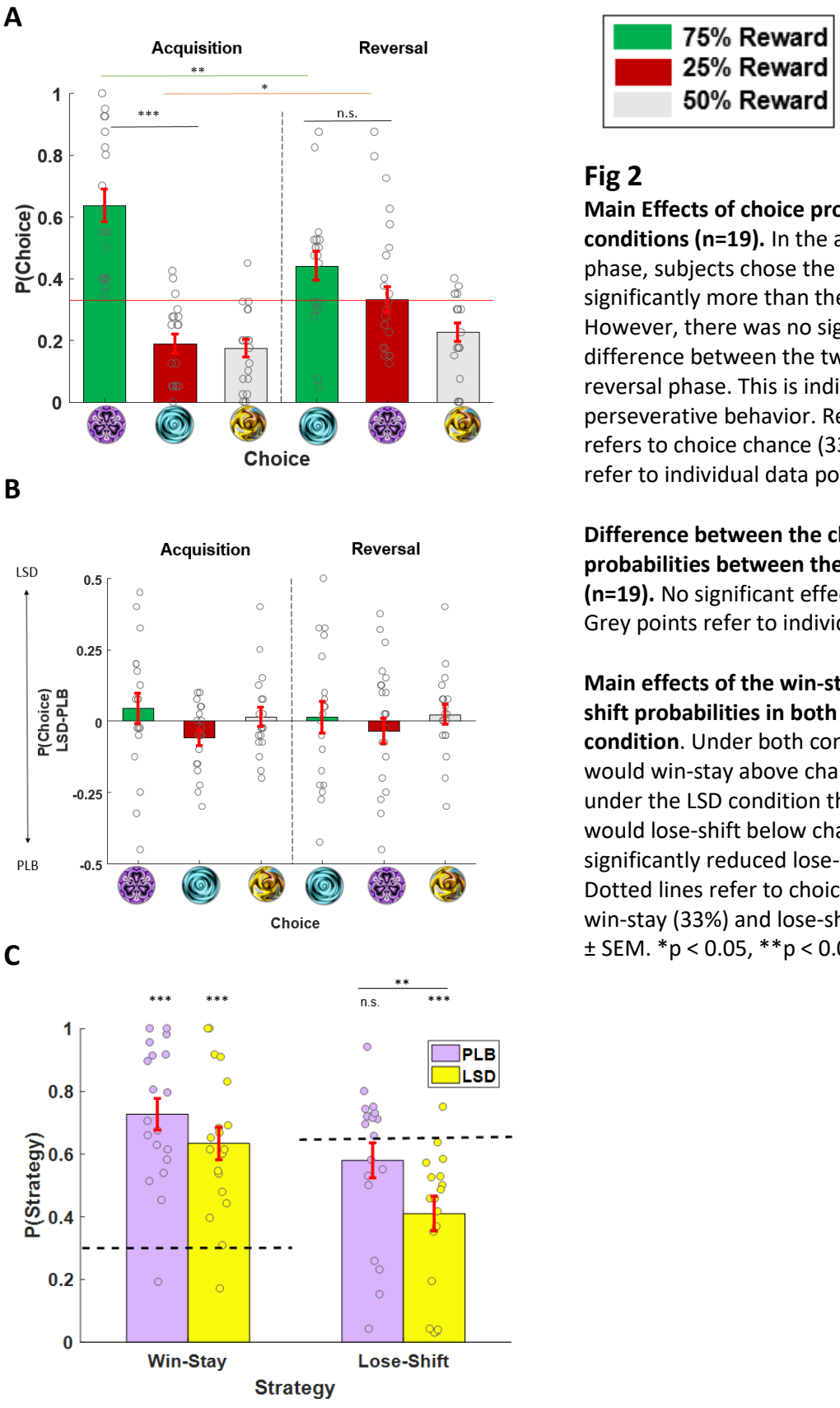

Fig 2

Main Effects of choice probabilities across conditions (n=19). In the acquisition phase, subjects chose the correct cue significantly more than the incorrect cue. However, there was no significant difference between the two cues in the reversal phase. This is indicative of perseverative behavior. Red dotted line refers to choice chance (33%). Grey points refer to individual data points.

Difference between the choice probabilities between the two conditions (n=19). No significant effects were found. Grey points refer to individual data points.

Main effects of the win-stay and lose-shift probabilities in both the PLB and LSD condition. Under both conditions, subjects would win-stay above chance. It was only under the LSD condition that subjects would lose-shift below chance. LSD significantly reduced lose-shift behavior. Dotted lines refer to choice chance for win-stay (33%) and lose-shift (66%). Mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.005.

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METHYLPHENIDATE

METHODS:

SUBJECTS

106 Dutch healthy volunteers were recruited for the study (53 women, 84 right-handed, 18-28 years of age, mean = 21.5, sd=2.3). The exclusion criteria were a history of psychiatric, endocrine or neurological disorders and abnormal or uncorrected hearing or vision. Further exclusion included pregnancy, autonomic failure, pulmonary, cerebrovascular, ocular and metabolic disorders, the use of anti-depressants or anti-psychotic drugs, and a first degree of family members with bipolar disorder, ventricular arrhythmia or schizophrenia (Swart et al., 2017). After the first day, four subjects dropped out (due to nausea, mild arrhythmia, long delay between test days). From the remaining subjects, 48 subjects received MPH on the first day.

STUDY DESIGN

Subjects underwent a placebo-controlled, double-blind, crossover designed study that consisted of a PLB condition and MPH condition. These two test sessions had an interval with a minimum of one week to a maximum of two months. The subjects received a capsule of 20 mg MPH (Ritalin, Norvartis) orally or a placebo (PLB). MPH has a plasma half-life of 120-180 minutes and reaches maximal plasma concentration after 120 minutes (Kimko, Cross, & Abernethy, 1999). The subjects began the cognitive test battery after a 50-minute waiting period. Subjects were asked to refrain from any alcohol and recreational drug use 24 hours prior to the testing as well as drinking caffeine or smoking tobacco on the day of testing (Swart et al., 2017). Subjects received credits or a monetary reimbursement for completing the study. The study was approved by the local ethics committee (CMO / METC Arnhem Nijmegen: protocol NL47166.091.13) and was pre-registered (NTR4653, http://www.tri-alregister.nl/trialreg/admin/rctview.asp?TC=465s3). The study is in accordance with the Helsinki Declaration of 1975.

BASELINE MEASURES

The Listening Span Test was used to assess working memory span (Daneman & Carpenter, 1980; Salthouse & Babcock, 1991). Subjects were presented with sets of pre-recorded sentences (which can consist of 2-7 sentences). During the playback of the recording, subjects were asked to simultaneously fill out a written questionnaire about the content of the sentence. After each set, subjects were asked to recall the last word of each sentence following the order in the recording. The number of words that a subject could successfully recall (for at least two out of three trials) reflects the subject's listening span. The listening span test was administered on day two of the task, prior to the capsule intake.

The Barratt Impulsiveness Scale (BIS-11) was used to assess trait impulsivity (Patton, 1995). The BIS-11 is composed of 30 questions that address common impulsive preferences and behaviors. The total ratings are indicative of impulsive tendencies. Subjects were asked to complete the questionnaire themselves between test days. (Table 3)

STATISTICAL ANALYSES

Learning:

To explore the effects of MPH on the probability of selecting the correct and incorrect choices in both the acquisition and reversal phase, we employed a repeated measures ANOVA with the following within-subject factors: drug (MPH, PLB), phase (acquisition, reversal) and valence (correct and incorrect) (IBM Corp, 2015). We included listening span and trait impulsivity as covariates of interest, and age as a covariate and gender as a between-subjects factor of no interest. (Additional logistic regression mixed models were used to disentangle the effects of drug, phase and the covariates on correct and incorrect cue independently. Refer to supplementary materials.)

Feedback Sensitivity:

Win-stay and lose-shift probabilities (both were corrected for chance – refer to LSD methods) were the dependent variables of a repeated measures ANOVA. The within subject factors were the drug conditions and we used the same covariates as the repeated measures ANOVA above. The Greenhouse-Geisser corrections were used when the assumptions of sphericity were violated.

As we investigated both the learning behavioral and feedback sensitivity, we used a Bonferroni corrected alpha of $p < 0.025$.

RESULTS

Table 3 **Covariates.** Values represent the mean ratings (standard deviation) across subjects.

No. of Subjects	Age	Listening Span	BIS
102	21.5 (2.31)	4.8 (1.07)	16.27 (3.56)

Listening span and baseline impulsivity: r(102)=0.23, p=.02

MPH ALONE DOES NOT AFFECT LEARNING

The repeated measures ANOVA found that there was a significance main effect of valence [Valence: F(1,99)=20.08,p=.000], indicating that subjects selected the correct choice significantly more than the incorrect choice across both drug sessions (Fig 3). There was no significant difference between performance in either phase [Phase x Valence: F(1,99)=.16, p=.6], indicating that there was no perseverative behavior. Drug alone had no effect on learning [Drug: F(1,99)=1.78,p=.1]. There was an established trend in which MPH affected the selection of the correct and incorrect cue [Drug x Valence: F(1,99)=2.81,p=.09] and this differed for each phase [Drug x Phase x Valence: F(1,99)=4.00,p=.04]. The effect of MPH on reversal learning showed a considerable trend towards significance.

Table 2. **Choice Probabilities.** Mean accuracy scores (standard deviation) per trial type in the acquisition and reversal phase under each drug condition (N=102).

Phase	Choice	PLB	MPH
Acquisition	Correct	0.69 (0.22)	0.70 (0.12)
	Incorrect	0.12 (0.09)	0.10(0.08)
Reversal	Correct	0.62 (0.21)	0.65(0.22)
	Incorrect	0.19 (0.12)	0.16(0.10)

LISTENING SPAN PREDICTS ACQUISITION LEARNING:

Listening span alone does not affect baseline performance [Phase x Valence x Listening Span: F(1,99)=1.86,p=.1]. However under the MPH condition, there was a trend in which listening span did affect task behavioral [Drug x Phase x Valence x Listening Span: [F(1,99)=3.76,p=0.06]. The function of listening span on learning under the MPH condition was specific to the acquisition phase [Drug x Valence x Listening Span: F(1,99)=8.79,p=.004] and not the reversal phase [Drug x Valence x Listening Span: F(1,99)=.64,p=.6]. Further, listening span was predictive of releasing the previously rewarded (correct) cue [Drug x Phase x Listening Span: F(1,99)=7.73,p=.006] but not the learning of the previously punished (incorrect) cue (only a trend) [Phase x Drug x Listening Span: F(1,99)=3.35,p=.07](ref to Fig 3). Subjects with greater listening span were better at selecting the correct cue in the acquisition phase under the MPH condition, whilst subjects with lower listening span did significantly worse [Drug x Phase x Valence x Listening Span: F(1,99)=7.04,p=.009]. Listening span and MPH did not predict the selection of either cue in the reversal phase [Correct: Drug x Listening Span: F(1,99)=.14,p=.7; Incorrect: Drug x Listening Span: F(1,99)=.44, p=.5].

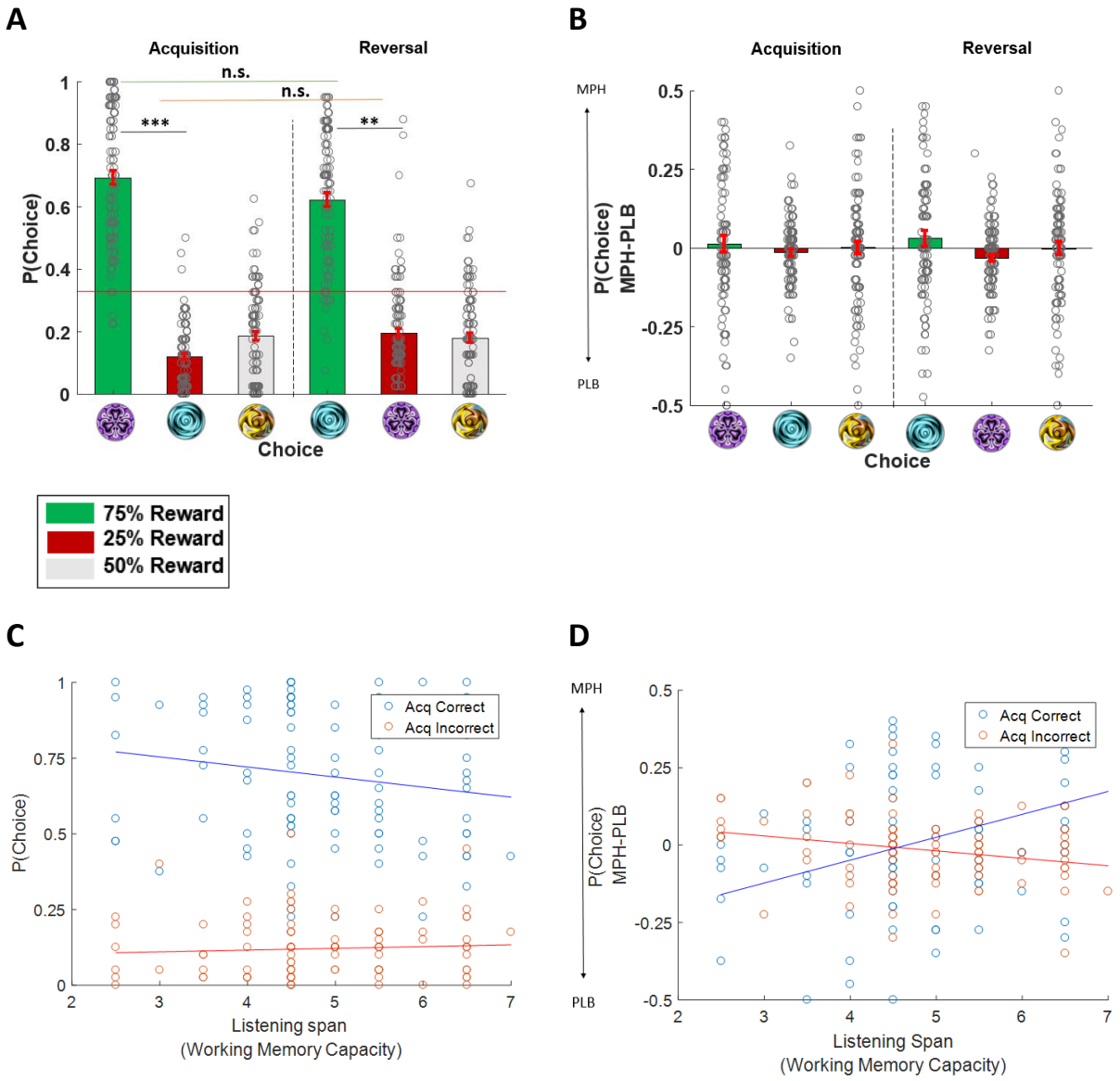


Figure 3. **A) Main effects of choice probabilities across conditions (n=102).** In the acquisition phase, subjects chose the correct cue significantly more than the incorrect cue. However, there was no significant difference between the two cues in the reversal phase. Red dotted line refers to choice chance (33%) Grey points refer to individual data points. Mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.005. **B) Difference in choice probabilities between the two conditions.** No significant difference was found between the two groups. Grey points refer to individual data points. Mean ± SEM. **C) Main effects of listening span on learning in the acquisition phase.** There is no significant relationship between listening span and the selection of the correct and incorrect cues. **D) Listening Span predicts MPH effects on learning in the acquisition phase.** Under the MPH condition, listening span was predictive of selecting the correct cue in the acquisition phase (p=.003). As listening span increased, subjects were better at selecting the correct cue. (There is a reliable trend in which listening span is negatively correlated with selecting the incorrect cue). Blue and red data points refers to individual subjects.

Trait impulsivity did not have an effect on learning [Drug x Valence x BIS: $F(1,99)=.71, p=.4$] in either phase [Drug x Phase x Valence x BIS: $F(1,99)=.01$, $p=.7$]. The control analysis included the covariates of no interest, gender and age. The drug effects were not affected by the covariates of no interest [Drug x Phase x Valence x Listening Span: $F(1,99)=7.82$, $p=.007$]. (The results of the logistic regression analysis confirm these effects. It can be found in the supplementary material).

TRAIT IMPULSIVITY PREDICTS FEEDBACK SENSITIVITY:

Subjects would win-stay significantly more than lose-shift [Valence: $F(1,99)=8.95, p=0.004$] and would win-stay more than chance [Intercept: $F(1,99)=39.01, p=.000$] , but lose-shift behavior did not differ from chance [Intercept: $F(1,99)=.19, p=.6$]. Drug alone had a significant effect on this behavioral [Drug: $F(1,99)=5.62, p=.01$]. Subjects would win-stay and lose-shift more under the PLB condition, than under the MPH condition (Fig 4A). There was a trend in which the effects of MPH on feedback sensitivity was valence specific [Drug x Valence: $F(1,99)=3.32, p=.06$].

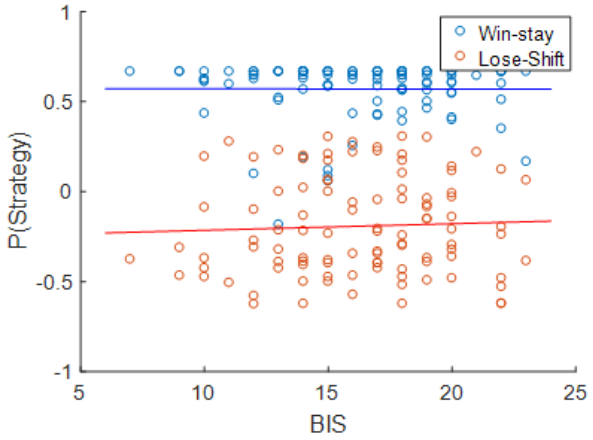
Baseline trait impulsivity predicted feedback sensitivity under the MPH condition [Drug x BIS: $F(1,99)=7.34$, $p=.008$]. This effect is absent in baseline performance [Valence x BIS: $F(1,99)=2.31, p=.1$]. MPH reduced lose-shift behavior more in subjects with higher trait impulsivity than in those with lower trait impulsivity [Drug x BIS: $F(1,99)=7.3, p=.008$] but did not affect win-stay tendencies [Drug x BIS: $F(1,99)=2.3$, $p=.1$] (Refer to Fig 4C). There was no effect of listening span on win-stay and lose-shift tendencies [Drug x Listening Span: $F(1,99)=.1, p=.6$].

The control analysis included the covariates of interest (listening span) and covariates of no interest, gender (between subject factor) and age (covariate). Age and gender had no effect on feedback sensitivity [Age: $X^2(1)=0.01, p=0.9$; Gender: $X^2(1)=1.12, p=0.3$]. The drug effects were not affected by the covariates of no interest [Drug x BIS: $F(1,97)=4.32$, $p=.02$].

In sum, listening span predicted the effects of MPH on acquiring initial stimulus-outcome contingencies. This resulted in more advance learning of the rewarded stimulus and avoidance of the punishment stimulus in subjects with greater working memory capacity. MPH had the opposite effect on subjects with a smaller working memory capacity. This is absent of any effect in reversal learning. Trait impulsivity predicted the effects of MPH on immediate behavioral adaptation to punishment cues. Under the influence of MPH, trait impulsivity was negatively correlated with lose-shift behavior.

A

B



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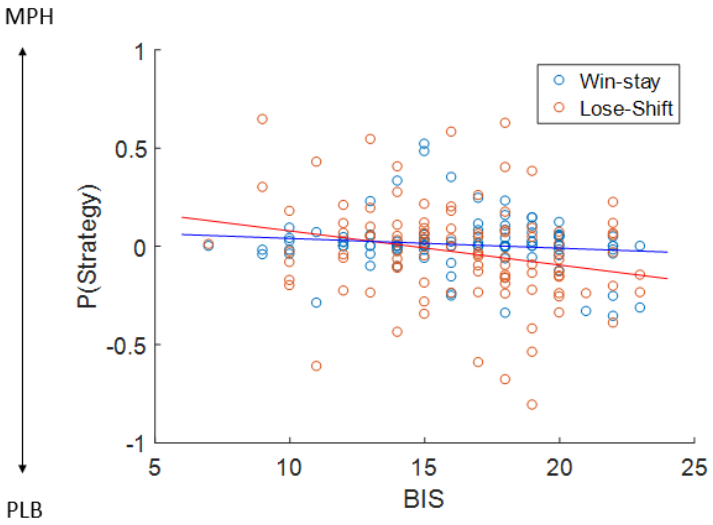


Figure 4.

A) Main effects of the win-stay and lose-shift probabilities in both the PLB and MPH condition.
Under both conditions, subjects would significantly win-stay above chance and lose-shift significantly below chance. There was no significant difference between the two conditions.
Dotted lines refer to choice chance for win-stay (33%) and lose-shift (66%). Mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.005.

B) Linear relationship between trait impulsivity and win-stay and lose-shift tendencies. Triat impulsivity did not predict feedback sensitivty in the baseline condition. Win-stay and lose-shift probabilities were corrected for chance. BIS: Barratt Impulsiveness Scale. Individual points refer to individual subjects.

C) Trait impulsivity predicted the effects of MPH on feedback sensitivity.
Under the MPH condition, trait impulsivity was significantly negatively correlated with lose-shift tendencies. Trait impulsivity was not predictive of win-stay behavior . Win-stay and lose-shift probabilities were corrected for chance. BIS: Barratt Impulsiveness Scale. Individual points refer to individual subjects.

MINDFULNESS BASED COGNITIVE THERAPY

METHODS:

SUBJECTS

This parallel-group, multicenter, randomized controlled study examined the effects of MBCT on adults with ADHD. 110 Dutch native subjects were randomly allocated to a MBCT with treatment as usual (TAU) or TAU alone groups. 110 subjects completed the at least one session of the PRL task, whilst 48 subjects completed both sessions. (Of the 62 participants who completed the task once, 41 completed the task prior to the intervention and 21 completed the task after the intervention). Inclusion criteria was older than 18, had a primary diagnosis of ADHD (according to the DSM-IV-TR and a structured Diagnostic Interview for ADHD (DIVA) in adults) and could read and write in Dutch. The exclusion criteria included a history of psychiatric illnesses, substance dependence, autism and any learning disability. Subjects could not have participated in a MBCT or MBSR (Mindfulness Based Stress Reduction) course prior to this. A psychiatric structured diagnostic interview (MINI-Plus) was used to see if the patients meet the exclusion criteria and the DSM-IV Axis II Disorders (SCID-II). Subjects were recruited through a referral from a specialist from one of the three participating outpatient clinics and from self-selection (Janssen et al., 2015).

STUDY DESIGN

Assessments were taken at baseline and 3 months after baseline. Subject's ADHD symptoms (the investigator-rated) were assessed using the Conners' Adult ADHD Rating Scale (CAARS-INV:SV) by a blinded clinical to assess the DSM-IV criteria for ADHD symptoms. The interview consists of 30 items that were rates on a 4-point Likert scale. The sevens subscales included an ADHD index, inattention/memory problem, hyperactivity/restlessness, impulsivity/emotional lability, problems with self-concept and three DSM-IV scales: inattentive symptoms, hyperactive-impulsive symptoms and ADHD symptoms (Conners, Erhardt, & Sparrow, 2004). For both groups, patients could continue using their ADHD medication (such as psychostimulants) and they were not withheld from any other psychosocial or psychoeducational treatments. Ethical approval was provided by the CMO Arnhem-Nijmegen for all the participant centres. (Registered under number 2014/206)(Janssen et al., 2015)

STATISTICAL ANALYSES

Question 1: Does PRL performance predict ADHD symptom severity?(n=110)

Learning:

Repeated measures ANOVA was used to analyze the learning behavior of the baseline performance on the PRL task of ADHD adults (n=110). The dependent variable was the

proportion of correct and incorrect choices per phase. The within subject factors included phase and valence and the covariate included was Conners' Adult ADHD Rating Scale (CAARS) rating the day of the task. As a control analysis, a repeated measures ANOVA with age (as covariate) and gender (as between subject factor) to examine if the significant effects remained.

Feedback Sensitivity:

Repeated measures ANOVA was implemented to analyze the feedback sensitivity on the first administration of the PRL task. The dependent variables included the win-stay and lose-shift probabilities for the entire trial. The within subject factors included valence and the covariate was the CAARS ratings scored at the time of the PRL task. The same control analysis as the learning repeated measures ANOVA was conducted.

We implemented a Bonferroni corrected alpha of 0.025 as we explored both learning and feedback sensitivity measures.

Question 2: Does change in PRL performance predict change in symptom severity as a function of the MBCT intervention? (n=48)

Learning:

Repeated measures ANOVA was used to analyze the change in learning behavior from pre to post intervention (TAU: n= 24, MBCT+TAU: n=24). The dependent variables were the difference between the performance scores of the first and second administration of the PRL task. The within subject factors included phase and valence, the between subject factor was the intervention and the covariate was the difference between the pre and post intervention CAARS ratings. As a control analysis, a repeated measures ANOVA with age (as covariate) and gender (as between subject factor) was used to examine if the significant effects remained.

Feedback Sensitivity:

Repeated measures ANOVA was implemented to analyze the difference in feedback sensitivity between the pre and post intervention. The dependent variables were the differences of the probabilities of win-staying and lose-shifting between the pre and post intervention PRL scores. The within subject factors included valence, the between subject factor was the intervention, and the covariate was the difference between the pre and post intervention CAARS rating. The same control analysis as the learning repeated measures ANOVA was conducted.

We implemented a Bonferroni corrected alpha of 0.025 as we explored both learning and feedback sensitivity measures.

Question 3: Does baseline performance predict the effectiveness of the MBCT intervention?(n=24)

The same methods were used as in question two, however, the dependent variables only included the baseline learning and feedback sensitivity scores from within the MBCT intervention (n=24).

RESULTS:

Question 1: Does PRL performance predict ADHD symptom severity?

ACQUISITION LEARNING PREDICTS ADHD SYMPTOM SEVERITY

Subjects successfully selected the correct cues significantly more than the incorrect cue [Valence: F(1,109)=202.84,p=.000], however, there was perseverative behavior [Phase x Valence: F(1,109)=100.81,p=.000] (Fig 5). There was an increasing trend in which learning predicted the CAARS rating [CAARS: F(1,108)=3.58,p=.06]. Learning in the acquisition phase predicted CAARS rating [Valence x CAARS: F(1,108)=9.5, p=.002], but not in the reversal phase [Valence x CAARS: F(1,108)=1.4, p=.2]. More specifically, the proportion of correct [CAARS: F(1,108)=9.7,p=.003] and incorrect cues [CAARS: F(1,108)=7.0,p=.009] in the acquisition phase both predicted CAARS rating. The learning from a previously rewarded or previously punished cue did not predict CAARS rating [Phase x CAARS: F(1,108)=1.2, p=.2]. The more accurately subjects performed in the acquisition phase, the less pronounced the symptom severity. Performance in the reversal learning did not predict CAARS rating.

FEEDBACK SENSITIVITY DOES NOT PREDICT ADHD SYMPTOM SEVERITY

Subjects would win-stay significantly more than lose-shift [Valence: F(1,108)=36.9,p=.000]. They would win-stay and lose-shift significantly above and below chance respectively [Win-stay: F(1,108)=142.3, p=.000; Lose-Shift: F(1,108)=42.5,p=.000]. There was no main effect of severity of ADHD symptom on feedback sensitivity [CAARS: F(1,108)=.5,p=.4], but there was a trend in which valence specific feedback sensitivity predicted CAARS ratings [Valence x CAARS: F(1,108)=4.23,p=.04]. There was a reliable trend that suggested that lose-shift behavior was positively correlated with CAARS rating [Lose-Shift x CAARS: F(1,108)=4.15,p=.04] than for win-stay behavior [Win-Stay x CAARS: F(1,108)=1.5, p=.2] (Fig 5B). The less pronounced the symptom severity, the less likely subjects were to lose-shift.

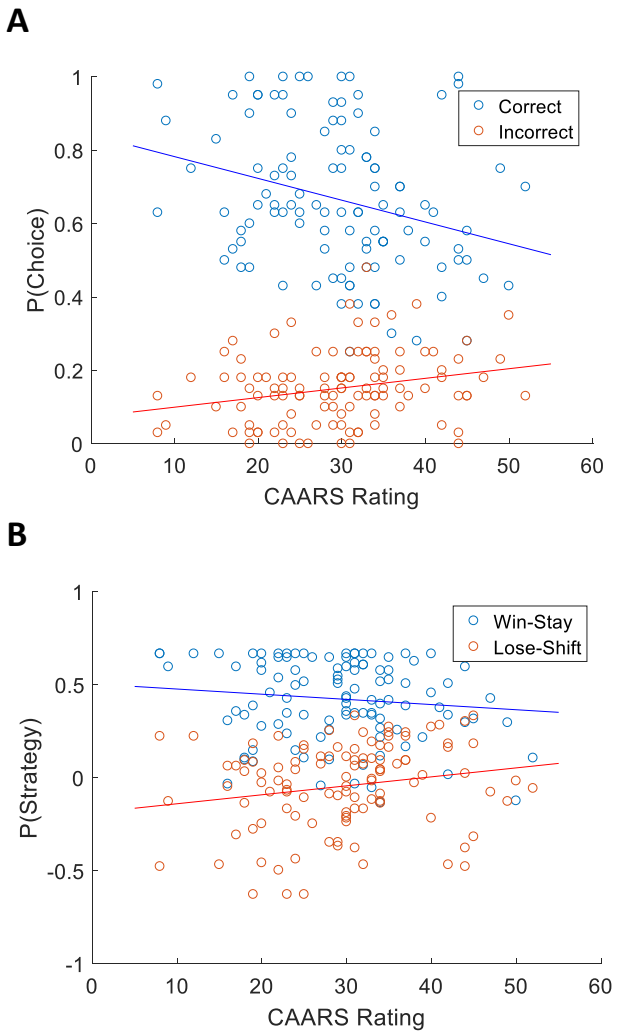


Figure 5.

A) ADHD symptom severity as a function of learning behavior in the acquisition phase. Selection of the correct cue was inversely correlated with CAARS rating, whilst the selection of the incorrect cue was positively correlated with the rating. The better the performance in the acquisition phase the lower the CAARS rating.

B) ADHD symptom severity as a function of feedback sensitivity CAARS rating closely predicts lose-shift behavior (only a trend) and not win-shift behavior. ADHD symptom severity was positively correlated with lose-shift behavior. Win-stay and lose-shift probabilities were corrected for chance. Data points reflect the baseline performance of each individual subject. CAARS: Conners' Adult ADHD Rating Scales

Question 2: Does change in PRL performance predict change in symptom severity as a function of the MBCT intervention?

IMPROVEMENT IN LEARNING DOES NOT PREDICT IMPROVEMENT OF SYMPTOM SEVERITY AS A FUNCTION OF THE MBCT

Paired sample t-test showed that the group that received the MBCT intervention had a greater reduction in ADHD symptoms than that of the TAU group [t(23)=2.31,p=.02] (Table 5). Change in PRL performance did not predict change in CAARS rating [CAARS $_{post-pre}$: F(1,48)=.05,p=.8] or the intervention type [Intervention: F(1,48)=1.02,p=.3].

Table 5. **Covariates.** Mean ratings (standard deviation) per group condition (N=24 per group). Differs significantly from the TAU (*p<0.05)

	AGE	CAARS DAY 1	CAARS DAY 2	CAARS DIFFERENCE
TAU	39(10.87)	28 (9.4)	32 (7.3)	-2.25(3.2)
MBCT+TAU	42(12.36)	22(9.8)	30(7.2)	-5.67(6.3)*

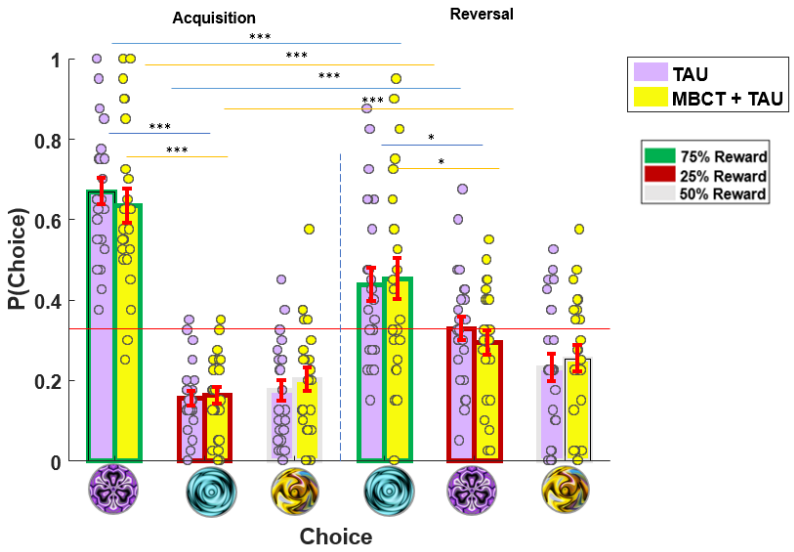
Table 6. **Choice Selection Probabilities**. Difference between pre and post intervention for each intervention. Mean accuracy scores (standard deviation) per trial type in the acquisition and reversal phase for each condition (N=48).

Phase	Choice	TAU	MBCT+TAU
Acquisition	Correct	0.04 (0.2)	0.06(0.2)
	Incorrect	-0.01(0.1)	-0.03(0.1)
Reversal	Correct	0.07(0.1)	0.07(0.2)
	Incorrect	-0.01(0.1)	-0.02(0.1)

CHANGE IN FEEDBACK SENSITIVITY DOES NOT PREDICT IMPROVEMENT IN SYMPTOM SEVERITY AS A FUNCTION OF THE MBCT

Changes in feedback sensitivity did not predict intervention type or change in CAARS rating [Intervention: F(1,45)=1.33,p=.2; CAARS $_{post-pre}$: F(1,45)=.51,p=.4]. There was a trend in which sensitivity to either reward or punishment predicted change in ADHD symptom severity [Valence x CAARS $_{post-pre}$: F(1,45)=3.24,p=.08]. This trend illustrated that change in lose-shift tendency was predictive of change in CAARS rating [Lose-Shift x CAARS $_{post-pre}$: F(1,45)=4.15, p=.04], but not change in win-stay [Win-Stay x CAARS $_{post-pre}$: F(1,45)=.73,p=.4].

A



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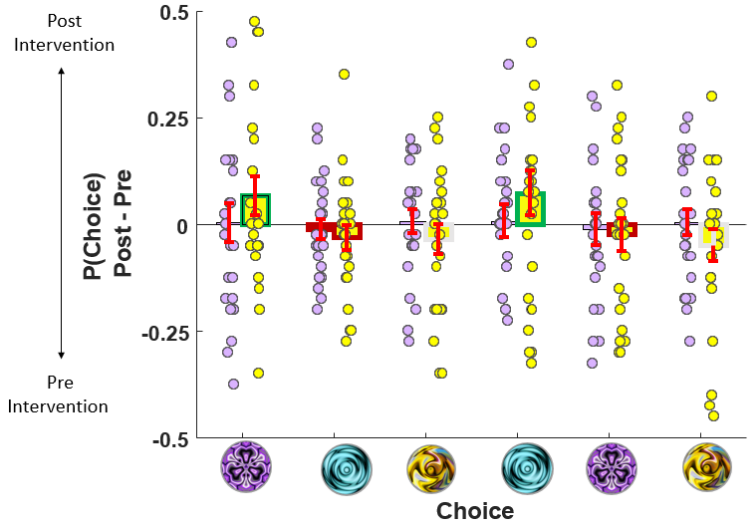

Figure 6. A). Baseline performance of PRL task for the TAU and MBCT interventions. For both interventions, subjects chose the correct cue significantly more than the incorrect cue. Further, they selected the correct cue significantly more in the acquisition phase than in the reversal phase and selected the incorrect cue significantly more in the reversal phase than in the acquisition phase. Although subjects successfully learned the correct and incorrect cues, they still exhibited perseverative behavior.
B) Difference between pre and post intervention performance of the PRL task for the TAU and MBCT interventions There was no significant difference between pre and post intervention for either intervention group. Nor was there a significant difference between the change in performance between the interventions. Mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.005.

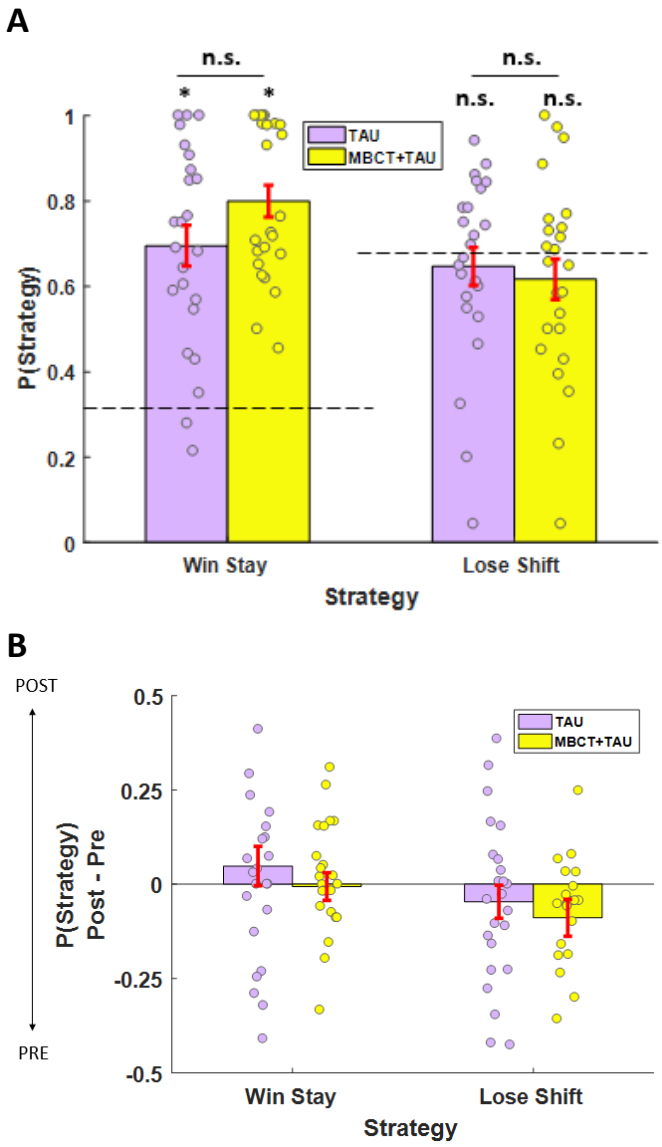

Figure 7. A) Baseline feedback sensitivity for both intervention groups. Prior to the interventions, both the TAU and MBCT+TAU groups would win-stay significantly above chance, however, lose-shift did not differ from chance. There was no difference between the baseline feedback sensitivity between the two groups. Dotted lines refer to choice chance for win-stay (33%) and lose-shift (66%). Mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.005.

B) Difference between pre and post intervention feedback sensitivity for both intervention groups. There was no difference between pre and post intervention for either group. There was no significant difference between the two interventions. Mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.005.

Question 3: Does baseline performance predict the effectiveness of the MBCT intervention?

BASELINE LEARNING DOES NOT PREDICT EFFECTIVENESS OF MBCT INTERVENTION

On Day 1, subjects selected the correct cue more than the incorrect cue [Valence: $F(1,22)=19.2, p=.000$], but there was some perseverative behavior [Phase x Valence: $F(1,22)=10.1, p=.004$] (Fig 6A). Baseline performance did not predict improvement in CAARS ratings [Valence x $CAARS_{post\text{-}pre}$: $F(1,22)=.00, p=.9$; Phase x Valence x $CAARS_{post\text{-}pre}$: $F(1,22)=.05, p=.3$].

BASELINE FEEDBACK SENSITIVITY DOES NOT PREDICT EFFECTIVENESS OF MBCT INTERVENTION

On Day 1, subjects would significantly win-stay more than lose-shift [Valence $F(1,22)=32.42, p=.000$]. Baseline feedback sensitivity did not predict change in the CAARS rating [Valence x $CAARS_{post\text{-}pre}$: $F(1,22)=.22$, $p=.6$].

In sum, the three cue PRL task is effective for assessing acquisition learning impairments but not reversal learning in ADHD adults. Symptom severity is negatively correlated with accuracy performance in the acquisition phase. In addition, there was a trend in which lose-shift behavior positively predicts symptom severity. Although the MBCT+TAU intervention group exhibited greater reduction in ADHD symptoms, MBCT+TAU did not significantly differ from the TAU intervention in terms of perseverative behavior or feedback sensitivity. Further, reduced cognitive flexibility or abnormal feedback sensitivity prior to the treatment did not affect the improvement in ADHD symptoms in the MBCT intervention.

DISCUSSION:

To our knowledge, this is the first study to examine the effects of MPH, LSD and MBCT on reversal learning and feedback sensitivity. There is an increasing body of evidence to suggest that MPH and MBCT are in fact cognitive enhancers (Moore & Malinowski, 2009; Rosemary Tannock, Schachar, & Logan, 1995) and anecdotal evidence that LSD can also be beneficial for problem-solving tasks (Fadiman, 2011). The aim of our study was to examine if these interventions in fact enhance reversal learning and alter feedback sensitivity. (Table 9)

Table 9 Summary results of the effects of the pharmacological and behavioral interventions on reversal learning and outcome sensitivity.

	Methylphenidate	**LSD**	**Mindfulness Based Cognitive Therapy**
Subjects	102 healthy adults	19 healthy adults	110 ADHD adults (48 adults completed the PRL task pre and post intervention)
Study Design	Double-blind Placebo-Controlled Cross-Over	Participant-blind Placebo-Controlled Balanced-Order	Investigator-blind Parallel-Group Balanced-Order
Learning	Improves learning in the acquisition phase	No main effect	No main effect
Outcome Sensitivity	Significantly reduces lose-shift	Significantly reduces both win-stay and lose-shift	No main effect
Within or between subject effects	Working memory predicted learning in the acquisition phase under MPH condition Trait impulsivity predicted punishment sensitivity under MPH condition	Not considered due to small sample size	Baseline reversal learning and feedback sensitivity did not predict effectiveness of the interventions

LSD

LSD REDUCES FEEDBACK SENSITIVITY

There's a renewed interest in using LSD to enhance creativity (Janiger & de Rios, 1989), boost cognition (Fadiman, 2011) and treat end-of-life anxiety (Gasser, Kirchner, & Passie, 2015). Over the last two decades there are new findings that probe the different facets of its mind-altering effects. We have demonstrated, for the first time, that 75 µg of LSD does not affect learning but it significantly reduces sensitivity to negative feedback.

Contrary to our hypothesis, LSD significantly reduced lose-shift behavior and an apparent trend towards reduced win-stay behavior as well. It is unclear if this reduction in feedback sensitivity is due to an abnormally blunted impact of feedback or the failure to use feedback correctly to guide subsequent behavior. However, as failure to update conditional stimulus-outcome contingencies did not result in impaired reversal learning, this could suggest that subjects had an appropriate understanding of the task rules, but now have a weaker representation of how to execute the appropriate corresponding action. Hence, subjects may rely on the preserved ability to use the expectation of a value to drive decision making, rather than relying on immediate probabilistic feedback. These results suggest that acute doses of LSD do not disrupt the allocation of attention toward stimulus and outcome, but may alter the balance between relevant and irrelevant associations with the environment. Previous studies on Psilocybin, another serotonergic agonist hallucinogen, show that Psilocybin reduced attentional tracking ability and had no effect on spatial working memory (Carter et al., 2005). For the PRL task, subjects are presented with three cues and the respective feedback simultaneously for less than three seconds. If attentional tracking ability is also reduced in subjects under the LSD condition, three seconds may be insufficient to detect and integrate a change in the outcome feedback. Furthermore, Psilocybin also increased indirect semantic priming (Spitzer et al., 1996). This can reflect the drug's ability to either increase the availability of remote associations or the reduced capacity to utilize contextual information (Spitzer et al., 1996). Hence, we cannot discount the potential distractions [i.e., the visual hallucinations (Dolder, Schmid, Haschke, Rentsch, & Liechti, 2016) or external factors] that could hamper the subject's ability to detect and to integrate the presented feedback.

LSD is a promiscuous and complex molecule that acts on multiple targets. LSD's mechanism of action is primarily mediated by the binding of the 5-HT1A and 5-HT2A receptors in the dorsal raphe. However, at higher doses, LSD will also modulate the D2 and 5-HT2A receptors in the VTA (De Gregorio et al., 2016). The PRL task has provided a potential insight to better understand if the behavioral effects of LSD primarily act through the serotonergic or dopaminergic systems or both. As addressed previously, DA governs the weight of the long-term consequences of our previous choices; whilst serotonin regulates our immediate behavioral adaptations to feedback sensitivity (den Ouden et al., 2013). DA activity incentivizes perseverative behavior and modulates learning rates from positive outcomes (Cools et al., 2009; den Ouden et al., 2013; Dodds et al., 2008; Rutledge et al., 2009). Given that LSD only modulated the tendency to change choices following immediate feedback and not the long-term

reinforcement of previous feedback, we can infer that cognitive flexibility is mediated through the serotonergic systems rather than dopaminergic systems.

Disorders such as Anorexia Nervosa (Glashouwer, Bloot, Veenstra, Franken, & De Jong, 2014), Obsessive Compulsive Disorders (Fullana et al., 2004), depression (Guimón, Las Hayas, Guillén, Boyra, & González-Pinto, 2007) and ADHD (Becker et al., 2013) are all characterized by heightened sensitivity to punishment. The implications of our findings are that 75 µg of LSD can potentially be used to reduce sensitivity towards reward and punishment without the expense of impairing learning. Our findings could support the current notion that LSD could have alleviate the engrained patterns of negative thinking exhibited by these mood and cognitive disorders without sacrificing cognitive flexibility.

METHYLPHENIDATE

The increased use of MPH by both ADHD and healthy students has raised questions on which facets of cognition are enhanced by this stimulant. Here we have analyzed the effects of MPH on learning and valence sensitivity. Due to the differential effects of MPH given the inter and intra-variability of the baseline striatal dopamine activity (Cools et al., 2008; van der Schaaf, Fallon, Ter Huurne, Buitelaar, & Cools, 2013), we further explored the role of baseline listening span and impulsivity as a function of MPH effects.

LISTENING SPAN PREDICTS EFFECTS OF MPH ON ACQUISITION LEARNING

We found that MPH improved the learning of initial stimulus-reward contingencies in the acquisition phase in subjects with greater working memory capacity, but had no effect on learning in the reversal phase. Our findings are consistent with previous research illustrating that MPH will improve learning in subjects with greater working memory capacities, whilst MPH will impair those with a low working memory capacity (Van der Schaaf et al., 2014). This is congruous with the well-known inverted-U-shaped relation between cognitive flexibility and dopaminergic activity (Cools & D'Esposito, 2011; Levy, 2009) . As working memory capacity is predictive of the baseline dopamine synthesis capacity in the striatum (Cools 2008; Landau 2009), subjects with greater working memory capacity have a higher dopamine synthesis capacity. It has been proposed that subjects with a faster rate of DA release will experience higher increases in extracellular DA when the DAT is inhibited (Volkow et al., 2001). This hypothesis has been confirmed with animal models, which showed that DAT blockade induced extracellular DA concentrations was dependent on baseline dependent effects (Hooks, Colvin, Juncos, & Justice, 1992). Hence, a higher level of extracellular DA would lead to more effective learning of stimulus-reward contingences, whilst lower levels of extracellular DA would impair it. However the underlying extracellular DA levels did not affect the breaking of old prepotent stimulus-reward contingencies or the relearning of a new stimulus-reward contingency as no perseveration was observed. We can attribute the lack of effect of MPH on reversal due to the lack of perseverative behavior in the baseline condition. The current literature suggests that MPH only promoted reversal learning in rats with reversal learning impairments, but not in healthy rats (Cheng & Li, 2013; Seu & David Jentsch, 2009).

TRAIT IMPULSIVITY PREDICTS EFFECTS OF MPH ON FEEDBACK SENSITIVITY

Our results demonstrate that MPH reduces sensitivity to probabilistic negative feedback and the degree to which this effect is pronounced is predicted by trait impulsivity. Under the MPH condition, trait impulsivity was negatively correlated with lose-shift behavior. Individuals with higher trait impulsivity have greater DA transporter availability (Costa et al., 2013), larger amphetamine induced DA release in the striatum (Oswald et al., 2007) and lower levels of D2 receptors in the Substania Nigra (SNc) and Ventral Tegmental Area (VTA) (Tournier et al., 2013). We could extrapolate from these findings that greater DA release in the striatum leads to reduced negative feedback sensitivity. Consistent with the current literature, subjects with lower levels of dopamine, such as Parkinson's Disease patients, show more lose-shift behavior (Bellebaum et al., 2016) whilst moderate levels favor lower lose-shift probabilities (Humphries, Khamassi, & Gurney, 2012).

A direct implication of our findings is that MPH impairs acquisition learning in memory with a low working memory capacity and increases feedback sensitivity in highly impulsive participants. ADHD patients have been associated with lower levels of D2/D3 receptor and DAT availability(Wise & Rompre, 1989), working memory deficits (Tannock, Ickowicz, & Schachar, 1995), high impulsivity (Aron, Dowson, Sahakian, & Robbins, 2003; Cepeda, & Kramer, 2000) and increased sensitivity to negative feedback (Carlson & Tamm, 2000). For ADHD patients with lower working memory spans and high impulsivity, the use of MPH can be a double-edged sword, as it would impair acquisition learning but also decrease sensitivity to negative feedback.

MINDFULNESS

The growing popularity of mindfulness among the public and the medical community warrants the investigation of the potential therapeutic improvement in ADHD adults receiving MBCT. Our current research addresses two key questions: First, we assess if the three cue PRL task can be used as a diagnostic tool to assess baseline ADHD symptoms and improvements of ADHD symptoms; Second, we then examined the effects of the MBCT invention on the performance of the PRL task and if baseline cognitive flexibility predicts the efficacy of the MBCT intervention.

PRL TASK IS NOT AN EFFECTIVE DIAGONISTIC TOOL FOR ADHD SYMPTOM SEVERITY.

Poor cognitive flexibility is a result of impulsive decision-making in ADHD (Chantiluke et al., 2014). The core features of ADHD patients are associated with oversensitivity to immediate feedback rather than by delayed reinforcement (Bari & Robbins, 2013; Stark et al., 2011). Whilst performance on the acquisition phase of the PRL may be a useful clinical marker for ADHD symptom severity, the PRL task fails to capture reversal learning capabilities in ADHD adults. Further, sensitivity to punishment is only marginally detected through the PRL task. Contrary to our hypothesize, the three cue PRL task is an ineffective diagnostic tool for assessing ADHD symptom severity.

MBCT DOES REDUCE ADHD SYMPTOMS BUT DOES NOT IMPROVE COGNITIVE FLEXIBILITY

Patients who received the MBCT intervention had a greater reduction in ADHD symptom severity than those in the TAU group. Contrary to our predictions, we did not a find a significant relationship in change in learning and feedback sensitivity for either intervention. This was unexpected given that previous findings have demonstrated that mindfulness interventions have promoted cognitive flexibility in an ADHD population (Greenberg et al., 2010; Lee & Orsillo, 2014; Moore & Malinowski, 2009). An eight-week mindfulness intervention may not be robust enough to effectively and significantly impact cognitive flexibility as the acquired mindfulness skills may not be easily transferable to different cognitive facets. However given that the PRL task could not accurately reflect the degree in which reversal learning capabilities and feedback sensitivity are impacted by ADHD symptom severity, improvement in the task may not reflect the success of either intervention.

Our study assessed the impact of baseline cognitive flexibility on the outcome of the efficacy of the MBCT. Previous evidence has demonstrated that cognitive inflexibility can negatively impact the brief training of skill acquisition (Johnco, Wuthrich, & Rapee, 2014). However, we found that baseline cognitive flexibility did not predict treatment outcome. Hence, it appears that pre-invention cognitive flexibility was not predictive of ADHD symptoms post-treatment or the overall treatment outcome. Hence, baseline cognitive flexibility does not hamper the effectiveness of either treatment.

CONCLUSION

Enhancing cognitive flexibility through pharmacological or behavioral means is at the core of humanity's desire to continually improve cognition through various forms of artificial enhancements and behavioral exercises. The methods of enhancing cognitive flexibility can take on many and diverse forms. We have shown that a NE-DA reuptake inhibitor and a 5-HT hallucinogen have dissociable effects on learning and feedback sensitivity. Whilst both pharmacological interventions are effective in reducing punishment sensitivity, only MPH was effective at improving learning in the acquisition phase. However, there are limitations to the effectiveness of MPH due to the central role of the baseline dopamine signaling. Given the large variability, the limited short-term effects and side effects, we examined the behavioral alternatives to these pharmacological approaches. Consist with the current literature, MBCT (combined with a psychosocial or medical treatment) seemed to be a less effective alternative to improving cognitive flexibility or altering feedback sensitivity compared to medication or psychosocial treatment alone. However, this should not be used as the rationale to not utilize MBCT altogether as other domains of cognitive function can be improved by mindfulness. The diversity of pharmacological and behavioral interventions draws critical attention to carrying out systematic and controlled studies to evaluate the truly efficacy of psychostimulants, hallucinogens and mindfulness interventions for enhancing reversal learning and altering feedback sensitivity.

LIMITATIONS:

LSD:

Due to the limited sample size (n=19), the covariates such as age and gender were not included in the analysis. The lack of diversity in the sample also limits the generalization of these findings to the remaining population. Due to the palpable psychosensory changes induced by 75 µg of LSD, it was impossible to keep the subjects blinded from the drug conditions. As the effect of 5-HT and DA on reversal learning and outcome sensitivity is dose and temporally dependent, it would be of interest to see the dose dependent effects of LSD on cognitive flexibility at different stages of the experience.

Methylphenidate:

Over 75% of the subjects that participated in the MPH study were university students, hence there is a possibility that subjects *hyper* performed (out of the three interventions, this was the only group that did not show perseveration in the baseline condition). Hence, the high level of education and cognitive function may be the cause for the lack of findings of the cognitive enhancing properties of MPH. The extrapolation of these findings to a general population should be taken with caution. Furthermore, to confirm the hypotheses derived from our findings of the dose-dependent effects of MPH, future studies should explore the effect of low and high drug doses effect on reversal learning and outcome sensitivity in healthy individuals.

Mindfulness Based Cognitive Therapy:

The larger improvement in ADHD symptoms within the MBCT+TAU may result from the frequency and intensity of contact, support, attention and positive expectations from healthcare professionals. A comparison of MBCT with wait-list controls may have produced the exaggerated effects of the MBCT. For future studies, the control group should match the MBCT in terms of frequency and intensity of contact and support. Whilst our overall findings were consistent, other pre-treatment factors were not considered, such as baseline working memory, impulsivity and use of psychostimulants due to our limited sample size. The role of mindfulness in adjustment to ADHD symptoms requires future longitudinal descriptive research to further understand the adjustment mechanisms. Training of novice mediators tends to first focus on concentrative focus (e.g., on the breath) before advancing to focusing on the quality of awareness (e.g., receptive attention) (Kapleau, 2000). Continued examination of MBCT in a clinical setting will further enrich our understanding of the underlying mechanisms of mindfulness and can additionally help us to develop strategies to maximize the effectiveness of MBCT.

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Supplementary Materials

We used the lme4 package in R studio to use logistic mixed-level model analysis to further disentangle the drug effects on the probability of selecting correct and incorrect stimuli (Bates et al 2013; R Development Core team 2015). Logistic regression models allowed for the accountability between and within subject variability. The models also included all random effects structures (Barr, 2013).

LSD

A logistic mixed level model analysis was conducted to assess the factors that affected the selection of the 1) correct cue 2) incorrect cue and 3) stay and shift behavior individually. We used drug and phase (only for choice) as the predictors. Our findings confirm the results from our repeated measure ANOVA, LSD does not affect the selection of the correct [Drug: $X^2(1)=.67,p=.4$] or incorrect cues [Drug: $X^2(1)=2.6,p=.1$]. Further, LSD did predict stay and shift behavior [Drug: $X^2(1)=4.8,p=.02$]. After performing a control analyses (by comparing the models), we examined if testing days improved the model fit. It had no effect on behavior or feedback sensitivity.

MPH

A logistic mixed level model analysis was conducted to assess the factors that affected the selection of the 1) correct cue 2) incorrect cue and 3)stay and shift behavior independently. We used drug and phase (only for choice) as the predictors and listening span and trait impulsivity as the between subject factors (both mean corrected). After performing a control analyses (by comparing the models), we examined if testing days, age and gender improved the model fit. There was no main effect of drug [$X^2(1)=.02,p=.8$] or phase [X^2 $(1)=2.4,p=.1$] for selecting the correct cue. There was a trend that reflected an interaction effect of drug, phase and listening span [X^2 $(1)=.91,p=.03$]. There was no main effect of drug [X^2 $(1)=3.6,p=.06$] or phase [X^2 $(1)=2.1,p=.1$] for selecting the incorrect cue. There was no interaction effect of phase, drug and listening span [X^2 $(1)=.03,p=.8$]. As for stay-shift behavior, there was no main effect of drug [X^2 $(1)=1.6,p=.1$]. There was a trend which suggested an interaction effect of the outcome of the previous trial, trait impulsivity and drug [X^2 $(1)=3.6,p=.04$]. Our findings are consistent with the repeated measures ANOVA results performed in SPSS.