

Aversive inhibition in adult ADHD and its restoration by mindfulness-based cognitive therapy: A behavioral pilot study

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Abstract

Background: Control over the tendency to make or withhold responses based on contextual Pavlovian information, might play a key role in understanding impulsivity/hyperactivity in ADHD. Here we set out to assess (1) the understudied relation between Pavlovian inhibitory control and hyperactivity/impulsivity in adults with ADHD and (2) whether this inhibition can be enhanced by mindfulness based cognitive therapy (MBCT).

Methods: 50 Adult ADHD patients were assessed before and after 8 weeks of treatment as usual (TAU) with (n=24) or without (n=26) MBCT. We employed a sophisticated, well-established Pavlovian-to-instrumental transfer task that quantifies Pavlovian control over instrumental behavior.

Results: Task results revealed (1) less aversive Pavlovian inhibition in patients with clinical hyperactivity/impulsivity; and (2) enhanced inhibition after TAU+MBCT compared with TAU.

Conclusions: Aversive Pavlovian inhibition plays a role in clinically relevant hyperactivity/impulsivity in adult ADHD and MBCT can be used to enhance this form of inhibition.

Introduction

Individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD) have difficulties with controlling their behaviour appropriately with respect to environmental demands. Two key cognitive systems that control our behaviour with respect to the environment are the Pavlovian and instrumental systems (Dickinson and Balleine, 2002; Dolan and Dayan, 2013). Especially problems in Pavlovian control of goal-oriented instrumental behaviors are associated with a wide variety of psychiatric problems (e.g. Dayan *et al.*, 2006; Heinz *et al.*, 2016; Hallquist *et al.*, 2018). This form of behavioral control has received relatively little attention in human and animal ADHD research (Natsheh and Shiflett, 2015), although it might be key to adaptive inhibitory control which has since long been proposed to be central to understanding problems in ADHD (Barkley, 1997). Moreover, aberrant Pavlovian control over instrumental behaviour can lead to maladaptive impulsivity in animals as well as in humans (Breland and Breland, 1961; Guitart-Masip *et al.*, 2014; Hinojosa-Aguayo and González, 2020). This form of control has been shown to depend on monoaminergic transmission relevant for understanding ADHD (Dalley and Roiser, 2012; Geurts *et al.*, 2013b; Salamone *et al.*, 2015) and can specifically be modulated by methylphenidate (Swart *et al.*, 2017). To fill this gap in the literature, we will test whether Pavlovian control over instrumental behaviour is indeed related to clinically relevant impulsivity/hyperactivity in ADHD. Therefore, we will first compare Pavlovian control in adult ADHD patients diagnosed with and without clinically relevant impulsivity/hyperactivity. Second, we will assess the hypothesis that a mindfulness-based cognitive therapy (MBCT), shown to improve impulsivity/hyperactivity in ADHD (e.g. Janssen *et al.* 2018), should accordingly also modulate Pavlovian inhibitory control.

A wide range of animals, including humans, are endowed with mechanisms shaped throughout evolution that drive behaviour (Dolan & Dayan 2013). These drivers take advantage of environmental information carried by stimuli that predict motivationally salient future events or outcomes. The instrumental control system enables us to use specific actions when confronted with a certain stimulus to obtain a specific outcome (i.e. stimulus-action-outcome learning or operant conditioning). This

system allows us to optimize our chances to achieve specific goals by learning what to do and what not to do. Complementary to this instrumental control system, the Pavlovian control system regulates automatic, motivational responses in reaction to external and internal stimuli (Dolan and Dayan, 2013). This system enables us to associate neutral stimuli with motivationally salient outcomes in the environment (i.e. stimulus-outcome learning or classical conditioning). These neutral stimuli acquire part of the motivational properties of the outcome they are associated with (i.e. predict). When encountering these previously neutral, but now conditioned, stimuli (CS) again, the automatic preparatory reaction to the outcome will now be elicited in response to these Pavlovian CSs. It has long been recognized that these two behavioural control systems do not act in separation, but interact: Pavlovian CS can (de)motivate ongoing instrumental behaviour based on the valence (appetitive or aversive) of the Pavlovian CS (Rescorla & Solomon 1967): Pavlovian CS that predict punishment (i.e. aversive Pavlovian CS) have the tendency to inhibit, whereas Pavlovian CS that predict reward (i.e. appetitive Pavlovian CS) can activate instrumental behaviour (Rescorla & Solomon 1967; Huys *et al.* 2011; Geurts *et al.* 2013a). These interactions between instrumental and Pavlovian control of behaviour are thought to be shaped by evolution and have adaptive properties in terms timing actions (i.e. when to make, and when not to make an action) to optimize gaining rewards and avoiding punishment at relatively low computational cost (Dolan & Dayan 2013). However, too much or too little influence of the Pavlovian system on instrumental behaviour has been proposed as a driver of several maladaptive behaviours (e.g. Dayan *et al.*, 2006; Heinz *et al.*, 2016; Hallquist *et al.*, 2018). Too much potentiation of instrumental behaviour by appetitive cues, or too little inhibition by aversive cues is linked to impulsive behaviour in real life (Watson *et al.* 2014; Garbusow *et al.* 2016; Heinz *et al.* 2016; Hallquist *et al.* 2017). This latter source of disinhibition, disinhibition in the face of aversive affect, has been widely recognized to play a role in externalizing psychopathology, mainly under the umbrella of negative urgency (Whiteside and Lynam, 2001) . Negative urgency has recently indeed been related to Pavlovian control over instrumental behaviour in healthy controls (Hinojosa-Aguayo and González, 2020). However, whether the impact of appetitive activating and aversive inhibitory processes on instrumental behaviour contributes to impulsivity in ADHD remains an open question.

We will test this specific hypothesis in ADHD patients diagnosed with and without clinically relevant impulsivity/hyperactivity symptomatology, i.e. comparing patients diagnosed with the combined subtype (including relevant impulsive-hyperactive symptomatology) with those with the primarily inattentive subtype (without diagnosed impulsivity/hyperactivity).

The hypothesis that both too strong appetitive PIT and too weak aversive PIT might drive impulsivity in ADHD can only be tested causally through an intervention study. A key prediction is that effective treatment of ADHD should modulate the effect of Pavlovian cues on instrumental behaviour. One candidate for this is MBCT. MBCT has significant beneficial effects in ADHD (Gu *et al.* 2017, Janssen *et al.* 2018, Hepark *et al.* 2017, Cairncross and Miller, 2016), as well as impulsivity symptoms trans-diagnostically (Franco *et al.*, 2016). It is a highly protocolled intervention that changes how patients deal with thoughts, emotions, bodily feelings and urges in reaction to both external and internal stimuli. Patients become more aware of internal and external triggers and following automatic patterns, thereby theoretically strongly linked to PIT, such as avoidance of aversive stimuli or attachment to appetitive stimuli, and learn to (initially) disengage from automatic reactivity (Segal *et al.* 2002, page 217). Indeed, MBCT has been shown to reduce hyperactive-impulsive symptoms (Gu *et al.*, 2017; Hepark *et al.*, 2017; Janssen *et al.*, 2018), improve self-reported adaptive inhibition (Hepark *et al.*, 2017; Janssen *et al.*, 2018) and increases experimentally measured behavioural inhibition (see for meta-analyses and critical notes: Lao *et al.* 2016; Vago *et al.* 2019). Moreover, previous findings from our group suggest that effects of MBCT on self-reported adaptive inhibition mediated the effects of MBCT on clinician rated ADHD symptoms (Geurts *et al.*, 2020). Taken together, to test the hypothesis that aberrant PIT may drive impulsive responding in ADHD, we will assess whether mindfulness-based cognitive therapy (MBCT) changes the inhibitory or activating effects of Pavlovian cues. In line with the hypothesized relation between impulsivity and Pavlovian control, we expect MBCT to diminish the motivating effect of appetitive Pavlovian CS and to enhance the inhibiting effect of aversive Pavlovian CS on instrumental behaviour, leading to more appropriate inhibition and less impulsivity respectively.

Methods

Trial design and procedure

This behavioural intervention study was embedded in a multi-centre randomized controlled trial investigating the impact of MBCT in addition to TAU on adults with ADHD (NCT02463396) (Janssen *et al.* 2015; 2018). For this trial, a total of 120 adults with ADHD according to the criteria of Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV-TR) (American psychiatric association 2000) were randomized to either MBCT in addition to treatment as usual (MBCT + TAU) or TAU only. The eligibility criteria, study procedure and CONSORT diagram are described fully in the main treatment outcome paper (Janssen *et al.* 2018). Clinical outcome measures were assessed before (T0) and after MBCT or TAU (directly after (T1), 3 (T2) months) data. Behavioural data on the PIT task were collected before (T0) and after MBCT or TAU (T1). On each of these two test-days, patients were seated in front of a laptop and conducted the PIT computer task.

Patients

For the current study, behavioural data on the PIT task were collected from a subset of patients assessed at one site (RadboudUMC): 68 patients were asked to participate. One patient declined, which resulted in 67 patients participating in the pre-intervention test session. On the post-intervention test session 60 (90%) patients participated and 7 declined to participate. Unfortunately, there was a loss of 10 data sets on pre-intervention due to a technical (back-up) error, leaving 50 full data sets (MBCT+TAU: n=24; TAU only n=26) to be analyzed (for demographics see table 1).

Intervention

Mindfulness-based cognitive therapy

MBCT (Segal, Williams, & Teasdale, 2002) is an 8-week group-based intervention of 2.5 hours each, plus a 6-hour silent day between session 6 and 7. In short, the programme included mindfulness practice (bodyscan, gentle yoga, sitting and walking meditation) combined with daily life practices, psycho-education, Cognitive Behavioural Therapy (CBT) techniques, group discussions,

and inquiry into present moment experiences. By this procedure patients are taught to become more aware of dysfunctional automatic patterns, such as avoidance of aversive stimuli or grasping of appetitive stimuli and to consciously disengage from these patterns (Segal *et al.* 2002). For further detail see (Janssen *et al.* 2015).

Treatment as usual (TAU)

TAU reflected the usual treatments of ADHD patients in various mental health centres across the Netherlands, consisting of pharmacotherapy and psychosocial treatment, such as psycho-education and cognitive behavioural therapy.

Assessments

Clinical assessments

Clinical assessments are presented in table 1. The primary outcome measure was total ADHD symptoms according to the 30-item Conners' Adult ADHD Rating Scale (Conners *et al.* 1999), scored by a blinded clinician (CAARS-INV). In line with the findings of the overarching RCT (Janssen *et al.*, 2018, $n = 120$), MBCT significantly reduced ADHD symptoms in our subsample of the total patient group with a moderate effect size (Treatment (MBCT/TAU) x Day(pre/post) interaction on CAARS-IVNV ADHD score: $F(1,48)=5.2$, $p=.028$; independent sample t-test pre MBCT: $t(48) = 1.7$, $p=.098$; post MBCT: $t(48) = 2.8$, $p=.007$; paired sample t-test (pre vs post): MBCT+TAU: $t(23) = 4.4$, $p<.001$; TAU: $t(25) = 3.7$, $p=.007$).

Pavlovian to instrumental transfer (PIT) task

We used a PIT task that allowed us to assess the influence of appetitive and aversive Pavlovian CS on instrumental approach actions. This task was identical to the approach blocks used in Huys *et al.* (2011, 2016) and Geurts *et al.* (2012). In short, the task consisted of an instrumental conditioning, a Pavlovian conditioning and a PIT stage (Figure 1).

[Figure 1 about here]

Instrumental conditioning

The instrumental task (Figure 1A) was a go/nogo task, framed in terms of collecting ‘good’ and ‘bad’ mushrooms. Patients chose whether to collect the mushroom by moving the mouse towards and clicking on the mushroom (go) within a response-window of 1.5 seconds, or not collect the mushroom by abstaining from a response for 1.5 seconds (nogo). The outcome (+/- 5 cents) was then presented in the middle of the screen. Reinforcements were probabilistic, with the ‘correct’ response for each mushroom leading to reward on 75% of the trials and to punishment otherwise. For the ‘incorrect’ response these probabilities were reversed. Correct trials were those on which they collected a ‘good’ mushroom or refrained from collecting a ‘bad’ mushroom. Patients thus had to learn the better response for each stimulus from the probabilistic, noisy reinforcement feedback. There were 3 ‘good’ (go) and 3 ‘bad’ (nogo) mushrooms, meaning that the possible actions (i.e. collect or not collect) could be followed by both rewards and punishments.

Analyses and results on the instrumental conditioning stage are reported in supplemental materials.

Pavlovian conditioning

The second part of the task consisted of a separate Pavlovian conditioning procedure. Five compound Pavlovian CS, consisting of a fractal visual stimulus (Figure 1B) and a tone, were deterministically paired with outcomes. The appetitive ($S^{P_{++}}$, $S^{P_{+}}$) and aversive ($S^{P_{-}}$, $S^{P_{--}}$) Pavlovian CSs predicted a gain/loss of 100 or 10 cents respectively while the neutral CS ($S^{P_{0}}$) was followed by an outcome of 0 cent. To ensure that patients paid attention, a query trial was presented on every fifth trial. Patients then had to choose between two different Pavlovian CS (Figure 1C) without any reinforcement. In addition, we asked patients to rate how much they liked the presented CS before and after the experiment on a visual analogue scale (VAS).

Analyses and results on the Pavlovian conditioning stage are reported in supplemental materials.

Pavlovian-Instrumental transfer phase

This was the main phase of interest. Patients needed to choose whether to collect (go) or not collect (nogo) the same mushrooms as in the instrumental training phase, while the Pavlovian CS now tiled the entire background (Figure 1D). No outcomes were presented during this phase to exclude further instrumental conditioning. Patients were instructed to continue performing the instrumental task; that choices were still earning them the same outcomes and were being counted; but that they would not be told about the outcomes during this phase. Thus, in this phase, we could assess the impact of the Pavlovian CS on the previously learned instrumental go/nogo choices.

Data analysis

The primary effect of interest was the activating and inhibiting impact of the appetitive and aversive Pavlovian CSs on instrumental go/nogo choices respectively.

First, we assessed the relation between clinical impulsivity-hyperactivity and PIT: In the introduction we introduced two possible links between hyperactivity-impulsivity on the one hand and appetitive and aversive PIT on the other: Impulsivity-hyperactivity could theoretically be instantiated differentially by (i) exaggerated appetitive PIT, i.e. too much instrumental potentiation in the face of an appetitive Pavlovian CS and (ii) diminished aversive PIT, i.e. too little inhibition in the face of an aversive Pavlovian CS (Watson *et al.* 2014; Garbusow *et al.* 2016; Heinz *et al.* 2016; Hallquist *et al.* 2017). We assessed these differential associations at baseline by assessing differences in PIT between the combined subtype (including hyperactivity-impulsivity) and the inattentive subtype (not including hyperactivity/impulsivity) of ADHD. Thus, we employed two generalized linear mixed effects models (GLMM) with respectively Pavlovian CS Appetitive ($S^{P_{++}}/S^{P_n}$) and Aversive (S^{P_n}/S^{P_-}) as within subject factor and ADHD subtype (combined/inattentive) as between-subject factor.

Second, to test whether MBCT modulated appetitive and aversive PIT we used a GLMM including the within-subject factors Pavlovian CS Valence (5 levels: $S^{P_{++}}/S^{P_+}/S^{P_n}/S^P/S^{P_-}$) and Day (Pre vs. Post treatment), and the between-subject factors Treatment Group (TAU+MBCT vs. TAU).

We used GLMMs to account for both between- and within-subject variability. We used the lme4 package in R (Bates et al., 2014; R Development Core Team, 2015). All GLMMs included all main effects and interactions as well as a full random effects structure to reduce inflation of Type I error (Barr et al., 2013).

Furthermore, to interpret the results of the above analyses as true changes in the interaction between Pavlovian and instrumental control, i.e. PIT, there should be no differences between the Treatment groups in task performance during the instrumental and Pavlovian training per se on Day 1 or a difference in change between the Groups from pre- to post treatment in these parts of the training. We assessed whether this was the case by using, where appropriate, t-tests and repeated measure ANOVA's with respectively average performance at the end of the instrumental training stage (mean correct after more than 5 stimulus presentations), average performance at the end of Pavlovian training (mean correct after more than 5 query trials) and VAS ratings from pre-to post Pavlovian conditioning as dependent variables.

Results

General PIT effects

Critically, across Treatment Group and Day we replicated the expected PIT effect: appetitive Pavlovian CS activated, whereas aversive Pavlovian CS inhibited go-actions (main effect of Pavlovian CS Valence: $X^2=11.5$, $p<.001$; simple contrast appetitive PIT (S^P_n/S^P_{++}): $X^2=4.9$, $p=0.026$); simple contrast aversive PIT ($S^P_n/S^P_{..}$): $FRS : X^2=7.4$, $p=.006$).

Aversive Pavlovian inhibition is related to clinical impulsivity-hyperactivity

Specific analyses, targeted at clinically diagnosed impulsivity/hyperactivity and its relation to aversive and appetitive PIT respectively (see introduction and methods), revealed that aversive PIT was decreased for those patients diagnosed with the combined subtype compared with those with primarily inattentive symptoms (Figure 2, Subtype (combined/inattentive) x Pavlovian CS Valence ($S^P_n/S^P_{..}$): X

$\chi^2=4.6, p<.031$). More specifically, behavioural inhibition by aversive Pavlovian CS was not significant in patients diagnosed with the combined subtype ($X^2=4.6, p=.22$) and significant for the inattentive subtype ($X^2=4.6, p<.001$). No such effects were found for appetitive PIT (Subtype (combined/inattentive) x Pavlovian CS Valence (S^P_n/ S^P_{++}): *FRS* : $X^2=0.1, p=0.73$).

MBCT increased aversive Pavlovian inhibition over instrumental behaviour

Notably, we found that MBCT modulated PIT as is revealed by a Treatment Group x Day x Pavlovian CS Valence interaction ($X^2=14.8, p=.005$, Figure 3). Simple contrast analyses showed that this interaction was driven by changes in aversive PIT (Treatment Group x Day x Pavlovian CS Valence (S^P_n/ S^P_{-}): $X^2=7.4, p=.006$) and not appetitive PIT (Treatment Group x Day x Pavlovian CS Valence (S^P_n/ S^P_{++}): $X^2<0.1, p=.86$). Indeed, as revealed by the pattern in Figure 3, aversive PIT was enhanced post -MBCT (Day x Pavlovian CS Valence (S^P_n/ S^P_{-}): $X^2=5.6, p=.018$), but not post -TAU (Day x Pavlovian CS Valence (S^P_n/ S^P_{-}): $X^2=3.3, p=.069$). Thus, MBCT increased the inhibitory effects of aversive Pavlovian CS on instrumental behaviour and left unchanged the activating effect of appetitive Pavlovian CS.

[Figure 2 about here]

Instrumental and Pavlovian training

To interpret the above findings as true changes in the interaction between Pavlovian and instrumental control, i.e. PIT, there should be no (explanatory) differences between the Treatment groups at Day1 or a difference in change from pre- to post treatment between the groups in task performance at the end of instrumental and Pavlovian training. Indeed, we did not find evidence for differences.

Instrumental conditioning was successful as revealed by an above chance performance across the group at the end of the instrumental training on both days (one-sample t-test on mean correct choices after >5 presentations vs. chance level (0.5 correct): Day1: $t_{(49)}=4.2, p<.001$; 0.59, 95% CI 0.54-0.63; Day2: $t_{(49)}=4.6, p<.001$; mean correct choices after >5 presentations: 0.61, 95% CI 0.57-0.67).

Moreover, performance did not differ between Treatment at Day 1 (two sample t-test on mean correct choices after >5 presentations): $t_{(48)} = 0.8$, $p=0.86$, 95% CI of difference: $-0.08 - 0.09$) nor was performance dependent on an interaction between Day and Treatment ($X^2<0.1$, $p=.99$). This was also the case for Pavlovian conditioning: Conditioning in terms of explicit associations between CS and outcomes resulted in above chance performance across Treatment group on both days (Day 1: one-sample t-test: mean = 0.88, 95% CI: 0.83-0.93, $t_{(49)}=14.7$, $p<.001$: mean = 0.91, 95% CI: 0.87-0.96; Day2, $t_{(49)}=19.5$, $p<.001$,) and no group differences arose (Day 1: two sample t-test: $t_{(48)} = -0.25$, $p=0.80$, 95% CI of difference: $-0.12 - 0.09$; interaction between Day and Treatment: $X^2=0.4$, $p=.53$). Moreover, VAS liking ratings from before to after conditioning showed the expected pattern (appetitive stimuli were judged appetitive and aversive stimuli as aversive after training: Time(2 levels: pre/post conditioning)x Pavlovian CS Valence (5 levels: $S^{P_{++}}/S^{P_{+}}/S^{P_{0}}/S^{P_{-}}/S^{P_{--}}$) at Day 1: $X^2=29.4$, $p<.001$) with again no difference in conditioning effects between the Treatment groups on Day1 (Group x Pavlovian CS Valence x Time (pre/post conditioning): $X^2=2.8$, $p=.093$) or as a function of change from pre- to post treatment (Group x Day x Pavlovian CS Valence x Time (pre/post conditioning): $X^2<.1$, $p=.85$).

Discussion

Theory and data suggest that hyper (re)activity and impulsivity might be related to exaggerated appetitive Pavlovian activation and diminished aversive Pavlovian inhibition (Watson *et al.* 2014; Garbusow *et al.* 2016; Heinz *et al.* 2016; Hallquist *et al.* 2017). This prediction, however, remained untested for ADHD. We present two key findings. First, an ADHD diagnoses with clinically relevant impulsivity/hyperactivity was accompanied by an *absence* of aversive Pavlovian inhibition, while an ADHD diagnoses without clinically relevant impulsivity/hyperactivity was accompanied by aversive Pavlovian inhibition, akin to multiple healthy control studies (e.g. Huys *et al.*, 2011; Geurts *et al.*, 2013a). In contrast to our expectations, we did not find a relation between appetitive Pavlovian activation and impulsivity/hyperactivity. Second, within a randomized controlled setting, MBCT enhanced this aversive Pavlovian inhibition across the whole group of patients.

Both our findings, the relation between impulsivity/hyperactivity and aversive Pavlovian inhibition and the strengthening of this inhibition through MBCT in ADHD, are particularly interesting when considering the wide ranging, adaptive, effects of Pavlovian inhibitory processes in more detail. Pavlovian conditioned reactions have since long been recognized to help the organism prepare (in a fast and computationally efficient manner) for the predicted outcome (Dickinson & Balleine 2002). In case of appetitive outcomes these ‘preparations’ increase the chances to benefit from this outcome. In the case of aversive outcomes, the Pavlovian behavioural reactions (e.g. inhibition) might prevent damage to the organism. Allowing predictors of aversive outcome (i.e. aversive Pavlovian CS) to influence behaviour thus might instigate adaptive behaviour. Moreover, aberrant Pavlovian mechanisms, e.g. too much appetitive attraction and/or too little aversive inhibition, are thought to play a role in psychiatric disorders such as major depressive disorder, different anxiety disorders, addiction (Huys *et al.*, 2015; Heinz *et al.*, 2016; Mkrтчian *et al.*, 2017) and personality disorders associated with impulsive behaviours

(Ly *et al.* 2016; Hallquist *et al.* 2017)

. In addition, it has been proposed that not only actions are under the influence of Pavlovian inhibitory mechanisms, but also our thoughts (Huys *et al.* 2012; Mendelsohn *et al.* 2014). Indeed, Huys and

colleagues recently provided empirical evidence that Pavlovian inhibitory processes have a central place in planning action sequences (Huys *et al.* 2012; Lally *et al.* 2017). This warrants future studies on the Pavlovian inhibitory mechanisms in especially impulsivity/hyperactivity in ADHD and with respect to MBCT that might advance our understanding of the neurocognitive mechanisms of both ADHD and the workings of MBCT respectively.

One question that follows from the current study is why ADHD patients with clinically diagnosed impulsivity/hyperactivity lack the aversive Pavlovian inhibition we normally observe in healthy populations (Huys *et al.*, 2011; Geurts *et al.*, 2013a) and in ADHD patients without overt impulsivity/hyperactivity (this study). First, we note that contingencies were learned by these patients as well as by the non-impulsive/hyperactive patients: performance on query trials during conditioning nor (changes in) VAS-ratings of the Pavlovian stimuli across Pavlovian conditioning nor instrumental performance differed between these patient groups. Thus, the difference might not be explained by differences in learning. Moreover, it is also not likely that within the PIT stage, these aversive Pavlovian CS were simply not noticed, because, likewise presented, Pavlovian CS with appetitive valence exerted their normal (invigorating) effect. Thus, the absence of the inhibitory effect has to be searched downstream, in the interaction effect itself. On a cognitive-psychological level this interaction effect might only surface when the aversive predictions are processed *and* used as guidance for steering instrumental behaviour. Disturbances might thus come about through not processing the aversive information, although present, as relevant for behavioral procedures. The finding that patients showed increased effects of aversive Pavlovian stimuli post MBCT might also be informative from this perspective. First, we note that the finding that MBCT increases the effect of aversive Pavlovian CS is in general accordance with a recent report on aversive Pavlovian conditioning (i.e. fear conditioning) before and after Mindfulness Based Stress Reduction (MBSR)(Hölzel *et al.* 2016). This study showed that through MBSR, healthy controls remained sensitive, as revealed by psychophysiological responses to the aversive Pavlovian CS (predictive of electrical shocks), whereas participants in the waitlist group lost this sensitivity. Our finding extends this by showing that MBCT might potentiate the inhibitory effect of an aversive Pavlovian CS in adult ADHD patients. We

speculate that this might be due to more openness to *guiding information* of contexts predicting adversity, instead of avoiding aversive information, in combination, maybe, with an enhanced tendency to not immediately react, facilitated by the training. Moreover, on a neurophysiological level it has been shown by our group that aversive Pavlovian inhibition depends on serotonergic signaling (Crockett *et al.*, 2009; Geurts *et al.*, 2013b; den Ouden *et al.*, 2015) and is also influenced by methylphenidate suggesting catecholaminergic involvement (Swart *et al.*, 2017). We thus hypothesize that aberrant monoaminergic signaling related to Pavlovian control might be at the roots of this disinhibition, paralleling the psychological process by which aversive information guides instrumental behavior. Moreover, our data suggest that this process can be changed by MBCT.

Several limitations of this study should be noted: First we note that our relatively small sample size precluded us from assessing differential aspects of MBCT on the patients with the combined versus the inattentive subtype of ADHD. This could have strengthened (or disproved) the suggestion that MBCT specifically remedies maladaptive aversive disinhibition. Moreover, including another active control treatment could have substantiated suggestions about the specificity of our result with regards to MBCT. With regard to the PIT paradigm we think this might be improved by using a more naturalistic cover story (subjects informally reported that the game was boring) and maybe more salient reinforcers (e.g. food, taste, shock, noise), which might make the task more ecologically valid and putatively more sensitive to change. Adding eye-tracking to this paradigm might also help to establish attentional components of the uncovered effect (e.g. more dwelling at the Pavlovian CS than at the instrumental stimulus) which might help to better understand the interindividual differences found here. Finally, because this paradigm has been shown to be sensitive to catecholaminergic modulation by methylphenidate and the current study suggests that it is also sensitive to change due to MBCT, it is interesting for future studies to assess whether this paradigm could have differential predictive properties in terms of treatment response for both pharmacological as well as psychotherapeutic interventions in ADHD.

In sum, our data suggests that the combined, but not the inattentive subtype of ADHD is associated with diminished aversive Pavlovian inhibition and that MBCT can enhance this inhibition. These findings offer new insights in the neurocognitive mechanisms of hyperactivity/impulsivity in the combined subtype of ADHD and point towards MBCT as an intervention that might influence these mechanisms.

Table 1. Baseline demographic and clinical characteristics

	MBCT+TAU (n=24)		TAU (n=26)		P (Phi/T statistics)
Demographic characteristics					
Female gender	13	54.2%	16	61.5%	.28 (Phi =-.075)
Age; M(SD)	42.6	12.4	39.0	10.5	.26 (T ₄₈ = -1.1)
Clinical characteristics					
Subtype of ADHD, DSM-IV					
Inattentive type	13	54.2%	16	61.5%	.87 (Phi =-.28)
Hyperactive/impulsive type	0	0%	0	0%	
Combined type	10	41.7%	9	34.6%	
Not otherwise specified type	1	4.2%	1	3.8%	
ADHD symptoms (CAARS-INV)					
Subscales:					
Inattention	16.9	5.2	18.6	3.8	.20 (T ₄₈ = 1.3)
Hyperactive/Impulsive	11.7	6.5	14.2	5.9	.15 (T ₄₈ = 1.5)
Total	28.6	9.4	32.8	8.4	.10 (T ₄₈ = 1.7)
Use of ADHD medication	17	70.8%	14	53.8%	.22 (Phi =1.53)

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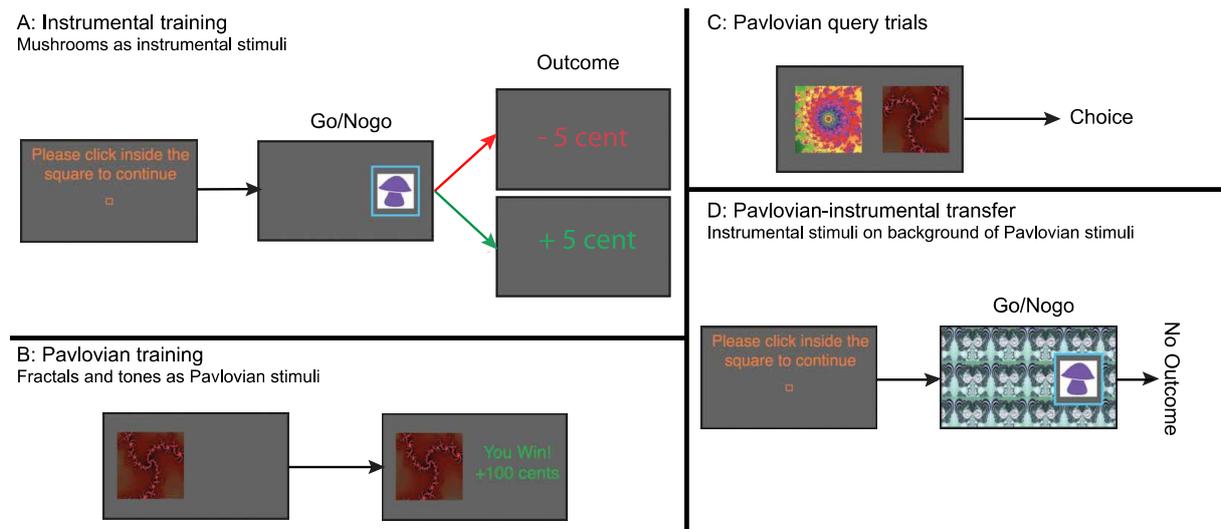


Figure 1 A. Instrumental conditioning. To centre the cursor, participants clicked in a central square.

Participants needed to choose whether to move the cursor towards the mushroom and click inside the blue frame onto the mushroom (go), or do nothing (nogo). Outcomes were presented immediately after go actions, or after 1.5 seconds (i.e. nogo). There were 3 “good” (go) and 3 “bad” (nogo) instrumental stimuli. Collecting a ‘good’ (correct go) and not collecting a ‘bad’ (correct no-go) stimulus was rewarded most of the time (75% veridical outcome). Vice versa, collecting a ‘bad’ (incorrect go) and not collecting a ‘good’ (incorrect no-go) stimulus was punished most of the time (75% veridical outcome). There were 60 trials in total. Instrumental stimuli were different for both days. **B.** Pavlovian conditioning. Participants passively viewed stimuli and heard auditory tones, followed by wins (+10/+100), losses (-10/-100), or neutral outcomes (0). There were five fractal/tone combinations. Each combination was displayed 12 times. **C.** On Pavlovian query trials, participants chose between two Pavlovian stimuli. Query trials were administered after every five Pavlovian conditioning trials. **D.** Pavlovian-instrumental transfer. Participants responded to the instrumental stimuli trained during the instrumental conditioning stage, with Pavlovian stimuli tiling the background. No outcomes were presented, but participants were instructed that their choices counted towards the final total. No explicit instructions about the contribution of Pavlovian stimuli towards the final total were given. During this phase we assessed the impact of the Pavlovian CSs on instrumental choice (go/nogo).

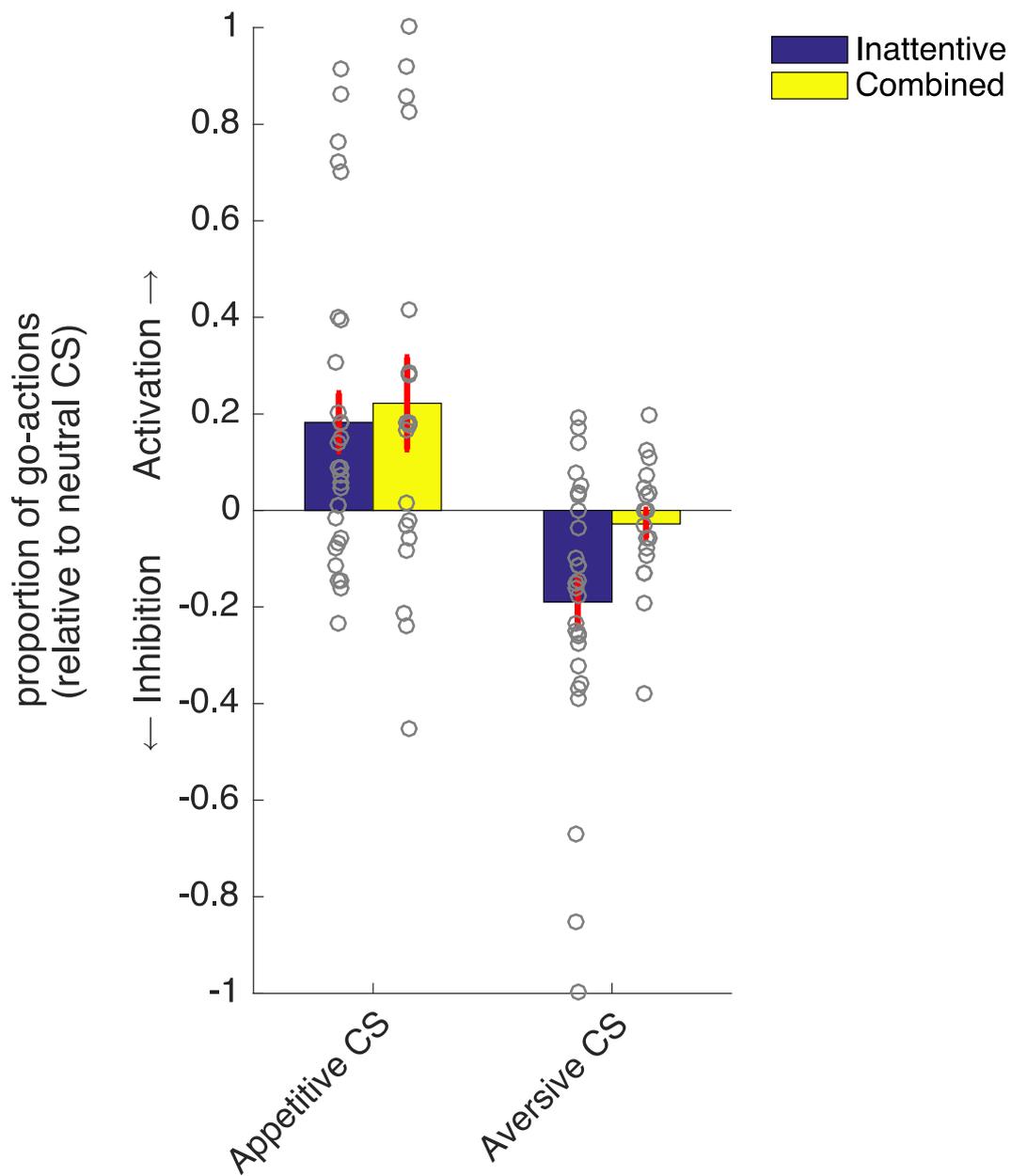


Figure 2 Relation between ADHD subtype (combined (yellow) vs. inattentive (blue)) and PIT. Patients with the inattentive subtype showed significant aversive inhibition of instrumental behavior in the context of an aversive Pavlovian conditioned stimulus (CS), while this was not the case for patients diagnosed with the combined subtype. There were no differences between ADHD subtypes in terms of appetitive activation of instrumental behaviour. Error bars represent standard errors of the mean.

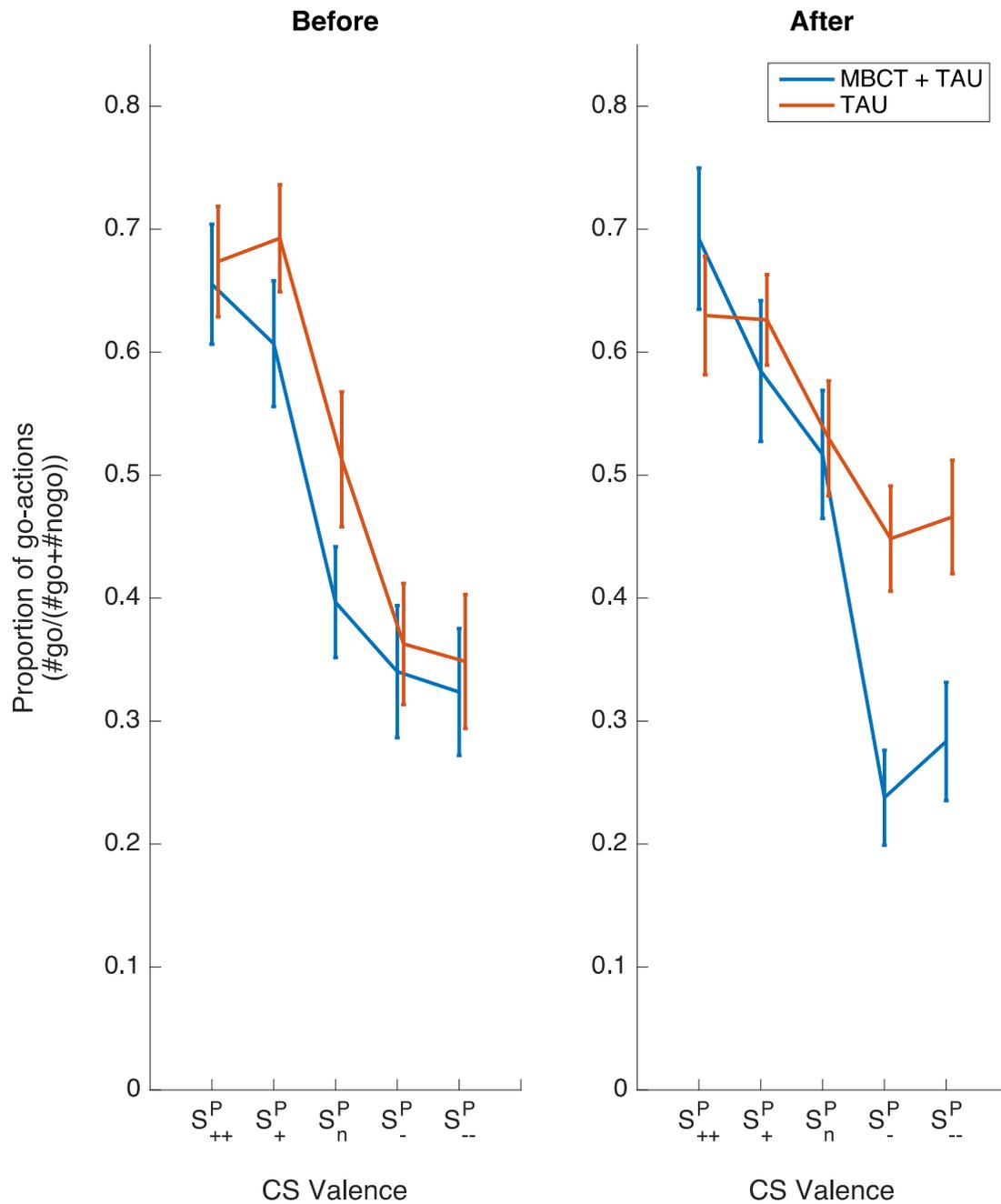


Figure 3 Behavioral data from the Pavlovian-instrumental transfer stage as a function of Treatment.

Shown are choice data (proportion of go-actions) as a function of Pavlovian CS Valence (S_{++}^P / S_+^P / S_n^P / S_-^P / S_{--}^P) and Day (before vs. after) for a group receiving mindfulness based cognitive therapy and

treatment as usual (MBCT+TAU, blue line) and a group receiving treatment as usual (TAU) only (red line). The group receiving MBCT shows increased aversive inhibition after MBCT ($p < .05$) compared to the TAU only group. Error bars represent standard errors of the mean

References

- American psychiatric association T** (2000). *Diagnostic and statistical manual of mental disorders*. Fourth edition, Text Revision. American Psychiatric Association: Washington, DC.
- Armstrong L, & Rimes KA** (2016). Mindfulness-Based Cognitive Therapy for Neuroticism (Stress Vulnerability): A Pilot Randomized Study. Elsevier B.V. *Behavior Therapy* **47**, 287–298.
- Cairncross M, & Miller CJ** (2017). The Effectiveness of Mindfulness-Based Therapies for ADHD. *Journal of Attention Disorders* **22**, 108705471562530.
- Campese VD, Kim J, Lázaro-Muñoz G, Pena L, LeDoux JE, & Cain CK** (2014). Lesions of lateral or central amygdala abolish aversive Pavlovian-to-instrumental transfer in rats. *Frontiers in behavioral neuroscience* **8**, 161.
- Campese VD, Sears RM, Moscarello JM, Diaz-Mataix L, Cain CK, & LeDoux JE** (2015). The Neural Foundations of Reaction and Action in Aversive Motivation. Springer International Publishing: Cham **27**, 171–195.
- Cartoni E, Balleine B, & Baldassarre G** (2016). Accepted Manuscript. Elsevier Ltd *Neuroscience and Biobehavioral Reviews*, 1–62.
- Conners CK, Erhardt D, & Sparrow EP** (1999). *Conners' Adult ADHD Rating Scales: Technical Manual*. 2 February. Multi Health Systems: New York.
- Corbit LH, & Balleine BW** (2016). Learning and Motivational Processes Contributing to Pavlovian-Instrumental Transfer and Their Neural Bases: Dopamine and Beyond. *Current topics in behavioral neurosciences* **27**, 259–289.
- Dayan P, & Seymour B** (2013). Values and actions in aversion. In *Neuroeconomics: Decision making and the brain* Ed. PW Glimcher. Academic Press.
- Dayan P, Niv Y, Seymour B, & Daw N** (2006). The misbehavior of value and the discipline of the will. *Neural Networks* **19**, 1153–1160.
- Dickinson A, & Balleine B** (2002). The role of learning in the operation of motivational systems. In *Steven's handbook of experimental psychology: Learning, motivation and emotion* 3rd edn Ed. CR Gallistel vol 3, pp497–534. John Wiley & Sons: New York.
- Dimidjian S, & Segal ZV** (2015). Prospects for a clinical science of mindfulness-based intervention. *American psychologist* **70**, 593–620.
- Dolan RJ, & Dayan P** (2013). Goals and Habits in the Brain. The Authors *Neuron* **80**, 312–325.
- Franco C, Amutio A, López-González L, Oriol X, & Martínez-Taboada C** (2016). Effect of a Mindfulness Training Program on the Impulsivity and Aggression Levels of Adolescents with Behavioral Problems in the Classroom. *Frontiers in psychology* **7**, 15.
- Garbusow M, Schad DJ, Sebold M, Friedel E, Bernhardt N, Koch SP, Steinacher B, Kathmann N, Geurts DEM, Sommer C, Müller DK, Nebe S, Paul S, Wittchen H-U, Zimmermann US, Walter H, Smolka MN, Sterzer P, Rapp MA, Huys QJM, Schlagenhauf F, & Heinz A** (2016). Pavlovian-to-instrumental transfer effects in the nucleus accumbens relate to relapse in alcohol dependence.

Addiction biology **21**, 719–731.

Geurts DEM, Huys QJM, Ouden den HEM, & Cools R (2013a). Aversive Pavlovian Control of Instrumental Behavior in Humans. *Journal of Cognitive Neuroscience* **25**, 1428–1441.

Geurts DEM, Huys QJM, Ouden den HEM, & Cools R (2013b). Serotonin and Aversive Pavlovian Control of Instrumental Behavior in Humans. *Journal of Neuroscience* **33**, 18932–18939.

Gu Y, Xu G, & Zhu Y (2017). A Randomized Controlled Trial of Mindfulness-Based Cognitive Therapy for College Students With ADHD. *Journal of Attention Disorders* **9**, 108705471668618.

Hallquist MN, Hall NT, Schreiber AM, & Dombrovski AY (2017). ScienceDirect Interpersonal dysfunction in borderline personality: a decision neuroscience perspective. Elsevier Ltd *Current Opinion in Psychology* **21**, 94–104.

Hebart MN, & Gläscher J (2015). Serotonin and dopamine differentially affect appetitive and aversive general Pavlovian-to-instrumental transfer. *Psychopharmacologia* **232**, 437–451.

Heinz A, Schlagenhauf F, Beck A, & Wackerhagen C (2016). Dimensional psychiatry: mental disorders as dysfunctions of basic learning mechanisms. *Journal of neural transmission* **123**, 809–821.

Hepark S, Janssen L, de Vries A, Schoenberg PLA, Donders R, Kan CC, & Speckens AEM (2017). The Efficacy of Adapted MBCT on Core Symptoms and Executive Functioning in Adults With ADHD. *Journal of Attention Disorders* **56**, 108705471561358.

Hölzel BK, Brunsch V, Gard T, Greve DN, Koch K, Sorg C, Lazar SW, & Milad MR (2016). Mindfulness-Based Stress Reduction, Fear Conditioning, and The Uncinate Fasciculus: A Pilot Study. *Frontiers in behavioral neuroscience* **10**, e0123512.

Hölzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, & Ott U (2011). How Does Mindfulness Meditation Work? Proposing Mechanisms of Action From a Conceptual and Neural Perspective. *Perspectives on Psychological Science* **6**, 537–559.

Huys QJM, Cools R, Gölzer M, Friedel E, Heinz A, Dolan RJ, & Dayan P (2011). Disentangling the Roles of Approach, Activation and Valence in Instrumental and Pavlovian Responding. Ed. A Rangel *PLoS Computational Biology* **7**, e1002028.

Huys QJM, Eshel N, O'Nions E, Sheridan L, Dayan P, & Roiser JP (2012). Bonsai Trees in Your Head: How the Pavlovian System Sculpts Goal-Directed Choices by Pruning Decision Trees. Ed. LT Maloney *PLoS Computational Biology* **8**, e1002410.

Huys QJM, Gölzer M, Friedel E, Heinz A, Cools R, Dayan P, & Dolan RJ (2016). The specificity of Pavlovian regulation is associated with recovery from depression. *Psychological Medicine*, 1–9.

Inzlicht M, Bartholow BD, & Hirsh JB (2015). Emotional foundations of cognitive control. Elsevier Ltd *Trends in Cognitive Sciences* **19**, 126–132.

Janssen L, Kan CC, Carpentier PJ, Sizoo B, Hepark S, Grutters J, Donders R, Buitelaar JK, & Speckens AEM (2015). Mindfulness based cognitive therapy versus treatment as usual in adults with attention deficit hyperactivity disorder (ADHD). *BMC Psychiatry BMC Psychiatry*, 1–10.

Janssen L, Kan CC, Carpentier PJ, Sizoo B, Hepark S, Schellekens MPJ, Donders ART, Buitelaar JK, & Speckens AEM (2018). Mindfulness-Based Cognitive Therapy v. treatment as usual in adults with

ADHD: a multicentre, single-blind, randomised controlled trial. *Psychological Medicine*, 1-11.

Kuyken W, Warren FC, Taylor RS, Whalley B, Crane C, Bondolfi G, Hayes R, Huijbers M, Ma H, Schweizer S, Segal Z, Speckens A, Teasdale JD, van Heeringen K, Williams M, Byford S, Byng R, & Dalgleish T (2016). Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse. *JAMA psychiatry* **73**, 565.

Lally N, Huys QJM, Eshel N, Faulkner P, Dayan P, & Roiser JP (2017). The Neural Basis of Aversive Pavlovian Guidance during Planning. *Journal of Neuroscience* **37**, 10215-10229.

Lattimore P, Mead BR, Irwin L, Grice L, Carson R, & Malinowski P (2017). Psychiatry Research. Elsevier *Psychiatry Research* **247**, 163-171.

Ly V, Borries von AKL, Brazil IA, Bulten BH, Cools R, & Roelofs K (2016). Reduced transfer of affective value to instrumental behavior in violent offenders. *Journal of Abnormal Psychology* **125**, 657-663.

Mendelsohn A, Pine A, & Schiller D (2014). Between Thoughts and Actions: Motivationally Salient Cues Invigorate Mental Action in the Human Brain. Elsevier Inc. *Neuron* **81**, 207-217.

Mkrtchian A, Roiser JP, & Robinson OJ (2017). Threat of shock and aversive inhibition: Induced anxiety modulates Pavlovian-instrumental interactions. *Journal of experimental psychology. General* **146**, 1694-1704.

Rescorla RA, & Solomon RL (1967). Two-process learning theory: Relationships between Pavlovian conditioning and instrumental learning. *Psychological review* **74**, 151-182.

Salamone JD, Pardo M, Yohn SE, López-Cruz L, SanMiguel N, & Correa M (2015). Mesolimbic Dopamine and the Regulation of Motivated Behavior. Springer International Publishing: Cham **27**, 231-257.

Segal ZV, Williams JMG, & Teasdale JD (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. The Guilford Press: New York, NY, US.

Spinhoven P, Huijbers MJ, Ormel J, & Speckens AEM (2017). Improvement of mindfulness skills during Mindfulness-Based Cognitive Therapy predicts long-term reductions of neuroticism in persons with recurrent depression in remission. *Journal of Affective Disorders* **213**, 112-117.

Strauss C, Cavanagh K, Oliver A, & Pettman D (2014). Mindfulness-Based Interventions for People Diagnosed with a Current Episode of an Anxiety or Depressive Disorder: A Meta-Analysis of Randomised Controlled Trials. Ed. J Laks *PLoS ONE* **9**, e96110.

van der Velden AM, Kuyken W, Wattar U, Crane C, Pallesen KJ, Dahlgaard J, Fjorback LO, & Piet J (2015). A Systematic Review of Mechanisms of Change in Mindfulness-Based Cognitive Therapy in the Treatment of Recurrent... Elsevier B.V. *Clinical Psychology Review* **37**, 26-39.

Watson P, Wiers RW, Hommel B, & de Wit S (2014). Working for food you don't desire. Cues interfere with goal-directed food-seeking. Elsevier Ltd *Appetite* **79**, 139-148.

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