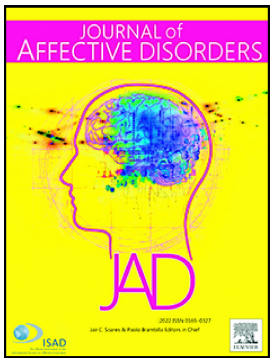

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Anhedonia and sensitivity to punishment in schizophrenia, depression and opiate use disorder

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ABSTRACT

Background. From a behavioural perspective anhedonia is defined as diminished interest in the engagement of pleasurable activities. Despite its presence across a range of psychiatric disorders, the cognitive processes that give rise to anhedonia remain unclear. **Methods.** Here we examine whether anhedonia is associated with learning from positive and negative outcomes in patients diagnosed with major depression, schizophrenia and opiate use disorder alongside a healthy control group. Responses in the Wisconsin Card Sorting Test - a task associated with healthy prefrontal cortex function - were fitted to the Attentional Learning Model (ALM) which separates learning from positive and negative feedback. **Results.** Learning from punishment, but not from reward, was negatively associated with anhedonia beyond other socio-demographic, cognitive and clinical variables. This impairment in punishment sensitivity was also associated with faster responses following negative feedback, independently of the degree of surprise. **Limitations**. Future studies should test the longitudinal association between punishment sensitivity and anhedonia also in other clinical populations controlling for the effect of specific medications. **Conclusions.** Together the results reveal that anhedonic subjects, because of their negative expectations, are less sensitive to negative feedbacks; this might lead them to persist in actions leading to negative outcomes.

Keywords: anhedonia, learning, reward, punishment, computational psychiatry

INTRODUCTION

Anhedonia is a multifaceted construct that encompasses at least two different definitions: as "the inability to experience pleasure" (Ribot 1896) and "diminished interest in engaging in pleasurable activities" (American Psychiatric Association, 2013). Whereas the first is more etymologically correct, the second includes the anticipatory, consummatory and motivational underpinnings of the hedonic process that better describes the variety of manifestations of anhedonia in clinical practice (Treadway & Zald, 2011). Anhedonia in fact may be conceptualised as a transdiagnostic symptom (Husain & Roiser, 2018; Nusslock & Alloy, 2017; Trøstheim et al.,2020), central to the diagnosis of Major Depression Disorder (American Psychiatric Association, 2013), Schizophrenia (Strauss & Gold, 2012) and Substance Use Disorder (Garfield et al., 2013), associated with a range of harmful consequences including higher rates of suicide (Ducasse et al., 2018) and poor clinical outcomes across the lifespan (Cohen et al., 2020; Covinsky et al., 2014; Vinckier et al., 2017). Yet, despite this prevalence across a range of psychiatric disorders, it is not clear how anhedonia develops and persists (Craske et al., 2016). As a result, treatments targeting the various psychiatric disorders associated with anhedonia are often not effective or are only partially effective in alleviating anhedonia itself. Antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs) for example, do not usually lead to a significant reduction in anhedonia (Argyropoulos & Nutt, 2013; Cao et al., 2019). Identifying the underlying neurobiology that generates anhedonia like symptoms is therefore key to improving treatment and ultimately improve human wellbeing (Kieslich et al., 2021).

Gathering and integrating information from the environment results in a representation of reality that helps individuals make predictions and guides action towards rewards and away from harm (Sutton & Barto, 2018). Humans use feedback from the world to guide their actions (Taquet et al., 2020) and the process of action selection generally aims to choose actions that lead to the avoidance of aversive and/or the attainment of appetitive outcomes. In this guise, anhedonia could be conceived as a form of

maladaptive action selection (Lewinsohn, 1974) whereby actions that lead to net positive outcomes fail to be selected for as often as expected. This might arise due to alterations in the learning processes that govern how beliefs about the outcomes that actions lead to are adjusted following feedback. Namely, attenuated learning from positive feedback (such that actions learning to positive outcomes are repeated less), attenuated learning from negative feedback (such that actions learning to negative outcomes are repeated more) or some combination of these two.

Despite the clear theoretical relevance of learning from positive and negative outcomes to understanding the emergence and maintenance of anhedonia, to date the effects observed empirically are murky (Robinson & Chase, 2017; Huys & Browning, 2021, Pike & Robinson, 2022). Some authors found a specific impairment in learning from reward (Der-Avakian & Markou, 2012, Pizzagalli et al., 2005) but this effect has not been found consistently (Brolsma et al., 2020, 2021). Similarly results the relationship between anhedonia and learning from negative feedback are mixed with some finding a positive effect (Murphy et al., 2003) and others a negative one (Lawson et al., 2017). Other findings suggest learning in anhedonia is blunted for both rewarding and punishing stimuli (Chase et al., 2010; Steele et al., 2007) or related to a general inconsistency among choices (Huys et al., 2013; Robinson & Chase, 2017).

Most of the tasks employed to study reinforcement learning from reward and punishments are bandit-type tasks in which the participants learn policies for optimal choices based on their own outcomes (Daw et al., 2006) expressed as a monetary reward or loss (Halahakoon et al., 2020). These tasks however do not consider explicitly the role played by impairments in executive control and working memory (Collins, 2018) that are crucial when evaluating anhedonia. In fact, responding to hypothetical items in a self-reported questionnaire (e.g., Snaith-Hamilton Pleasure Scale, SHAPS) implies a certain ability in abstraction/mental representation and a preserved retrieval memory (Strauss & Gold, 2012),

cognitive functions that are impaired in schizophrenia (Khalil et al., 2022), depression (Zacková et al., 2021) and substance use disorders (Ramey & Regier, 2019).

In this study we seek to understand whether anhedonia is associated with increased or decreased sensitivity from negative and positive feedback in the context of a cognitive task. To do this we use the Wisconsin Card Sorting Task (WCST), a well-known task that measures inflexible persistence and abstract reasoning (Berg, 1948; Grant & Berg, 1948). Participants were presented with a card and asked to match it with four stimulus cards based on colour, shape and number of items displayed on each card. Based on feedback provided to them (right or wrong) following each choice, participants were expected to learn the underlying matching rule and then accurately sort each following card. Recently, the task has been used to infer learning from positive and negative feedback by examining participants trial by trial switch/stay decisions. The Attentional Learning Model (ALM) (Bishara et al., 2010, Cella et al., 2013; Farreny et al., 2016; Gläscher et al. 2019; Steinke et al., 2018) decouples learning from positive ("correct") and negative ("wrong") feedback and quantifies the rate at which attentional weights towards visual cues change in response to rewarding (i.e., "correct") and punishing (i.e., "wrong") feedback. In this study, we extend this approach by using the WCST in conjunction with the ALM to relate valenced learning to anhedonia severity. This enables us to identify and quantify how anhedonia relates to learning, and in particular whether anhedonia results in enhanced or attenuated learning following positive and negative feedback. We also relate response times (RTs) to the ALM parameters building on previous research that has shown that anhedonia is related to a failure in adjusting RTs following feedback (Steele et al., 2007).

The aim of the current study is twofold. First we evaluate how the ALM parameters which index learning from positive and negative feedback are associated with anhedonia severity in a sample of healthy controls and patients with a diagnosis of Schizophrenia, Major Depressive Episode and Opiate Use Disorders. Second, we investigate the association between RTs and ALM parameters. Based on the

assumption that more cognitively demanding processes require more processing time we hypothesise that subjects will be faster in responding after positive compared to negative feedback. In the WCST, negative feedback would suggest that the guessed matching rule is incorrect and then would require the participants to figure out a new matching rule also based on their previous attempts. We also expect RTs to be directly and positively related to the degree of surprise so that highly unexpected feedback is associated with slower RTs. Lastly we looked at whether greater levels of anhedonia are associated with a compromised adjustment in term of RTs following feedback through alterations in learning.

METHODS

Participants

We enrolled n=50 healthy control subjects with no history of psychiatric illness and n=141 patients seeking treatment at the outpatients' service of a public community-based mental health service in the North of Italy from 2014 to 2019. Inclusion and exclusion criteria are detailed in the **Supplementary I**. Both the healthy controls and the clinical populations came from a convenience sample.

Procedure

After signing an informed consent, the subjects underwent an interview during which socio-demographic data were collected. The study has been approved by the Local Ethic Committee (Comitato Etico Parma, PROT. Nr. 13235 del 14/04/2014). Diagnosed patients were also asked to state the time duration of their illness and their prescribed psychopharmacological treatment. Participants performed a computerised version of the Wisconsin Card Sorting Test (WCST) and filled out two questionnaires assessing state anhedonia (Snaith-Hamilton Pleasure Scale) and depressive symptoms (Calgary Depression Scale for subjects with SZ and Hamilton Depression Rating Scale for subjects with OUD and MDE, and healthy controls) (see **Supplementary I**). Both the healthy controls and the clinical populations were recruited as part of a broader project, aimed at describing the anhedonia(s) through self-report questionnaires in different clinical populations. Participants filled out three more

questionnaires to assess trait anhedonia (Physical Anhedonia Scale, Social Anhedonia Scale, and Temporary Experience of Pleasure Scale). A subset of these participants (which comprise the participants we include here for analysis) also completed the WCST. Separately each subject was tested on verbal learning and declarative memory (HVLT-R) and verbal (LNS) and spatial (SS) working memory (see **Supplementary I**).

Anhedonia Assessment

The Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) is a 14-item self-report scale used to assess physical and social anhedonia. The items assess 4 domains of the hedonic experience: interests-hobbies (items 1,4,9), social relationships (items 2,7,8,13,14), sensory experiences (items 5,6,11,12) and food related experiences (items 3,10). Each item provides four possibilities of response: "fully agree", "agree", "disagree" and "absolutely disagree". The classic scoring considers an attribution of zero points to both the affirmative answers, while for negative ones a point is awarded; the total score ranges from 0 to 14 points, where a higher score indicates greater severity of the hedonic deficit. The established cut-off to identify someone as anhedonic is 2. Because this scoring might result in a skewed distribution, in these analyses we adopted an alternative scoring (Trøstheim et al., 2020) where the four responses are rated on a four-point likert scale with a total score that ranges from 14 to 56.

Task

The Wisconsin Card Sorting Test (WCST), Computer version (Berg, 1948; Harris, 1990; Robinson et al., 1980;) is a computer test that measures cognitive domains such as the tendency to persevere, abstract thinking skills, and other executive functions – activities that are often impaired in individuals with frontal lobe damage.

The test is composed of four “stimulus cards”: a red triangle, two green stars, three yellow crosses and four blue circles, arranged on the top of the screen. At each trial the participant is faced with a new

"response card". The subject must guess the association between each of the response cards and one of the four stimulus cards, according to either colour, shape or number criteria. The computer program, at each attempt, will only say if the choice that the patient has made is right or wrong, without ever revealing the criterion (**Figure 1**). When the subject learns the correct rule, it remains identical for 10 consecutive trials, then the rule changes and the subject, blind to the rule change, has to understand the new rule. The test ends when the subject completes six categories, or all the cards have been used. The classic scores adopted in the WCST are detailed in the **Supplementary I**.

Figure 1. Schematic representation of the WCST

[Figure 1 here]

Note. *For the first trial, for example, the stimulus cards 1, 2 and 3 are plausible. The participant chooses the first card, matching the colour, however, the feedback tells the subject that the answer was wrong. At the second trial the participant knows that* ***colour*** *is a wrong match, so he/she can decide between number and shape. The subject chooses the second card, matching the* ***number****. This time the feedback tells him/her that the answer was correct. The subject should keep this rule for the following trials, every 10 trials the rule changes and the participant has to guess again.*

Statistical Analysis

After fitting participants trial by trial responses in the WCST task to the ALM (see **Supplementary II**), we examined how parameters from the model related to anhedonia severity indexed by SHAPS (where high scores indicate high anhedonia). To do so we built a series on linear model with anhedonia as the dependent variable and the ALM parameters, the classic scores at WCST, the cognitive tests and socio-demographic variables as predictors. In patients only we also control the association between the ALM parameters and anhedonia for the duration of illness and the medications (see **Supplementary III**).

After ascertaining which ALM parameter is specifically associated with state anhedonia we wanted to better understand the meaning of the ALM parameters in term of RT as a proxy of information processing.

To do so, we first computed two new parameters for each trial, namely surprise and valence. Surprise is reflected by the squared prediction error (PE^2) and it is a measure of how unexpected each feedback is. We choose a quadratic prediction error (PE) to increase the weight on more surprising outcomes (see details in **Supplementary IV**). Surprise here is a measure of rule-change and it's slightly different from the prediction error as usually considered in the reinforcement learning literature. Valence defines the feedback on each trial so that trials can have either a positive valence (coded as 1) if the feedback on a trial was "correct" and a negative valence (coded as 0) when the feedback was "wrong". We then build a mixed effect model to understand how long it takes for a subject to respond (RT) based on the previous trial's valence and surprise (see Supplementary). Because we were interested in clarifying what the reward and punishment sensitivity mean in relation to information processing, we entered the ALM parameters in the above model as a fixed effect interaction (see **Supplementary IV**).

Lastly, we looked at whether the association between anhedonia and RTs following feedback is mediated by the ALM parameters at an individual level (**Supplementary V**).

RESULTS

Participant characteristics are depicted in **Table 1 (see also Supplementary I)**.

[Table 1 here]

Association between the ALM Parameters and Anhedonia

After fitting all the participants trial by trial responses in the WCST task to the ALM, we examined how parameters from the model related to anhedonia severity indexed by SHAPS (where high scores indicate high anhedonia). Among the 12 sequential learning models, the smallest (best) mean BIC belonged to the model that constrained F=1, but allowed the other parameters (R, P, and D) to vary freely. This was the same as the best-fitting model identified in earlier work (Bishara et al., 2010) in a sample of healthy

subjects and patients with substance use disorder. The best-fitting model will be henceforth referred to as the attention learning model (ALM).

Results on models comparison, model fit and the validity of the parameters are detailed in the **Supplementary II**.

In our ALM, *R* and *P*, correspond to learning parameters for, reinforcing (positive) and punishing (negative) feedback respectively whilst decision consistency (*D*), defines the degree to which response probabilities are determined by the current attentional weights, similar to a softmax in reinforcement learning models of choice (Daw et al., 2006; Wilson & Collins, 2019).

Initially we examined the relationship between anhedonia with *R*, *P*, and *D* separately. This revealed that only *P* (gamma(189)=-0.112, 95%CI=-0.209, -0.016; p (uncorrected) = 0.022, p (corrected for multiple comparisons)=0.066), but not *R* (gamma(189)=-0.057, 95%CI=-0.177, 0.042; p=0.228) nor the *D* (gamma(189)=0.046, 95%CI=-0.056, 0.148; p=0.376), correlated negatively with anhedonia. In other words, greater learning from negative feedback (expressed by *P*) was associated with lower levels of anhedonia but was not associated with learning from positive feedback or decision consistency. The correlations between the *P*- and the *R*- parameters with anhedonia were significantly different from each other (difference=-0.308; 95%CI=-0.483, -0.097; z=2.858; p=0.004). Interestingly, despite anhedonia being a core symptom in the diagnosis of depression, P (nor R or D) was not associated with depression (*P* parameter G-K gamma(180)= -0.056, 95%CI=-0.154, 0.040; p=0.252; *R* parameter G-K gamma(180)= 0.022, 95%CI=-0.091, 0.134; p=0.699; *D* parameter G-K gamma(180)= -0.057, 95%CI=-0.170, 0.055; p=0.318). The association between *P* and anhedonia also remained significant when controlling for depressive symptoms (partial correlation r_p(179)=-0.145, p=0.05, VIF=1.013).

To further examine whether the relationship between anhedonia and the *P* parameter was stronger in any specific diagnostic group we looked at whether there was an interaction between the *P* parameter and the diagnostic group (diagnosis coded as 1=depression, 2=opiated use disorder, 3=schizophrenia and 4= controls, depressed as a referral category; df=183) in predicting anhedonia. There was no

significant interaction between the *P* parameter and the diagnosis (F=0.5037, p=0.478), nor an effect of the diagnostic group (F=0.0062; p=0.937). The *P* parameter, instead, was still significantly and negatively associated with anhedonia (F=4.478; p=0.0356; Estimate= -4.524; SE=2.22; t=-2.034).

Next, to control for collinearity between model parameters, we entered Anhedonia as the dependent variable in a linear model with all 3 parameters (P, R, D) as predictors. Of the 3 model parameters, *P* was the only significant predictor of anhedonia (Model 1a (187), beta=-0.195; p=0.017; VIF=1.185). Beyond the ALM parameters the association between anhedonia and the punishment sensitivity was still significant when controlling for and the classic scores at WCST (Model 1b (170); beta=-0.229; p=0.037, VIF=2.14), the cognitive tests (Model 1c (166), beta=-0.229; p=0.037, VIF=2.142) and socio-demographic variables (Model 1 (162), beta=-0.233, p=0.037, VIF=2.258). In the latter model gender was also negatively associated with anhedonia score (beta=-0.169; p=0.032) so that males were more anhedonic than females. This could be due to the sample (Table 1) in which males were more numerous than females. Details on each model can be found in the **Supplementary III**

To further test the robustness of the effect we used the 'model averaging' approach (Ossola et al., 2020). This approach involves first running every single combination of models given the independent variables. For example, running a model only with two of the variables, only three, only four and so on. Each time with a different combination of independent variables. Our original model (Model 1) included 15 variables, thus this involved running 32,767 nested models. Then the betas of each variable are averaged across all models, weighting them on the model's BIC (Bayesian Information Criterion) (Freckleton, 2011). This exercise revealed a significant effect of only the *P* parameters in explaining the anhedonia scores (weighted estimates = -0.117, 95% CI = -00259, -0.2081, see **Supplementary III**). Moreover, the best fitting model (out of 32767), according to the lowest BIC score was the one including only the *P* parameter as predictor of the anhedonia scores (BIC=508.43).

In patients only, to examine whether the association between the *P* parameter and anhedonia might be affected by medications or duration of illness we entered these as predictors in Model 1. We performed this analysis not as secondary results of any specific interaction between the *P* parameter and the diagnostic group (coded as 0=controls and 1=patients, see **Supplementary III**) but rather because controls have no information about the duration of illness or psychopharmacological treatments. Medications acting on dopamine and serotonin in fact can affect the information processing of valenced information (Vellani et al., 2020; Godlewska & Harmer, 2020). In the patient group only, again, the *P* parameter was still significantly associated with anhedonia even when controlling for the duration of illness and the medications (Model 1d (106), beta=-0.286; p=0.037; VIF=2.272 see **Supplementary III**) beyond the factors included in Model 1. Antipsychotics were also negatively associated with anhedonia score (beta=-0.240; p=0.028).

Lastly, to explore whether the relationship between anhedonia and *P* was different among the three diagnostic categories, we reran the same linear model this time interacting *P* with the diagnostic group (diagnosis coded as 1=depression, 2=opiated use disorder and 3=schizophrenia). When exploring the interactions between the *P* parameter and the diagnostic group (i.e. which patient group participants belonged to) these were not significant (depressed as a referral category, df=115; Opiate: Estimate= -1.84; 95%CI=-7.12, 3.44; p=0.492; Schizophrenia: Estimate= -3.60; 95%CI=-9.65, 2.46; p=0.242; Opiate**P* parameter: Estimate= 3.52; 95%CI=-4.27, 11.30; p=0.372; Schizophrenia**P* parameter: Estimate= 0.58; 95%CI=-6.84, 8.01; p=0.877) whereas the *P* parameter was still significantly and negatively associated with anhedonia scores (Estimate= -6.15; 95%CI=-12.32, 0.00; p=0.050). This supports the idea that the effect we find is related to anhedonia as a transdiagnostic symptom rather than pertaining to anhedonia in a specific clinical group.

Association between the ALM Parameters and the RTs

After ascertaining which ALM parameter is associated with state anhedonia we wanted to better understand the meaning of the ALM parameters in term of RT as a proxy of information processing.

To do so we explored how long it takes for each subject to make a decision, depending on how much the positive or negative feedback on the previous trial was expected. Specifically, we extracted trial-by-trial estimates of surprise (defined as the squared prediction error) from the ALM and examined how surprise and feedback valence (positive/negative) on the previous trial (trial t-1), related to RTs on the subsequent trial (trial t) (Model 2, see **Supplementary IV**). We hypothesised that surprising trials should be associated with longer RTs because (usually) surprise is generated when there is a recent rule change (either the current rule no longer applies generating a large negative surprise signal or a new rule has been identified generating a large positive surprise signal) necessitating cognitive processing as participants need to revise beliefs; when surprise is low, participants can generally opt to continue with their existing policy.

The regression revealed an effect of valence, an effect of surprise, and an interaction between the two (**Model 2, Figure 2, Supplementary IV,** df=13463). The effect of valence reflects that subjects were significantly faster after positive compared to negative feedback (t(190)=-13.56, p<0.001). The effect of the surprise reflects that, as expected, subjects were faster when trials were unsurprising compared to surprising (t(190)=8.294, p<0.001). The interaction between valence and surprise arises as subjects had similar RTs following surprising and unsurprising negative feedback (t(190)=-0.649, p=0.517, paired sample t-test) but were significantly slower following surprising positive feedback compared to unsurprising positive feedback (t(190)=3.128, p=0.002). This interaction is likely because whether surprise is high or low following negative feedback, participants are in “search” mode, attempting to examine what the rule has changed to and this is cognitively demanding. But the difference between high and low surprise following positive feedback likely has differing demands on cognitive resources as this is the difference between identifying a new rule following a period of search versus continuing with an existing one.

Figure 2. Interaction between valence and surprise in predicting the RT in the following trial in the whole sample

[Figure 2 here]

Note. *On the Y axis the z transformed RTs. Lower RTs mean faster responses. On the X axis the squared prediction error of the previous trial (t-1). Lower values of squared prediction error means that the trial was expected (i.e., easier). Higher levels suggest a more surprising trial. The moderating variable (M) is the valence of the previous trial (t-1). Hence the previous trial can be correct (blue -light grey-, positive valence) or wrong (red -dark grey-, negative valence)*

Next, we examined how these RT effects related to punishment sensitivity. Specifically, we entered the *P* parameter from the ALM – which quantifies sensitivity to negative feedback - in the lagged regression above. This revealed an interaction between valence and the *P* parameter (**Figure 3, Supplementary IV** df=13463). This was the result of at increasing levels of P, participants were slower in responding after a wrong trial compared to a correct trial. In other words, subjects with greater sensitivity to negative feedback (quantified via the *P* parameter) took longer to process negative compared to the positive feedback. This indicates that greater propensity to adjust one's own choice behaviour after receiving negative feedback is associated with slower time to process further stimuli.

Figure 3. Interaction between valence and the *P* parameter in predicting the RT in the following trial at varying levels of *P* parameter

[Figure 3 here]

Note. *On the Y axis the z transformed RTs. Lower RTs mean faster responses. On the X axis the P parameter. The colours reflect the valence effect so that in red -dark grey- is depicted the association between surprise and RT following negative feedback (wrong) and in blue -light grey- following a positive feedback (correct).*

The diagnostic group had no effect on the RTs analyses (see **Supplementary IV**)

Mediation effect of ALM parameters on the relationship between anhedonia and the RTs

Having found evidence that anhedonia was associated with reduced sensitivity to negative feedback (*P* parameter), and that the *P* parameter is associated with slower RTs following negative relative to positive feedback, next we evaluated whether the *P* parameter played a mediating role between anhedonia and RTs following negative feedback (see **Supplementary V** for further details). We found a significant mediating effect of P in the relationship between anhedonia and the RTs following a negative feedback (indirect effect(188)=-0.0024, BCa CI=-0.0060,-0.0001) (**Figure 4**). This suggests that greater levels of state anhedonia are associated with lower level of punishment sensitivity (Estimate=-0.0136; 95%CI= -0.023, -0.004; SE=0.005; t=-2.780 p=0.006). In turn, lower levels of punishment sensitivity are associated with faster response times following negative feedback (Estimate=0.1937; 95%CI=0.013, 0.374; SE=0.092; t=2.1167; p=0.035). The direct effect between Anhedonia and RTs following negative feedback was at trend (Estimate =0.0095; 95%CI= -0.001, 0.021; SE=0.005; t=1.703, p=0.0902) so we refrain from speculating further as to this relationship.

Figure 4. Mediation model

[Figure 4 here]

Note. *Standardised regression coefficient for the relationship between anhedonia and RTs following a negative feedback as mediated by learning from punishment. There was a significant indirect effect of anhedonia on RTs following negative feedback through learning from punishment controlling for RTs following positive feedback (indirect effect=-0,0024, BCa CI=-0.0060,-0.0001). *p<0.05*

Together, our results suggest that anhedonia is associated with a lower punishment sensitivity which leads to a dulling of post-error slowing (low RTs following negative feedback). Furthermore, in this sample the slowing of RT following errors was not influenced by how surprising the feedback was, suggesting that negative outcomes were overall perceived as expected by the participants.

DISCUSSION

Our results show that valence plays a key role in responses in the WCST and anhedonia. We first showed that high levels of anhedonia negatively related to sensitivity to punishment in the task and not with sensitivity to reward. In other words, highly anhedonic patients displayed a diminished responsiveness to negative outcomes and punishing feedback. We did not find an association between choice consistency and anhedonia. Next we showed that valence of feedback (i.e. whether feedback was positive or negative) interacted with surprise in predicting participants response times on the subsequent trial. Specifically, surprising feedback took more time to be processed than non-surprising in the case of positive feedback which was absent in the case of negative feedback. Interestingly response times following a wrong response was proportional to learning from punishment such that those that were less sensitive to negative feedback - often those with high levels on Anhedonia - were faster in responding after a wrong answer. Because slowing down after negative feedback was also inversely related to anhedonia we concluded that biased processing of information in a manner that supports negative expectations was linked to a greater inability to experience pleasure. This means that greater levels of anhedonia are associated with a faster response following negative feedback through an impairment in learning from punishment. That is, participants with higher levels of anhedonia are faster in responding following negative feedback as these are less surprising and do not lead to a physiologic post-error slowing.

Our results show that high levels of anhedonia negatively correlate with sensitivity to punishment but not with sensitivity to reward. In other words, highly anhedonic patients consistently display a diminished responsiveness to negative outcomes and punishing feedback, which is reflected in faster response times following negative feedback. We also did not find an association between choice consistency and anhedonia. Previous studies suggested that a greater response variability, often referred as temperature in a soft-max choice equation (Daw et al., 2006), is a key parameter driving

decision-making in anhedonia that leads to noisier more variable choices (Huys et al., 2013; Robinson & Chase, 2017).

Our results of impaired learning from negative feedback seems to contrast with the negativity bias theory of depression (Gotlib & Joormann, 2010; Watters & Willimas, 2011) according to which patients experiencing depressive symptoms, including anhedonia, weight more negative outcomes than positive one (Padrão et al., 2013; Alloy & Abramson, 1979). Under this theory, a diminished interest in engaging in pleasurable activities is then a consequence of increased learning from negative feedback.

Our results however are more in line with a reference-point dependent learning (Hunter & Daw, 2021; Palminteri & Lebreton, 2021) according to which pessimistic beliefs *precede* alterations in learning so that negative outcomes may conform to pessimistic expectations. For example, an outcome such as losing $1 can be perceived as a punishment if the average expected value from the environment is positive (+10$). The same outcome, however, when the environment is one in which negative outcomes are large and commonplace (e.g. the average expected outcome is -2$), is perceived as neutral or positive (Palminteri et al., 2015). Of note in the first case the prediction error, defined as the difference between the expected and the actual outcome, is greater than in the second case, leading to a greater integration of the information. Hence, under this setup, negative feedback sensitivity would be lower in anhedonic patients owing to prior pessimistic beliefs which reduce the impact of negative outcomes in changing behaviour. Because the hedonic tone results from the net engagement in pleasurable and unpleasurable activities (Fortunati et al., 2015; Huys & Browning, 2021), anhedonic subjects that persist in undesirable activities might lower their hedonic tone, perhaps in a vicious cycle that maintains or even worsens the anhedonia.

When testing these assumptions in clinical populations Vandendriessche and collaborators (2022) demonstrated that depressed anhedonic subjects do not differ from healthy controls in their ability to

learn from positive outcomes; negative outcomes, instead, seems to exert little effect of patient learning compared to positive ones with a general difficulty in updating negative expectation (Kube et al., 2020; Everaert et al., 2017). This behaviour could also be interpreted as an impairment in the Pavlovian instrumental bias. This cognitive bias suggest that healthy subjects find extremely difficult to approach a stimulus previously associated with punishment (Guitart-Masip et al., 2011). Pavlovian bias has been found reduced in depressed individual and negatively associated with the improvement in anhedonic symptoms (Huys et al., 2016).

This hypothesised mechanism is not conceptually different from the Learned Helplessness (LH) model of depression (Seligman & Maier, 1967). According to the LH model after being exposed to unpredictable aversive shocks animal show impaired escape learning even in new environment. Here, similarly, the perception of action-outcome independence generates a sense of uncontrollability that prevents subjects from actively avoid punishing outcomes in new situation (Lieder et al., 2013; Song & Vilares, 2021). More generally, these findings might be explained by the assumption that people routinely experiencing adverse responses in some areas of their life tend to expect failure in any other (Cecchi et al., 2021; Huys & Browning, 2021). This cognitive distortion would reduce their susceptibility to be affected by adverse events and, in turn, lead the anhedonic subject to persist in punishing behaviour. The fact that they might not learn to avoid punishment would result in a maladaptive behaviour that sustains a feeling of helplessness over the outcomes (Willinger et al. 2021).

The association between anhedonia and some WCST scores has been previously observed (Vogel et al., 2013; Franke et al., 1993; Barrantes-Vidal et al., 2003); however, due to the heterogeneity of the cognitive functions measured by the WCST (Steinke & Kopp, 2020), it hasn't yet been possible to provide a clear-cut interpretation of the results. The ALM parameters suggest that learning in anhedonic subjects does not occur according to the negative bias theory of depression; instead, punishment was associated with decreased learning and faster response times, due to pre-existing negative expectations.

The association between punishment sensitivity and anhedonia remained significant even after controlling for the classic WCST, suggesting that the ALM parameters offer additional information about underlying processes.

When entering socio-demographic variables, males were more anhedonic than females. This is in line with previous findings (Langvik et al., 2016) that show how men are usually more anhedonic than female whereas female are higher in neuroticism and depressive symptoms.

The association remained strong also when clinical measures were controlled for, such as illness duration and medications. Interestingly, no clinical measure was able to predict anhedonia except for antipsychotic medication that were associated with lower levels of anhedonia. This could be related to the patients' treatment. In fact, depressed subjects that are the most anhedonic (Trøstheim et al., 2020) are prescribed antipsychotics only when they show psychotic symptoms, and this was an exclusion criterion in our sample. Even though literature suggest that different clinical population might have qualitative different subjective experience of anhedonia (De Fruyt et al., 2020; Fortunati et al. 2015; Sussman & Leventhal 2014) we did not find any effect of the diagnostic group so that state anhedonia was negatively associated with punishment sensitivity in patients diagnosed with schizophrenia, depression or opiate use disorder. These results might be only apparently in contrast with previous literature that found specific impairments in learning from positive outcomes in major depressive disorder (MDD) (e.g., Mukherjee et al., 2020). Our approach is in fact dimensional and focused on anhedonia, whereas previous studies that compared patients with a diagnosis of MDD and healthy controls, might be more informative on the categorical nature of the disorder that, beyond anhedonia, can also include a constellation of symptoms such as sadness, pessimism, or guilt feelings. Future studies should probably employ tasks more specifically designed to disentangle the learning rate and the representation of the expected value for reward and punishment and explore the association of these

parameters with questionnaires aimed at evaluating social, physical anticipatory and consummatory anhedonia (Kangas et al., 2022).

Our results that response times after positive feedback are faster than after a negative one confirms previous results adopting the same task in healthy populations (Barceló 2003; Díaz-Blancat et al., 2018; Kopp & Lange, 2013; Lange et al., 2016; Lange & Dewitte, 2019; Steinke et al., 2021).

Trials in the WCST can be categorised in repeat trials, switch trials, and inference trials. Repeat trials are those that follow positive feedback. Switch trials are those that follow negative feedback. Inference trials are a sub-type of switch trials. Inference trials happen when the participant receives two consecutive negative feedbacks when the sorting rules change. In inference trials, the participants should in theory have all necessary information in order to infer the prevailing category by exclusion. According to our approach, inference trials should then be defined as trials with a negative valence and a low surprise. In line with our results that subjects are slower in responding to more surprising trials only when these follow a positive feedback, Díaz Blancat and colleagues (2018) noticed an effect of trial so that the responses on the first trial following positive feedback (i.e., higher surprise) were significantly slower than the second and third trials following positive feedback (i.e., lower surprise). Similarly previous studies failed in finding a difference in term of response times between switch and inference trials (Steinke et al., 2021; Lange et al., 2016).

More recently, by applying a reinforcement learning model to the WCST, Steinke and colleagues (Steinke et al., 2020 a,b,c) found that the model-based learning rate following positive feedback was significantly greater than following a negative one. Assuming that RTs are a direct proxy of information processing (De Boeck & Jeon, 2019), it is possible that our findings that RTs following negative feedback are not proportional to the squared prediction error is in fact due to a lower negative learning rate in our sample. **Limitations.** The current study is not free from shortcomings. First the cross-sectional design limits any conclusion on the causal relationship between punishment sensitivity and anhedonia. Future studies should test the hypothesis of anhedonia being causal to the impairment in learning from

negative feedback. Secondly when comparing patients against clinical population we can't rule out the effect of medications and duration of illness. Even though we controlled for socio-demographic and clinical factors future research should test this association directly. Lastly, we selected specifically three clinical populations in which anhedonia represent a core feature. Future research should also consider other clinical populations such as bipolar, eating and personality disorders in which impairments in the hedonic process, even though not diagnostic, are enduring and associated with global impairment (Trøstheim et al., 2020).

Here, when approaching the WCST we considered learning from negative feedback as a form of punishment which would be treated similarly to learning from negative outcomes. These, however, are three distinct aspects within the motivational learning theories that can hence be evaluated with different tasks.

A first fundamental approach is to distinguish between Pavlovian and Instrumental Control (Guitart-Masip et al., 2014; Yee et al., 2022). Pavlovian control refers to when a stimulus has a contingent relationship with an outcome, that can be either a reward or a punishment and it is independent from the agent response. Instrumental control, instead, is the determination of a behavioural outcome (i.e., response), that can be either an approach or an avoidance, in light of the contingency between the response and the outcome. In Instrumental Control hence the behaviour (approach or avoidance) is controlled by its consequences (reward or punishment). Based on this perspective, Behaviour and outcome can delineate four possible scenarios: positive reinforcement, the active approach following a rewarding stimulus; negative reinforcement, the active avoidance following the removal of an aversive outcome; reward omission, the passive approach due to the removal of the rewarding outcome; and punishment, the passive avoidance due to a negative outcome. Whereas the first two possibilities strengthen the responding, the second two associations weaken the agent response.

In this study we interpreted the learning from negative (i.e., wrong) feedback as punishment, relying on the assumption that in the WCST subjects should learn not to stick with the chosen rule. The WCST, however, not having an actual reward (i.e., money or a primary reinforcer) does not allow a clear-cut

distinction between punishment and negative reinforcement. The WCST structure and the impossibility to explicit determine the participants' reference point (i.e. expectations) (Pessiglione & Delgado, 2015) might also be the source of the discrepancy between our findings and previous literature in anhedonia in depression. Future studies adopting other hot-cognitive tasks that involves a reward (Roiser & Sahakian, 2013), should further dissect whether the impairment from learning from negative feedback observed in our sample also extend to other dimension of Instrumental or Pavlovian learning.

Conclusions. Summing up, we found that an impairment in punishment sensitivity, which is mirrored by a faster response following negative feedback, is associated with higher levels of anhedonia. The results are of theoretical and practical importance. First the findings suggest that anhedonia should be considered as separate from depressive symptoms and interpreted as a consequence of cognitive distortions rather than their cause. Second, the study suggests that negative expectation might lead the subjects to persist in actions leading to negative outcome. In doing so it helps clarify the relationship between information processing, motivational system and psychopathology. Treatment aimed at addressing anhedonia should hence focus on improving learning from negative feedback. Actual psychological treatments for anhedonia (Craske et al., 2019; Ito et al., 2021) focused specifically on fostering the reaching of positive stimuli. Our results suggest that cognitive behavioural approaches should also teach patients that actions that are perceived as overall leading to a negative outcome can be further dissected in smaller actions with mixed values. Learning to identify these smaller behaviours could help the patients in increasing awareness on the disorder and learning to avoid those specifically related to punishing behaviours.

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Table 1. Participants' characteristics

	Altogether n=191
Socio-demographic	
Age	42.57 (12.16)
Gender (n. female, %)	80 (41.9)
Work (n. employed, %)	149 (78)
Civil status (n. partnered, %)	82 (42.9)
ALM parameters	
Reward	0.733 (0.366)
Punishment	0.405 (0.416)
Decision	0.750 (1.429)
WCST scores	
Completed Categories (CC)	0.043 (0.027)
Perseverative errors (PE)	0.113 (0.103)
Perseverative errors (nPE)	0.169 (0.159)
Trial first category (TFC)	0.253 (0.207)
Failure Maintain Set (FMS)	0.010 (0.013)
Cognitive Measurement	
Declarative memory (HVLT-R)	21.44 (5.41)
Spatial Working Memory (SS)	14.08 (3.43)
Verbal Working Memory (LNS)	12.52 (3.51)
Psychopathology	
SHAPS	22.73 (6.08)
Depressive symptoms (z-scored)	0 (1)
HAMD (n= 133)	7.47 (8.93)
CDSS (n= 49)	2.82 (3.25)
Clinical variables	**Patients only (n=141)**
Illness duration in years	15.63 (11.18)
Medications	
Antipsychotic (n, %)	87 (61.7)
Mood Stabilisers (n, %)	29 (20.6)
Antidepressant (n, %)	71 (50.4)
GABAergic (n, %)	49 (34.8)
Opiate substitute (n, %)	22 (15.6)
Diagnosis	
Major Depressive Episode (n, %)	45 (31.9)
Opiate Use Disorder (n, %)	46 (32.6)
Schizophrenia (n, %)	50 (35.5)

Note. Number represents mean (SD) unless otherwise specified; n=12 subjects did not complete the cognitive measurements; n=9 subjects did not complete the depressive assessment. WCST=Wisconsin Card Sorting Test; HVLT-R=Hopkins Verbal Learning Test – Revised; LNS=Letter-Number Sequencing; SS=Spatial Span; HDRS=Hamilton Depression Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia

Highlights

- The process of action selection generally aims to avoidance aversive and/or attain appetitive outcomes.
- We fit an attentional learning model to the WCST in a sample of anhedonic subjects.
- Anhedonia is associated with a failure to learn and adjust one's decisions when actions lead to harm.
- Learning relates to anhedonia trans-diagnostically while controlling for other cognitive functions
- Patients hence persist in undesirable activities that lower their hedonic tone.

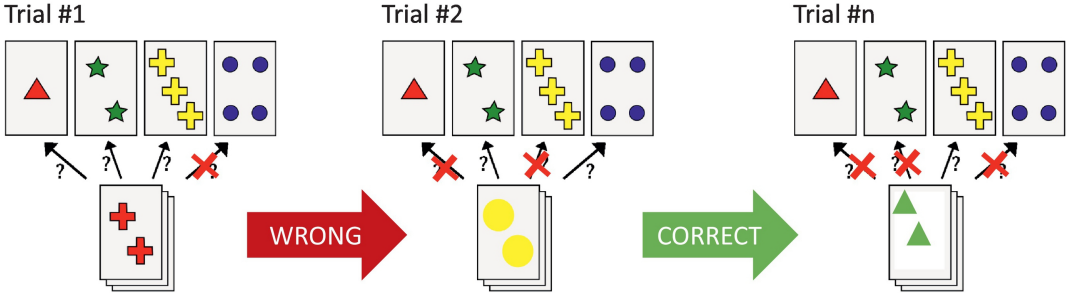

Figure 1

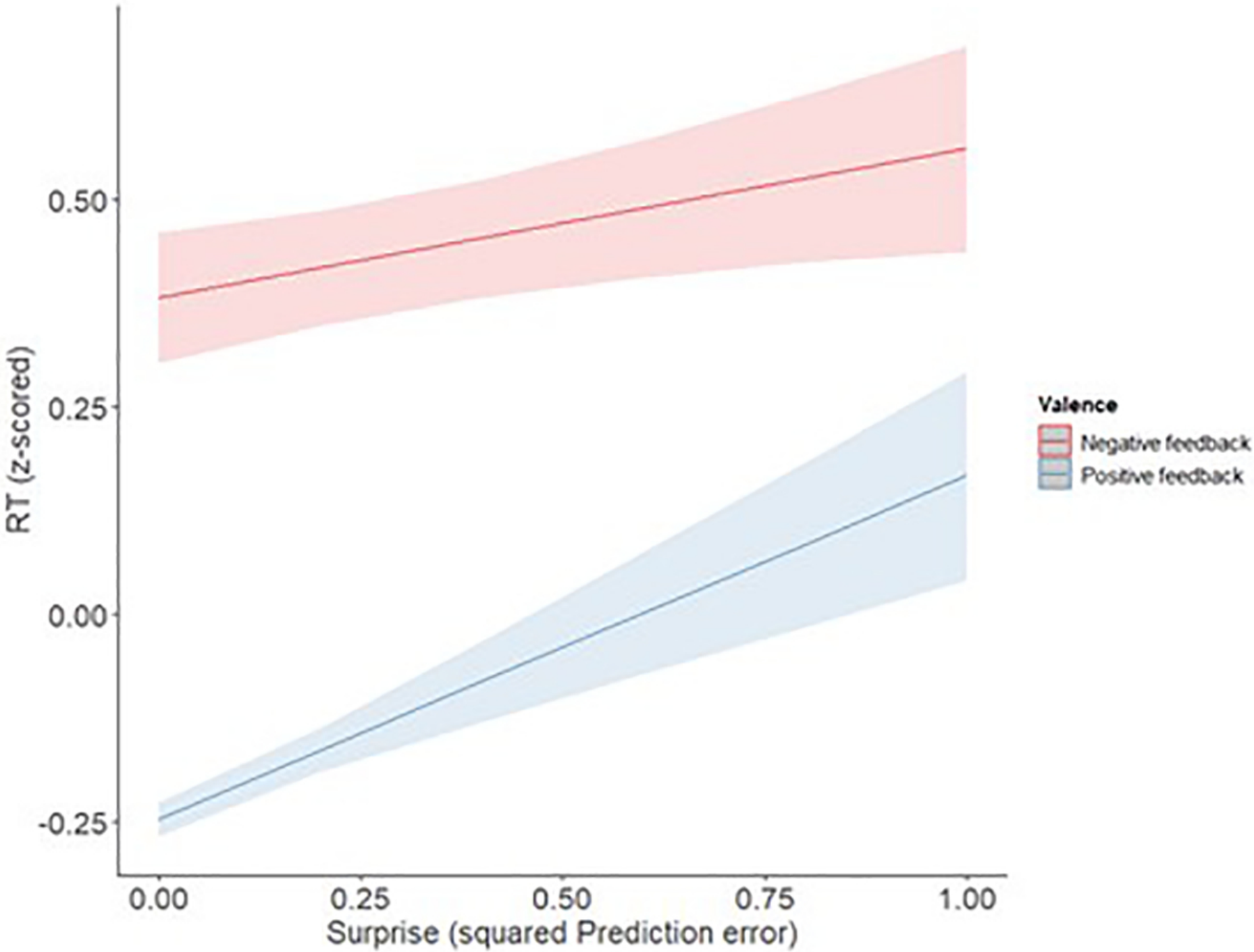
0.50
0.25
0.00
-0.25
RT (z-scored)
0.00
0.25
0.50
0.75
1.00
Surprise (squared Prediction error)
Valence
Negative feedback
Positive feedback

Figure 2

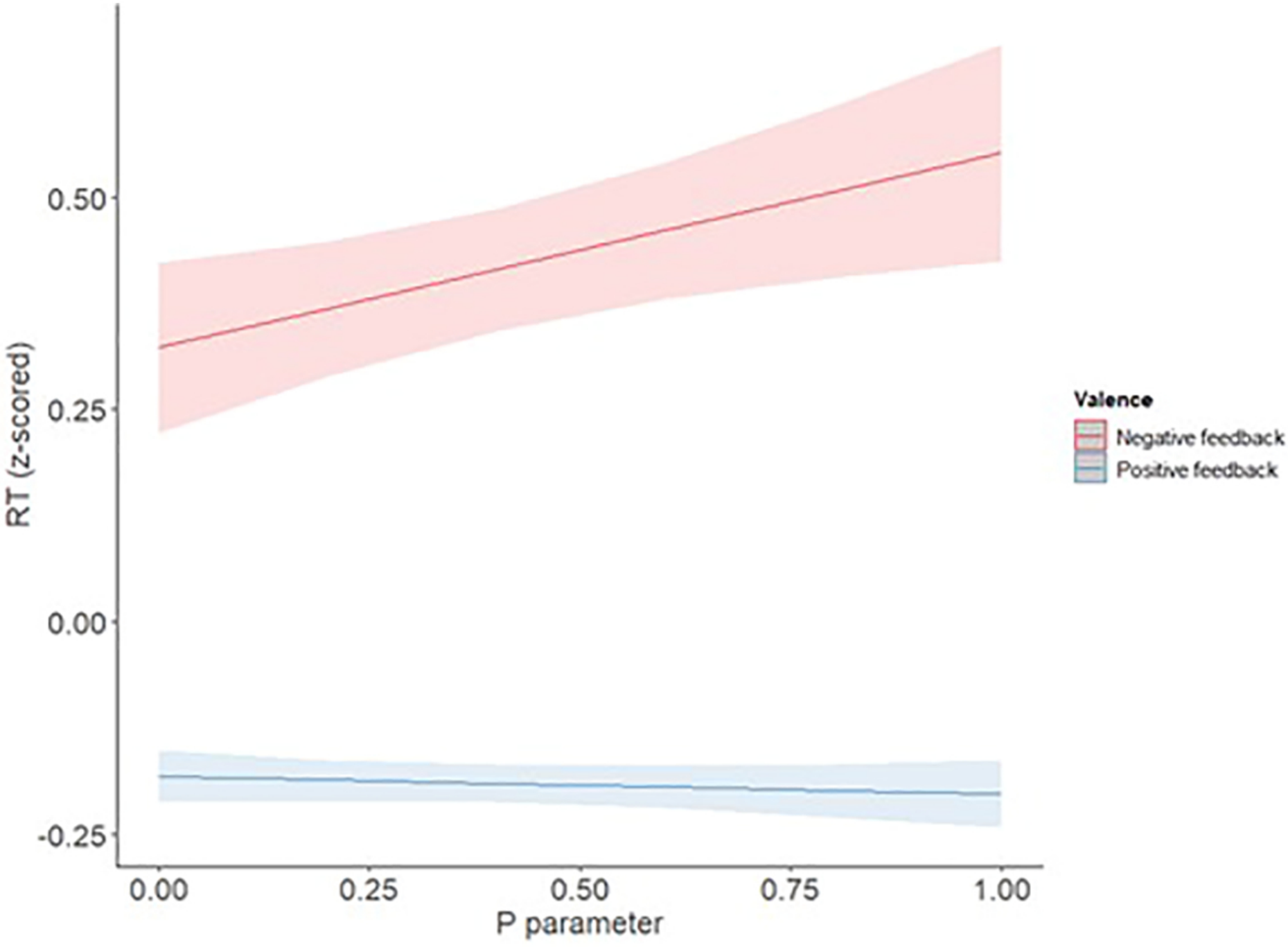
0.50
0.25
0.00
-0.25
RT (z-scored)
0.00
0.25
0.50
0.75
1.00
P parameter
Valence
Negative feedback
Positive feedback

Figure 3

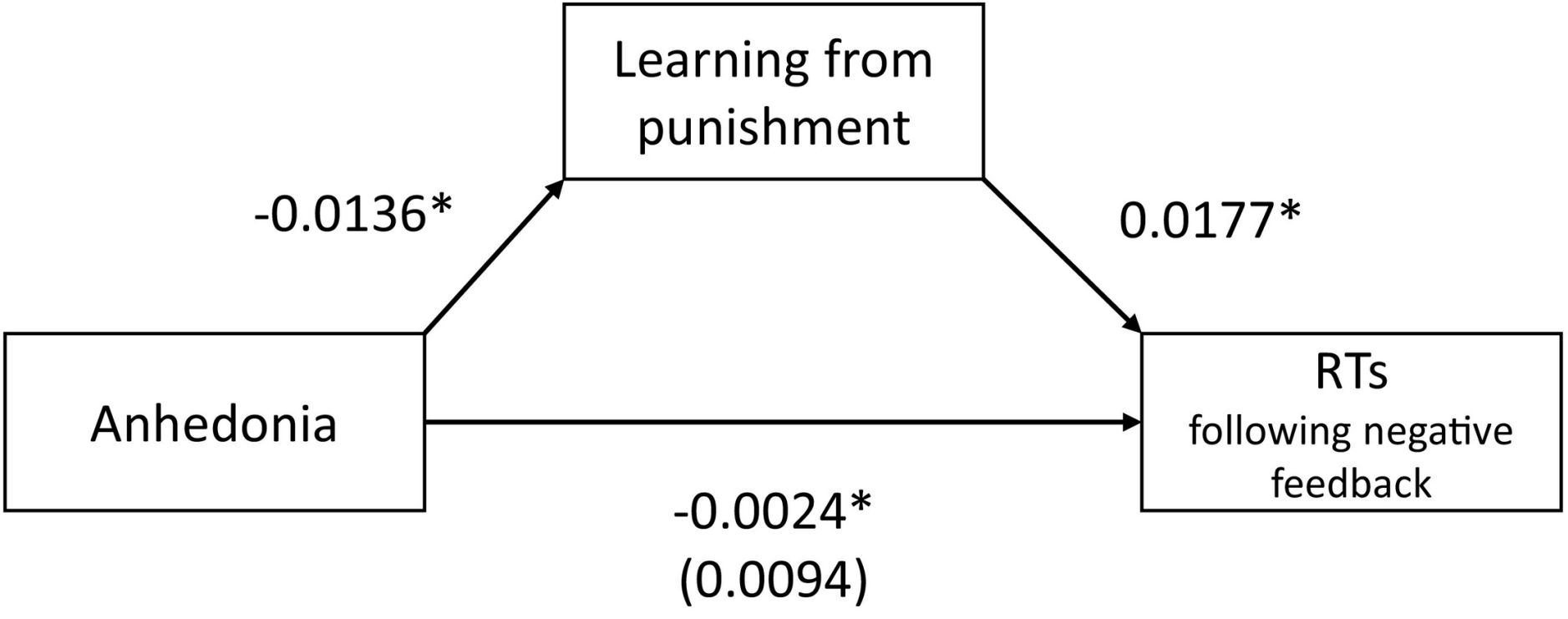
Learning from punishment
-0.0136*
0.0177*
Anhedonia
RTs following negative feedback
-0.0024*
(0.0094)

Figure 4