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Social Learning in Depression: Evidence from Computational Modelling, Neuroimaging, and Neurotransmitter Depletion

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Declaration

I confirm that this is my own work and that the use of all materials from other sources has been properly and fully acknowledged.

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Abstract

Major depressive disorder is commonly associated with altered processing of social stimuli, as well as with impaired learning from non-social outcomes. While a plethora of research has examined these aspects in isolation, few integration attempts have been made. That is to say, studies that examine *social* learning in depression and link task-based measures to real-life interpersonal experiences are lacking. Given that learning from social outcomes is crucial for successful interpersonal interactions, it is important to assess how this process may be affected in depression. The current work aimed to address this question, on both the behavioural and the neural level.

Specifically, study 1 explored task-based social learning in individuals with high (HD) and low (LD) depressive symptomatology and related learning parameters derived from computational modelling to reports of everyday social experiences. Study 2 extended this approach to the neural level, examining how the neural encoding of social learning signals is altered in HD subjects and how these alterations relate to real-life interpersonal experiences. Moreover, study 3 investigated the involvement of different neurotransmitters in the learning process by assessing neural and behavioural responses during social learning after dietary dopamine or serotonin (precursor) depletion in healthy volunteers.

It was found that HD individuals demonstrated deficits in social learning, which were associated with increased experiences of negative interpersonal encounters (study 1) and reduced social engagement motivation (study 2) in everyday life. In addition, HD subjects displayed altered social reward prediction signals in the insula, temporal lobe and parietal lobe, the latter of which were linked to decreased real-life social engagement motivation (study 2). Notably, the changes in social reward prediction encoding observed in HD individuals closely resembled those found in healthy subjects after serotonin depletion, while prediction-related dopamine depletion effects were mainly seen in frontal cortex areas (study 3). These findings suggest that depression symptoms are associated with impaired social learning responses, on both the behavioural and the neural level, which are linked to changes in real-life social experiences and may be underpinned by altered serotonin functioning.

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1 General Introduction

Major Depressive Disorder (MDD) is thought to affect 4.4% of the world population and is among the leading causes of global disease burden (Ferrari et al., 2013). The core diagnostic criteria for depression are sustained sad mood and loss of interest or pleasure in previously enjoyable activities (i.e. anhedonia). Other symptoms include weight loss/ gain, insomnia/ hypersomnia, psychomotor agitation/ retardation, fatigue, diminished self-esteem, decreased concentration, decision-making difficulties, and suicidal thoughts (American Psychiatric Association, 2013).

Depression is commonly associated with deficits in social processing (Kupferberg, Bicks, & Hasler, 2016; Rottenberg & Gotlib, 2008), as well as with altered learning performance (Chen, Takahashi, Nakagawa, Inoue, & Kusumi, 2015). However, there seems to be little integration of the evidence for these impairments, with most studies examining either learning-unrelated responses to social stimuli or learning from non-social feedback in MDD. Given that learning from social outcomes is crucial for successful interpersonal interactions, it seems particularly important to assess how social learning may be affected in depression. The current work aimed to address this question on both the behavioural (study 1) and the neural (study 2) level. Additionally, the involvement of neurotransmitters in social learning was investigated (study 3) to identify possible pharmacological treatment targets for the potential social learning deficits in MDD. Below, relevant studies on social processing and (mostly non-social) learning in depression are reviewed, and the involvement of different neurotransmitters in the learning process is highlighted.

1.1 Social Processing in Depression

1.1.1 Behavioural Studies

Major depressive disorder has been linked to a range of social factors. For instance, not having a close friend or partner to confide in is associated with an increased vulnerability to MDD (Brown, 1986), and the loss of an intimate relationship, through breakup or death, is a major trigger for depression onset (Kendler et al., 1995). In addition, experiencing interpersonal problems has been related to longer MDD episode duration (Brown & Moran, 1994), and perceived social criticism is predictive of depression relapse (Hooley & Teasdale, 1989). Moreover, depression chronicity has been linked to reduced social integration and the experience of more negative social encounters (Hölzel, Härter, Reese, & Kriston, 2011). Conversely, high perceived emotional support and large social networks appear to have a protective effect against developing depression (Santini, Koyanagi, Tyrovolas, Mason, & Haro, 2015), and greater interpersonal support is associated with better responses to antidepressant treatment (Trivedi et al., 2005).

Given the positive effect of social engagement, it is particularly problematic that depressed subjects commonly show signs of social withdrawal. Specifically, studies using a variety of methodologies, including self-report, interviews, and corroboration by family members, have found that depressed individuals have smaller social networks and spend less time with people in their social circle compared to healthy controls (Brim, Witcoff, & Wetzel, 1982; Gotlib & Lee, 1989; Rottenberg & Gotlib, 2008; Youngren & Lewinsohn, 1980). Moreover, withdrawn behaviour in children is a predictor of the development of depression in adolescence or adulthood (Caspi, Moffitt, Newman, & Silva, 1996; Ollendick, Greene, Weist, & Oswald, 1990), and reduced social network sizes are apparent even after MDD remission (Gotlib & Lee, 1989). Thus, social withdrawal appears to occur throughout the trajectory of MDD, making it a potential trait marker for depression and an important target for further investigation.

It has been proposed that social withdrawal in MDD may be linked to reduced (i.e. anhedonic) responsiveness to pleasant social interactions, or to heightened sensitivity to unpleasant social outcomes (Kupferberg et al., 2016; Rottenberg & Gotlib, 2008). That is to say, depressed subjects may withdraw from social situations because they do not find them pleasurable, or because they want to protect themselves from potential interpersonal rejection (Kupferberg et al., 2016). In line with this suggestion, individuals with depression symptoms demonstrate higher social anhedonia scores and expect to experience weaker positive responses to social situations than controls (Setterfield, Walsh, Frey, & McCabe, 2016). Moreover, MDD patients show reduced pleasure in response to peer approval (Davey, Allen, Harrison, & Ycel, 2011) and a negative association between depression symptom severity and positive responses to social acceptance feedback has been observed (Caouette & Guyer, 2016). Importantly, such signs of social anhedonia have been linked to heightened levels of social withdrawal (Silvia & Kwapil, 2011).

In addition, social withdrawal in depression may also be related to hyper-responsivity to negative social outcomes. Notably, depression symptoms are associated with increased expectancies of negative evaluations from others (Caouette & Guyer, 2016), and individuals with high levels of depressive symptomatology report expecting stronger negative responses to social situations than controls (Setterfield et al., 2016). Moreover, women with high, compared to low, rejection sensitivity have been shown to develop more depression symptoms in response to negative social outcomes (Ayduk, Downey, & Kim, 2001). Additionally, heightened expectation of peer rejection has been linked to subsequent social withdrawal, which, in turn, has been found to predict increases in depressive symptomatology (Zimmer-Gembeck, Nesdale, Webb, Khatibi, & Downey, 2016).

Given the above link between hyper-responsivity to negative social outcomes and social withdrawal, another factor that could contribute to social disengagement in MDD is the presence of negative biases in the interpretation of, and attention to, social cues (reviewed in Bourke, Douglas, & Porter, 2010). Specifically, it has been shown that depressed individuals

are more likely to classify ambiguous facial expressions as negative, and are less likely to categorise them as positive, compared to controls (Hale, 1998; Leppänen, Milders, Bell, Terriere, & Hietanen, 2004; Levkovitz, Lamy, Ternochiano, Treves, & Fennig, 2003; Surguladze et al., 2004). Further, it has been observed that the tendency to see sadness in ambiguous faces is predictive of depression maintenance at six months follow-up (Hale, 1998), and that ambiguous faces are perceived as less negative during MDD remission (Bouhuys, Geerts, & Gordijn, 1999; although lower classification accuracy of neutral faces persists; Leppänen et al., 2004). Moreover, individuals with and at risk for MDD demonstrate an enhanced ability to recognise fearful faces, while their recognition accuracy for happy faces is impaired (Bhagwagar, Cowen, Goodwin, & Harmer, 2004; Gur et al., 1992; Masurier, Cowen, & Harmer, 2007; Surguladze et al., 2004).

In addition, depressed individuals display attentional biases towards negative facial expression (see Peckham, McHugh, & Otto, 2010 for a meta-analysis including social and non-social stimuli). For instance, in a dot-probe task, in which a target is preceded by faces with different expressions, depressed subjects respond more quickly when the target is shown following a negative rather than a positive expression (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann, Talbot, & Gotlib, 2007; Leyman, De Raedt, Schacht, & Koster, 2007). Similarly, depressed participants demonstrate slower responses than controls when asked to detect a happy face in a 'crowd' of neutral faces compared to detecting a sad face (- an effect that is especially strong in individuals with comorbid anxiety; Suslow, 2005; Suslow et al., 2004).

While the above research did not link the observed negative biases to social withdrawal, other studies have examined responses to faces especially in relation to approach and avoidance behaviour. For instance, it has been found that depressed subjects demonstrate higher withdrawal tendencies than controls when shown an image of a face and asked how many steps they would take towards or away from the depicted person (Derntl et al., 2011; Seidel et al., 2010). Moreover, in a task in which a joystick needed to be pulled (signalling approach)

or pushed (signalling withdrawal/ avoidance) in response to happy or angry faces, depressed patients, unlike controls, did not show faster approach towards happy compared to angry faces (Radke, Güths, André, Müller, & de Bruijn, 2014).

The above evidence indicates that depressed subjects show reduced sensitivity to positive social feedback, such as peer approval and positive facial expressions, and increased responsiveness to negative social stimuli, like peer rejection and negative facial expressions, with some support for the suggestion that these factors are related to social withdrawal.

1.1.2 Neuroimaging Studies

In line with the behavioural findings, a range of neuroimaging studies have observed alterations in the neural processing of social stimuli in depressed subjects (reviewed in Stuhrmann, Suslow, & Dannlowski, 2011). For instance, during a gender classification task with faces displaying different emotional expressions, depressed individuals demonstrate higher amygdala, insula, cingulate gyrus, temporal lobe, fusiform gyrus and parietal lobe activity to negative faces than controls (Fu et al., 2008; Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012). Similarly, the presentation of masked negative faces has been shown to result in stronger amygdala, insula, medial frontal, medial temporal and fusiform gyrus responses in depressed compared to healthy participants (Sheline et al., 2001; Suslow et al., 2010). Notably, in both the gender classification and the masking paradigm, the emotional expressions were task-irrelevant (and in the second task subliminal). Thus, the increased responses to negative faces in visual and salience processing regions appears to be 'automatic' in depression, which is consistent with the behavioural findings of (involuntary) negative biases. Accordingly, it has been found that depressed individuals with high, compared to low, levels of negative biases show increased inferior frontal gyrus activation to task-irrelevant negative social (and non-social) scenes (in a visual search task; Gollan et al., 2015). The increased engagement of frontal regions may indicate an enhanced need for, or decreased efficiency of, a mechanism that downregulates the bottom-up processing of

negative stimuli. In line with this suggestion, functional connectivity studies have shown that PFC and ACC regions, which are thought to be involved in emotion regulation (Bush, Luu, & Posner, 2000), show decreased functional connectivity with the amygdala during facial processing in depression, potentially indicating an impaired downregulation mechanism (Chen et al., 2008; Dannlowski et al., 2009).

However, it should be noted that not all findings are consistent. Other studies using the gender classification task have observed *decreased* activity to negative faces in depressed compared to control participants in the amygdala, hippocampus, parietal lobe, superior frontal lobe and dorsolateral to medial prefrontal cortex (PFC; Fu et al., 2008; Lawrence et al., 2004). Similarly, in an emotion matching task, depression scores were found to be *negatively* correlated with dorsolateral PFC responses to angry faces (MacNamara, Klumpp, Kennedy, Langenecker, & Phan, 2017). A possible partial explanation for these inconsistencies is that the observed results may depend on what contrasts are used in the fMRI analysis. In particular, most of the above studies which found *increased* neural activation in depressed subjects contrasted negative faces (or scenes) with positive ones (Godlewska et al., 2012; Gollan et al., 2015; Suslow et al., 2010), while studies reporting *decreased* responses in depression used neutral faces or shapes as a contrast for negative stimuli (Lawrence et al., 2004; MacNamara et al., 2017). Notably, a study examining the neural response to facial expressions against baseline showed that, numerically, depressed subjects displayed bilaterally increased responses to *neutral* faces in the amygdala (Sheline et al., 2001). Thus, it is possible that the apparently decreased responses to negative stimuli in depressed subjects are, in fact, due to enhanced responses to the neutral contrast condition.

Additionally, which neural effects are observed in depression may also depend on the relevance of the emotional faces to the task. For instance, a review of facial expression processing studies in depression noted that most studies using subliminal or implicit processing of faces found abnormal amygdala activity in depression, whereas only half of the

studies using explicit emotion matching or emotion recognition paradigms did. This difference may partly be due to more cognitive processing during explicit tasks (Stuhrmann et al., 2011).

The above results indicate that depression is associated with altered neural processing of negative faces, although the direction and location of these neural effects depends on the utilised contrasts and paradigms. Similarly, evidence suggests that positive faces are processed differently in depressed compared to healthy individuals. Specifically, it has been found that, compared to controls, depressed subjects display reduced activity to happy faces in the striatum, amygdala, temporal lobe, insula, thalamus, and midbrain (Gotlib et al., 2017; Lawrence et al., 2004; Victor, Furey, Fromm, Öhman, & Drevets, 2010). These neuroimaging results are in line with the abovementioned behavioural findings of decreased sensitivity to positive social stimuli (i.e. social anhedonia) in depression.

Notably, the link between brain responses to positive social stimuli and social anhedonia has been directly examined with the use of a social evaluation task. In this task, subjects are shown photographs of strangers and asked to rate their liking of the depicted individuals. Additionally, participants are told that some of the depicted people have, in turn, rated whether they like the participant. In the MRI scanner, subjects are shown images of individuals who supposedly liked them, and whom they either liked or did not like in return, to assess brain responses to mutual compared to non-reciprocated liking. Using this task, it has been found that both higher social anhedonia and higher depression scores are associated with enhanced responses to mutual liking in the medial PFC, dorsolateral PFC and precuneus, as well as with stronger dmPFC - ventral striatum functional connectivity (Healey, Morgan, Musselman, Olino, & Forbes, 2014). Similarly, another study, which used the same paradigm to examine neural responses to the receipt of positive social feedback independent of the participants' own preferences, observed increased amygdala, insula, inferior parietal, inferior frontal, and temporal cortex activity to received liking in depressed compared to control participants (Davey et al., 2011). The authors of both studies propose that the observed findings may indicate that depressed subjects interpret positive social feedback more negatively than

controls, potentially because they expect that initial liking may eventually result in rejection. This negative processing signal may be downregulated by frontal regions, in line with the PFC – striatum connectivity results. However, it should be noted that, while the functional complexity of the task makes the findings difficult to interpret, the authors' suggestion does not appear particularly plausible. What is especially problematic is that the authors' argument relies heavily on reverse inferences based on the engaged brain regions, rather than an *a priori* functional definition of the task (see below).

The authors of the above studies further argue that the (suggested) enhanced negative interpretation of social feedback in depressed individuals may be linked to social withdrawal. While this was not examined by the above research, other studies have directly assessed the relation between neural responses to social cues and withdrawal behaviour. For this purpose, a paradigm was developed in which participants were shown images with emotional facial expressions and instructed to pull (signalling approach) or push (representing avoidance or withdrawal) a lever depending on the background colour of the image. In this task, depressed individuals, compared to controls, demonstrated decreased orbitofrontal cortex (OFC) responses to the avoidance (vs. approach) of angry faces, while their OFC activity was increased to the approach (vs. avoidance) of happy faces (Derntl et al., 2011). Notably, the region of the OFC in which group effects were found has previously been implicated in the anticipation of negative events (Kringelbach & Rolls, 2004). Consequently, the authors argue that the above results suggest that depressed subjects associate approach behaviour with potential negative outcomes (e.g. rejection), even in the presence of positive social cues (such as a happy expression). Moreover, depressed individuals may not be able to appropriately anticipate and engage with negative social cues, showing less adaptive withdrawal/ avoidance processing than controls (Derntl et al., 2011). Again, this interpretation relies mainly on reverse inferences.

The above findings indicate that depressed individuals demonstrate altered neural processing of both positive and negative social stimuli in a range of tasks, including gender discrimination,

emotion matching, social evaluation and approach-withdrawal paradigms. However, as mentioned above, for many of the utilised tasks it is not clearly defined which functions are engaged in either or both of the conditions that are contrasted in the fMRI analysis. Thus, many of the aforementioned result interpretations rely on reverse inferences based on the assumed function of the brain regions in which group effects were observed. This approach is somewhat problematic, especially because social cognition is complex and engages several functions that may partly be supported by the same brain area (Lieberman, 2006). Further research with functionally more well-defined tasks is thus called for. It may be particularly beneficial to utilise learning tasks with social outcomes, as learning mechanisms have been made explicit with the use of computational modelling, and social learning in depression is an important, but under-investigated, research area (see below).

1.1.3 Relation between Social Processing and Learning

It is noteworthy that in most of the above studies, especially in those using paradigms in which facial expressions were task-irrelevant, participants did not need to 'utilise' the social/ emotional information they were presented with. This stands in contrast to real-life situations in which emotional information is not merely passively or incidentally processed but is crucial to navigate the social environment. That is to say, in everyday life, individuals are actively engaged in social encounters, and it is possible that the very interaction of depressed subjects with other people may create situations that foster depressive behaviours (Joiner, 2000). A particularly interesting mechanism through which this may occur has been suggested by the behavioural theory of depression. This theory holds that reductions in pleasant and increases in unpleasant social experiences may partly be the result of depressed subjects' impaired ability to evoke positive responses from other people (Lewinsohn, 1974; Lewinsohn, Sullivan, & Grosscup, 1980). In other words, it is not merely the case that depressed individuals subjectively experience the social environment as more negative, but they may, though their own behaviour, be objectively exposed to more negative social encounters.

In line with this suggestion, previous studies have found that depressed individuals show less appropriate behaviour during social interactions than controls, as they make less eye contact, smile less, speak more monotonously, time their responses less fittingly, and are less likely to offer help to others (reviewed in Rottenberg & Gotlib, 2008 and Segrin, 2000; see also Setterfield et al., 2016). Importantly, inappropriate social behaviour has been shown to elicit fewer positive responses to, and even rejection of, depressed subjects by their interlocuters (Segrin & Abramson, 1994). The ability to elicit positive social feedback, which is based both on general social skills and on a more specific capacity to adjust behaviours to particular situations, is thought to be *learned* through repeated interpersonal interactions (Ladd & Mize, 1983). This raises the possibility that the increased (objective) experience of negative social interactions in depression may, at least partly, be the result of deficits in learning from social feedback.

Additionally, it is also possible that potential social learning deficits in depression may contribute to the *subjective* experience of the social environment as more negative. This could be the case because impaired learning may lead to increased uncertainty about what to expect from interpersonal encounters, and the association between uncertainty, which tends to be regarded as aversive by depressed individuals (Carleton et al., 2012), and social situations may make the latter appear more negative.

Based on the above reasoning, it could thus be hypothesised that potential social learning impairments in depression may contribute to the increased (subjective and objective) experience of negative social encounters and may, thereby, contribute to social withdrawal.

1.1.4 Summary

In summary, the studies discussed above indicate that depression is associated with social withdrawal, as well as with deficits in social processing, on both the behavioural and the neural level. Specifically, it has been found that depressed subjects have fewer close relationships and spend less time with people in their social circle than controls. This social disengagement

appears to be present before, during and after acute depression episodes and may contribute to the onset and maintenance of MDD. Moreover, social withdrawal may be linked to other social processing deficits observed in depression. For instance, depressed subjects demonstrate decreased pleasure in response to positive social outcomes (i.e. social anhedonia), expect more negative social feedback, and display negative bias in the interpretation of and attention to social cues (such as emotional facial expression). Additionally, on the neural level, altered responses in a variety of regions, including the amygdala, insula, temporal gyrus, precuneus and PFC, have been observed in depressed subjects in response to positive and negative social outcomes. However, the direction of these effects depends on the utilised fMRI contrasts and paradigms, and findings are often difficult to interpret due to the use of tasks that are not functionally well-defined. Moreover, links between task-based responses and everyday social behaviour are often not experimentally assessed, and many of the utilised paradigms involve only passive or incidental processing of social/ emotional stimuli. Given that in real life the active use of social information is necessary, it is important to consider how depressed individuals utilise and learn from positive and negative information to guide their expectations and behaviour. The limited available research on social learning in depression, as well as evidence relating to learning from non-social outcomes, is discussed below.

1.2 Learning in Depression

1.2.1 Behavioural Studies

Learning what outcomes to expect, either in response to one's actions or while passively observing a situation, is crucial for everyday functioning. This is particularly true for social situations, in which other people's responses need to be predicted to enable successful interpersonal interactions. As discussed above, it has been suggested that the impaired ability to elicit positive feedback from others, due to a lack of learned social skills, may contribute to the onset and maintenance of depression (Lewinsohn, 1974). However, despite this

theoretical motivation, the importance of social stimuli in everyday life, and the abovementioned evidence for impaired social processing in MDD, very few studies have examined learning from social outcomes in relation to depression.

The limited available evidence indicates that individuals at risk for depression may demonstrate reduced learning from positive social feedback, while showing enhanced learning from negative social outcomes (Pechtel, Dutra, Goetz, & Pizzagalli, 2013; Wiggert et al., 2017). The former evidence was obtained with the use of a signal detection paradigm, in which participants are asked to distinguish between two highly similar stimuli, while receiving more positive feedback for the correct identification of one of the stimuli. Using this task, it has been found that remitted depressed participants demonstrate reduced reward biases; i.e. they are less bias towards identifying a given stimulus as the one that is more highly reinforced, compared to controls. This effect was seen across monetary and purported social reinforcement (Pechtel et al., 2013). However, it should be noted that subjects were aware that the 'social' outcomes – the words 'Well done!' displayed on the screen – were computer-generated. It is thus questionable whether this feedback can be regarded as truly social.

More convincing social feedback was utilised by research assessing the relation between depression symptoms and social conditioning. In this study, participants were presented with pictures of a person with a neutral facial expression, followed by a short video of the same individual making a neutral statement (e.g. 'It's windy outside') or a negative comment about the participant (e.g. 'You're getting on my nerves'). One month after this conditioning phase, subjects were asked to rate their arousal in response to the neutral faces that had been displayed during the task. Interestingly, depression scores positively correlated with arousal ratings to the pictures of those individuals who had made negative statements during the task, indicating that the social conditioning effect may have been stronger in subjects who experienced more depression symptoms (Wiggert et al., 2017).

The above research provides limited evidence for an association between MDD (risk) and changes in learning from social feedback. In addition, there is a plethora of studies examining

learning from non-social outcomes in depression. For instance, using the same signal detection task as Pechtel and colleagues (2013) with monetary outcomes, a range of studies have observed reductions in reward biases in medicated (Fletcher et al., 2015; Liu et al., 2011; Vrieze et al., 2013) and unmedicated (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008) depressed participants. Moreover, decreased reward biases have been reported in individuals at risk for MDD, although these effects were only seen if subjects demonstrated high depression scores, and not if they were experiencing few depression symptoms themselves (Liu et al., 2016; Luking, Pagliaccio, Luby, & Barch, 2015).

At first sight, the above findings may suggest that deficits in learned reward biases are linked to acute MDD symptoms rather than to depression risk. However, it should be noted that impaired reward biases have been observed in remitted MDD patients, even when controlling for residual depression symptoms (Pechtel et al., 2013). Additionally, no alterations in reward biases have been found in individuals with subclinical levels of depression, although the severity of their symptoms was similar to that of a clinically depressed group which did demonstrate diminished reward learning (Liu et al., 2011). A potential explanation for the inconsistent findings may be that reduced reward biases are not related to depression symptoms in general, but are specifically linked to a lack of pleasure or interest in rewarding experiences (i.e. to anhedonia). This suggestion is in line with the observation that individuals at risk for depression who did *not* demonstrate impaired reward bias learning also did not show any signs of (anticipatory) anhedonia compared to controls (in questionnaire measures; Liu et al., 2011, 2016; Luking et al., 2015). By contrast, depressed individuals who displayed decreased reward biases demonstrated increased anhedonia levels compared to controls (Pizzagalli, Iosifescu, et al., 2008; Vrieze et al., 2013), and an association between heightened anhedonia scores and reduced reward biases has previously been reported (Huys, Pizzagalli, Bogdan, & Dayan, 2013; Luking et al., 2015). These findings highlight the importance of linking learning impairments to specific deficits or symptoms to aid the result interpretation.

Learning in MDD has been further examined with Pavlovian conditioning paradigms in which participants are presented with cues followed by positive, neutral, or negative non-social outcomes. In such tasks, no group differences in punishment learning were found with the use of explicit assessments such as outcome predictions or choices between the conditioned cues (Lawson et al., 2017; Robinson, Overstreet, Charney, Vytal, & Grillon, 2013). By contrast, implicit skin conductance measures have provided some evidence for enhanced punishment conditioning in MDD patients (Nissen et al., 2010), although other studies have found signs of reduced aversion conditioning in individuals with and at a familial risk for depression (Otto et al., 2014; Waters, Peters, Forrest, & Zimmer-Gembeck, 2014). These inconsistent findings may partly be due to variations in the utilised unconditioned stimuli (shocks vs. unpleasant tones) and differences in the tested samples (adult depression patients vs. children at risk for MDD). Further studies using systematic variations in stimuli and sample characteristics are needed to clarify under which circumstances implicit physiological conditioning responses are increased or decreased in individuals with or at risk for depression.

With regards to reward processing, Pavlovian conditioning studies have demonstrated reduced reward learning in both medicated and unmedicated depression patients, with patients providing less accurate contingency predictions during or after the conditioning phase than controls (Kumar et al., 2008; Robinson et al., 2013). However, it should be noted that not all studies have found group differences in Pavlovian reward learning (Lawson et al., 2017; Rupprechter, Stankevicius, Huys, Steele, & Seriès, 2018). Interestingly, there appears to be a relation between the utilised paradigms and the observed effects. Specifically, studies that showed impaired reward conditioning in depressed individuals used paradigms in which outcome contingencies changed throughout the task, while studies that observed no group effects utilised tasks with stable contingencies. It may thus be the case that Pavlovian reward conditioning in depression is particularly impaired in uncertain, unstable environments.

Further evidence for abnormal learning in depression comes from decision-making paradigms in which participants are required to choose between two or more options which probabilistically or deterministically yield positive, neutral, or negative outcomes. At least three different types of paradigms can be distinguished, namely magnitude-based, interleaved valence-based, and coupled valence-based tasks. In magnitude-based tasks, the different choice options are associated with varying outcome *magnitudes,* with rewarding and aversive outcomes being presented in separate blocks. Thus, throughout each block, participants only experience feedback of one valence, and their aim is to maximise or minimise the magnitude of rewarding or aversive outcomes, respectively. Moreover, in interleaved valence-based tasks, each option (or combination of options) is associated with neutral outcomes or feedback of one particular valence (e.g. rewards). In other words, for a given stimulus (combination), subjects can only receive neutral outcomes or feedback of *one* valence (i.e. rewards *or* punishments), although stimuli (combinations) that can yield rewards are interleaved with stimuli (combinations) that can yield punishments. Finally, in coupled valence-based tasks participants choose between options that are probabilistically associated with rewards and punishments. That is to say, for every stimulus (combination), subjects will obtain rewards on some trials and punishments on other trials, but the probability with which a given choice yields positive or negative outcomes differs between options.

Using magnitude-based decision-making tasks, it has been shown that individuals with high depression scores demonstrate enhanced punishment and impaired reward learning compared to controls (Beevers et al., 2013; Blanco, Otto, Maddox, Beevers, & Love, 2013; Cooper et al., 2014; Maddox, Gorlick, Worthy, & Beevers, 2012). Findings from these studies are generally consistent, except that Beevers and colleagues (2013), unlike the others, did not observe any group differences in reward learning. The authors argue that this may be the case because their task did not require much cognitive effort, and more automatic processing may not be impaired in depression. However, it is worth noting that reward learning deficits in depression have been found in another paradigm that presumably involved even less cognitive

effort than Beevers and colleagues' task (as it included only two instead of four choice options and more gradual magnitude changes; Blanco et al., 2013). Thus, other factors besides cognitive effort requirements are likely to play a role in the absence of group differences in the study of Beevers and colleagues (as further discussed below).

Contrary to the above observations, research examining learning performance with interleaved valence-based tasks has found no alterations in punishment learning in depressed subjects compared to controls (Johnston et al., 2015; Kumar et al., 2018; Wen Hua Liu, Valton, Wang, Zhu, & Roiser, 2017; Rothkirch, Tonn, Köhler, & Sterzer, 2017). Moreover, findings regarding reward learning are notably inconsistent: while some studies have observed impaired learning from deterministic and probabilistic rewards in MDD (Herzallah et al., 2013; Kumar et al., 2018), others have found no such reward learning deficits in depressed individuals (Bakker et al., 2018; Gradin et al., 2011; Johnston et al., 2015; Liu et al., 2017; Rothkirch et al., 2017). Rothkirch and colleagues (2017) argue that these inconsistencies may be due to variations in the medication status of the participants. Specifically, they suggest that the blunted reward learning observed in some studies may be the result of antidepressant treatment, given that past research has shown that commonly prescribed serotonergic antidepressants can reduce reward processing (McCabe, Mishor, Cowen, & Harmer, 2010). However, this argument is not consistent with findings of impaired reward learning in unmedicated depressed patients (Herzallah et al., 2013; Kumar et al., 2018). In fact, evidence from a study assessing medicated and unmedicated MDD patients with the same paradigm suggests that serotonergic antidepressants blunt punishment learning while leaving reward learning unaffected (i.e. impaired; Herzallah et al., 2013). Thus, an alternative explanation is needed to account for the above inconsistencies (see below).

Findings from research using coupled valence-based tasks are similarly inconsistent. For instance, impaired reward learning in subjects with high levels of depression symptoms has been found in some studies (Kunisato et al., 2012), but not in others (Cavanagh, Bismark, Frank, & Allen, 2011; Chase et al., 2010). However, it is noteworthy that the study which

observed group effects included a very short decision time limit (750ms) compared to the other studies (2500ms – 4000ms). Thus, as the authors concede, it cannot be ruled out that the group differences were driven by depressed subjects' inability to respond within the small time window due to motor impairments (which are commonly seen in depression; Caligiuri & Ellwanger, 2000).

The above findings of decision-making paradigms reveal that when group effects are found they quite invariably demonstrate impaired reward and improved punishment learning in depressed individuals compared to controls. However, an inconsistency arises from the fact that a range of studies do not find any group effects in learning from either valence. In this context, it is interesting to note that most paradigms which observed enhanced aversion learning in depression included separate reward and punishment blocks, while tasks in which no group effects were found incorporated positive and negative outcomes in an interleaved or coupled manner. A factor that may contribute to the inconsistent findings is, therefore, that in interleaved or coupled tasks participants are often instructed to maximise their winnings, while in paradigms with separate punishment blocks subjects are asked to minimise negative outcomes. Notably, it has been argued that task performance is optimised when the task goals are framed in a way that is in line with the participants' motivational state (Maddox & Markman, 2010). Given that depressed individuals are thought to be more motived by punishment avoidance than by reward seeking (Trew, 2011), it may thus be the case that the emphasis of aversion minimisation in tasks with separate punishment blocks facilitates aversion learning in depression.

Moreover, with regards to reward learning, a detailed comparison of the utilised tasks points to an intriguing possible explanation of why inconsistent results have been observed: across different decision-making paradigms, most studies that reported reward learning deficits in depression used high magnitude reinforcements, while studies that did not find any group effects utilised comparatively low magnitude outcomes (see Table 1). Two studies arguably do not fit this pattern. However, as discussed above, one of these studies may have found

group differences due to the use of unusually short decision-making times (Kunisato et al., 2012). Moreover, in the other study, different reimbursements were used for depressed and control participants, (namely a free analysis of an anatomical MRI scan, and money based on task points, respectively,) which could have influenced performance differentially (Liu et al., 2017). For all other studies, the abovementioned pattern holds, namely that larger, but not smaller, reinforcements were associated with group differences in reward learning performance. It is thus possible that individuals with or at risk for depression mainly demonstrate reward learning deficits when high magnitude outcomes are involved. This may be the case because reduced reward sensitivity in depression is particularly apparent for high reward magnitudes, or because healthy controls perform particularly well for high incentives, thus making group differences more apparent. This suggestion is in line with previous findings that healthy subjects enhance their performance as reward magnitudes increase, while depressed individuals show no such magnitude-dependent performance changes (Cléry-Melin et al., 2011).

It should be noted that the effect of reward magnitude may be specific to (explicit) decision-making tasks, as the abovementioned signal detection paradigm (in which more implicit learning biases are assessed) revealed reduced reward learning in depression even when small monetary rewards were used. Moreover, the observed pattern of findings leaves open the question of whether depressed individuals display impaired learning from social outcomes. This is the case because, on the one hand, social outcomes are not easily quantifiable, but, on the other hand, impairments in the processing of social stimuli have been observed in depression (as discussed above).

Table 1: *Overview of findings from decision-making tasks using differing outcomes*

Study reference	Reward learning deficits found in depression?	Rewarding outcome
Blanco et al., 2013	Yes	40-100 points
Maddox et al., 2012	Yes	40-100 points
Cooper et al., 2014	Yes	20-100 points
Herzallah et al., 2013	Yes	25 points
Kumar et al., 2018	Yes	10 Dollars
Kunisato et al., 2012	Yes	*10 Yen
Bakker et al., 2018	No	0.2 Euros
Rothkirch et al., 2017	No	0.5 Euros
Johnston et al., 2015	No	1 voucher
Beevers et al., 2013	No	0-10 points
Cavanagh et al., 2011	No	‘correct’
Chase et al., 2010	No	‘correct’
Gradin et al., 2011	No	2 drops of water
Liu et al., 2017	No	**50 points + smiley face

*The decision time limit was very short in this study (750ms).

**Healthy control participants were given money for these points, while depressed participants received an MRI scan analysis.

1.2.2 Computational Modelling Studies

The findings discussed above have given an indication that, under certain circumstances, depression is associated with reduced reward and enhanced punishment learning. However, learning relies on many subprocesses, including the formation and updating of outcome predictions, memory mechanisms, and the valuation of received rewards and punishments. Given that standard analyses do not provide any information as to which of these aspects may be affected in depression, computational modelling methods have been utilised to address this question.

Computational models (as used in psychology) provide a mathematical description of the sub-processes underlying a particular behaviour and give insights into individual differences in this behaviour through the use of mechanistically meaningful parameters. Specifically, models aiming to capture learning performance usually include the following steps: firstly, the prediction value of the available cues (i.e. of the conditioned stimuli or decision-making options) is initialised. This prediction value reflects how strongly a given cue is associated with positive or negative outcomes and it is commonly initialised at the midpoint between the largest and smallest possible outcome values. For instance, if the model codes rewards as 1 and punishments as -1, the starting prediction value may be set to 0, indicating that it is initially unknown which outcome a given cue is more strongly associated with. Secondly, once an outcome has been received (following passive observation or an active choice), a prediction error is calculated by subtracting the prediction from the outcome value. The outcome value may either be set to a fixed number for all participants (e.g. 1 for rewards and -1 for punishments) or it may be determined with the use of an individualised valuation parameter that represents the reward and punishment sensitivity of a given participant. Thirdly, the prediction value of the cue (/chosen option) that preceded the outcome is updated by adding the prediction error, multiplied by a learning rate parameter, to the previous prediction value. The learning rate determines how large the change in the prediction value is, with smaller learning rates resulting in smaller updates, and thus in the integration of prediction errors

across a larger number of trials. Moreover, if the received outcome was larger than expected, future prediction values will be increased, whereas if the outcome was smaller than expected, future prediction values will be decreased. In this way, predictions become increasingly accurate over time.

In addition to the above steps, models for decision-making (rather than passive conditioning) include a step in which a so-called softmax (or similar) function is used to calculate the probability of the participant's choices under the model. This sigmoidal function depends on a temperature parameter, as well as on the relative prediction values of the available options (which, in turn, depend on all other model parameters). The temperature parameter determines how close the prediction values of the available options need to be for the participant to reliably choose (i.e. exploit) the option with the higher value, rather than making exploratory choices of the alternative option. Given that the probability of the participant's choices under the model, as indicated by the softmax function, depends on all model parameters, the best fitting parameters for a particular participant can be determined by maximising this probability. Specifically, using an optimisation procedure such as gradient ascent, the log likelihood of the joint probability of the participant's choices across all trials can be maximised by strategically adjusting the model parameter values (until the global maximum of the log likelihood estimate is reached). This method reveals the learning rate, outcome valuation, and temperature parameters, as well as any additional parameters added to more advanced models, that are likely to underlie a given participant's learning performance (assuming an appropriate model was identified). These parameter values can then be compared between depressed individuals and controls to assess which aspects of the learning process may be impaired in depression.

Using this approach, a number of studies have found that depression is associated with altered model parameter values. For instance, the examination of temperature parameters has shown that depressed individuals make more *exploratory* choices than controls in coupled valence-based tasks, as well as in paradigms in which only rewarding and neutral outcomes are

present (Kunisato et al., 2012; Rupprechter et al., 2018). By contrast, in a punishment minimisation magnitude-based learning task, individuals with high depression scores displayed temperature parameter values that were indicative of increased *exploitation* compared to healthy volunteers (Beevers et al., 2013). However, it should be noted that whether exploration or exploitation is the better strategy depends on the task structure, and the above studies observed impaired reward and enhanced punishment learning performance in depressed participants, respectively (Beevers et al., 2013; Kunisato et al., 2012). Thus, it may be the case that depressed individuals' exploration behaviour is suboptimal during reward maximisation but not during punishment minimisation. This suggestion is supported by the previous finding that depressed subjects show particularly increased exploratory behaviour on reward trials on which exploitation would have been the ideal strategy (Blanco et al., 2013). Thus, alterations in learning performance in depression may partly be driven by the fact that depressed individuals make more random, exploratory choices when aiming to gain rewards, whereas they are able to exploit even small value differences to make optimal choices when aiming to avoid aversion.

In addition, several studies have reported reduced positive and increased negative learning rates in depression (Beevers et al., 2013; Chase et al., 2010; Cooper et al., 2014). These findings suggest that, compared to controls, depressed individuals adjust their predictions less when receiving outcomes that are better than expected and more when obtaining feedback that is worse than expected. Interestingly, this finding may be linked to negative attention biases in MDD, as training depressed subjects to attend to positive stimuli appears to 'normalise' their negative learning rates (Cooper et al., 2014). However, it should be noted that, contrary to the findings above, some studies have observed *decreased* negative and *heightened* positive learning rates in depressed subjects (Beevers et al., 2013; Chase et al., 2010; Dombrovski et al., 2010). Yet, again, it needs to be considered that as tasks (and models) differ, optimal learning rates will also vary. Notably, despite the differing directions of the learning rate results, the above studies consistently observed improved punishment and

impaired reward learning in depression (or no group effects). This implies that, compared to controls, depressed subjects' learning rates were likely more optimal when updating predictions based on negative feedback and less optimal when updating predictions based on positive outcomes.

Moreover, evidence from somewhat more advanced models with additional parameters suggests that depressed individuals show reduced memory-based integration of values over time, as well as increased punishment and decreased reward sensitivity (Byrne, Norris, & Worthy, 2016; Dombrovski et al., 2010; Huys et al., 2013; Mkrtchian, Aylward, Dayan, Roiser, & Robinson, 2017; Rupprechter et al., 2018). The latter findings are in line with the observation of negative biases and anhedonia in depression (as discussed in relation to social processing above; Kupferberg et al., 2016).

It is worth mentioning that a number of studies have not found any differences in model parameters between depressed and healthy individuals (Bakic et al., 2017; Kumar et al., 2008; Wen Hua Liu et al., 2017; Moutoussis et al., 2018; Rothkirch et al., 2017). In this context, it should be considered that parameter values are derived from the best fitting *assessed* model in a given study, but that this does not guarantee that the utilised model accurately captures the participants' learning processes. In some studies, a different (non-assessed) model, which may have yielded parameter group differences, may have been able to better account for subjects' learning performance. The latter criticism could, of course, be aimed at any computational modelling study, but extensive model validation can partly address this issue. For instance, the estimated model parameters can be used for data simulation to assess whether the simulated data captures the performance pattern observed in the participants' data. Moreover, fitting the model back to the simulated data can determine how well the utilised parameters can be recovered. Given that this type of validation was not conducted in some of the abovementioned studies, it cannot be ruled out that the use of inappropriate models may partly account for the lack of observed group differences in the model parameters.

All in all, the above studies suggest that some aspects of the learning process, such as the exploration vs. exploitation trade-off, prediction updating, or outcome sensitivity, appear to be altered in depressed individuals. The behavioural manifestations of these alterations are likely underpinned by changes in depressed subjects' neural processing during learning, which have been examined with the use of neuroimaging, as discussed below.

1.2.3 Neuroimaging Studies

As is evident from computational models described above, learning involves at least two crucial steps: firstly, at the time of the cue presentation, the predicted value of the available stimuli is assessed. This value is formed based on repeated associations between the stimuli and positive or negative outcomes. Secondly, at the time of the outcome receipt, the predicted and actual outcome values are compared and a prediction error (PE) is computed. The latter is then used to update the prediction value of the preceding stimulus to allow for a more accurate outcome prediction in the future. Moreover, decision-making (as opposed to passive, Pavlovian learning) additionally requires the selection of an action, such as the approach of one of several stimuli based on the predicted stimulus values.

A range of brain areas have been implicated in the above learning processes (e.g. reviewed in Ernst & Paulus, 2005; Khani & Rainer, 2016; Lee, Seo, & Jung, 2012). Specifically, a network of regions including the striatum, amygdala, insula, orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) is thought to be involved in the representation of prediction (/expected) values during cue presentation. In this network, the subcortical regions provide value representations which are integrated with other information, such as uncertainty and effort or delay costs, in the OFC and ACC (Bezzina et al., 2008; Croxson, Walton, Reilly, Behrens, & Rushworth, 2009; Holland & Gallagher, 2004; Palminteri et al., 2012; Rushworth & Behrens, 2008).

Moreover, the prediction error signal is thought to be computed in the midbrain, with the substantia nigra and ventral tegmental area (VTA) representing reward PEs and the habenula

encoding punishment PEs (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Cohen, Haesler, Vong, Lowell, & Uchida, 2012; Schultz, Dayan, & Montague, 1997). This PE signal is passed on to the hippocampus and striatum, where it is involved in memory acquisition and updating (Fernández, Boccia, & Pedreira, 2016) and value computation and action selection, respectively (Chase, Kumar, Eickhoff, & Dombrovski, 2015; Frank, 2006; O'Doherty et al., 2004).

It should be noted that the evidence for the varying roles of different brain regions in the learning process is mostly derived from animal research. As is evident in the findings describes below, this distinction may be less apparent in human neuroimaging studies. This is the case because brain areas encoding PEs likely receive inputs from prediction encoding regions, and vice versa (see section 1.3 for further details). This may lead to an overlap between areas found to encode prediction and PE values with the use of neuroimaging, especially given the low spatial resolution of functional magnetic resonance imaging and the fact that BOLD signals may reflect the *inputs* to specific areas (as represented in local field potentials; Logothetis, 2003).

Evidence suggests that in depressed individuals the above neural learning processes may be impaired. Only few studies report findings relating to neural prediction encoding, with most papers focusing on PE-related results. The little research assessing prediction signals has yielded somewhat inconsistent results. For instance, it has been found that during Pavlovian conditioning with electric shocks MDD patients display reduced punishment prediction representations in the habenula compared to controls (Lawson et al., 2017). Moreover, in a decision-making paradigm with water drop rewards, depressed individuals were shown to demonstrate lower reward prediction-related activity in the hippocampus and posterior parahippocampus than controls (Gradin et al., 2011). By contrast, no group differences in prediction encoding were observed during either conditioning or decision-making tasks when monetary outcomes were utilised (Lawson et al., 2017; Rothkirch et al., 2017). These limited findings suggest that depressed subjects may display abnormal neural prediction signals in

regions related to behavioural avoidance and memory encoding, but that these deficits may potentially be limited to primary (and not secondary) rewards and punishments.

Research into neural PE encoding in depression is somewhat more extensive. For instance, it has been found that medicated depressed subjects show reduced reward PE encoding in the ventral and dorsal striatum, the midbrain, and the hippocampus (Gradin et al., 2011). Moreover, higher self-reported depression scores in unmedicated individuals have been shown to be associated with decreased reward PE encoding in the NAcc and putamen (Bakker et al., 2018), while higher anhedonia scores in unmedicated depressed individuals appear to be correlated with lower reward PE signals in the medial OFC (Rothkirch et al., 2017). Moreover, medicated depressed patients have been reported to display decreased reward PE signals in the ventral striatum and in the dorsal ACC, while reward PE encoding in the VTA, rostral ACC, hippocampus, and posterior cingulate cortex (PCC) was shown to be *increased* when compared to controls. Notably, the heightened PE-related responses in the latter regions were due to reduced 'deactivation' in depressed subjects compared to healthy volunteers. The authors interpret these findings as indicating that PE signals are blunted in depressed subjects by arguing that increased 'deactivation' represents stronger PE encoding (Kumar et al., 2008).

The above suggestion is plausible, given that higher 'deactivation' indicates a stronger negative covariation between BOLD responses and model-derived PE values. However, these results raise the question of why the PE signal was negatively encoded in this study. In this context, it is worth considering that a negative covariation between BOLD responses and PE values that are computed by coding rewards as 1 and omissions as 0 is equivalent to a positive covariation between BOLD signals and PE values that are calculated by coding rewards as 0 and omissions as -1. Thus, it may be the case that the rostral ACC, hippocampus, and PCC (positively) encoded reward omission (i.e. 'punishment') PEs and that this signal was reduced in the depressed sample. By contrast, the ventral striatum and dorsal ACC may have encoded reward PEs (showing a positive covariation with BOLD responses) which were equally attenuated in MDD patients.

At first sight, the above proposal may seem to be inconsistent with previous findings of *enhanced* punishment PE signals in depression. Specifically, in an interleaved valence-based decision-making task depressed subjects have been found to display increased NAcc and substantia nigra punishment PE encoding (Liu et al., 2017). However, when considering the regions in which group effects were seen, it becomes apparent that enhanced or reduced punishment PE encoding in depressed individuals was mainly seen in areas with high dopamine or serotonin innervation, respectively (De Deurwaerdère & Di Giovanni, 2017). It may thus be the case that varying neurotransmitter deficits in depression may differentially affect punishment learning (potentially depending on the utilised task or the tested sample). This suggestion is in line with the distinct roles of dopamine and serotonin in the learning process, which are discussed in detail below (see section 1.3).

The above findings indicate that depressed individuals show impaired prediction representations in the midbrain and hippocampus (when primary outcomes are used), as well as altered PE encoding in regions such as the midbrain, striatum, hippocampus and ACC. It should be noted that, besides the above learning related research, there are a number of studies that have examined neural responses in anticipation and response to positive and negative outcomes using tasks with no learning component. An exhaustive description of these studies is beyond the scope of the current discussion which is focused specifically on *learning* in depression. However, some of these studies are relevant in the current context, as they have assessed neural prediction and PE responses (despite the lack of learnable associations). Using this approach, it has been found that depressed subjects show increased PE encoding in the rostral ACC and parahippocampus (Steele, Meyer, & Ebmeier, 2004), as well as marginally decreased prediction-related activity in the ACC (Chase et al., 2013), compared to controls. By contrast, prediction and PE representations in the striatum appear to be unaffected in depression when non-learning paradigms are used (Chase et al., 2013; Greenberg et al., 2015; Rutledge et al., 2017).

Based on the latter findings, it has been argued that PE computation *per se* is not impaired in depression. However, there are several issues with this interpretation. Firstly, it is not statistically valid to draw a conclusion based on the absence of group differences (as the null hypothesis of no group effects can only be rejected and not confirmed based on available evidence when standard, non-Bayesian analyses are conducted). Secondly, the depressed participants included in the above studies were medicated, which leaves open the possibility that antidepressant treatment may have 'normalised' striatal PE responses (although some learning studies have observed blunted striatal reward PEs in medicated patients; Gradin et al., 2011). Thirdly, while it is plausible that PE 'surprise' signals are present in non-learning contexts, these signals cannot be used to update future outcome predictions when there are no contingencies to be learned (which participants are aware of). Thus, the processing of PE signals may differ depending on the context in which they occur. Consistent with this suggestion, previous research has shown that striatal, hippocampal and frontal regions are differentially engaged depending on whether or not outcome contingencies are predictable/ learnable (Rodriguez, 2009; Tanaka et al., 2006). Therefore, it does not seem justified to draw conclusions about learning-related PE encoding in depression based on non-learning paradigms.

1.2.4 Summary

In summary, the above studies suggest that learning from non-social outcomes is altered in depression, on both the behavioural and the neural level. While some behavioural studies do not observe any group differences in learning, this appears to only be the case when the task goals are not framed in line with participants' motivational state, or when low magnitude rewards are used. Otherwise, behavioural studies have consistently demonstrated impaired reward and enhanced punishment learning in depressed compared to control participants. This finding is consistent with the broader literature indicating that depression is associated with reduced sensitivity to reward (i.e. anhedonia) and increased responsivity to aversion (as discussed in the context of social processing above; Kupferberg et al., 2016).

Furthermore, neuroimaging findings tentatively suggest that neural prediction encoding in depression may be especially impaired when primary outcomes are utilised, with group effects seen in the habenula and (para-)hippocampus for punishment and reward prediction, respectively. Moreover, depressed individuals display diminished reward PE signals in the dorsal and ventral striatum and dorsal ACC, as well as potentially blunted punishment (/reward omission) PE representations in the rostral ACC, hippocampus, and PCC. In addition, increased punishment PE encoding has been observed in the NAcc and substantia nigra of depressed subjects. As mentioned above, these seemingly inconsistent findings may be due to the distinct effects of dopamine and serotonin on punishment learning (which may be more or less apparent depending on the utilised tasks or the tested samples). It is thus important to gain a better understanding of the roles of these neurotransmitters in the learning process, which will also provide insights into how different pharmacological treatments may impact the learning deficits observed in depression.

1.3 Neurotransmitter Involvement in Learning

1.3.1 Role of Dopamine in Learning

1.3.1.1 Mechanistic Considerations based on Animal Studies

The neurotransmitter dopamine (DA) has been widely implicated in the learning process (e.g. see Watabe-Uchida, Eshel, & Uchida, 2017 for a review). Specifically, DA neurons are thought to be involved in the computation of outcome prediction and prediction error signals. Evidence for this suggestion comes from studies in primates and rodents showing that DA neurons demonstrate the following firing pattern during reward learning: initially, phasic DA activity is minimal when prediction cues are presented, while high DA firing rates are observed in response to (unexpected) rewarding outcomes, paralleling the presence of a large prediction error (PE). During learning, the DA response gradually shifts from the time of the outcome to the time of the cue presentation, mirroring the formation of outcome predictions and the decrease of reward PEs. That is to say, after cue-outcome associations have been learned,

many DA neurons fire in response to the predictive cue and show no phasic activity to the reward receipt, in line with the absence of PEs for fully predicted outcomes. Moreover, if an expected reward is omitted, DA firing drops below baseline at the time point when the outcome was predicted to occur, representing a negative PE signal (Schultz, Apicella, & Ljungberg, 1993). Thus, the response pattern of DA neurons closely resembles the computational modelling mechanisms described above (Suri & Schultz, 1999), which has been corroborated by several more recent studies (Day, Roitman, Wightman, & Carelli, 2007; Enomoto et al., 2011; Flagel et al., 2011; Hart, Rutledge, Glimcher, & Phillips, 2014).

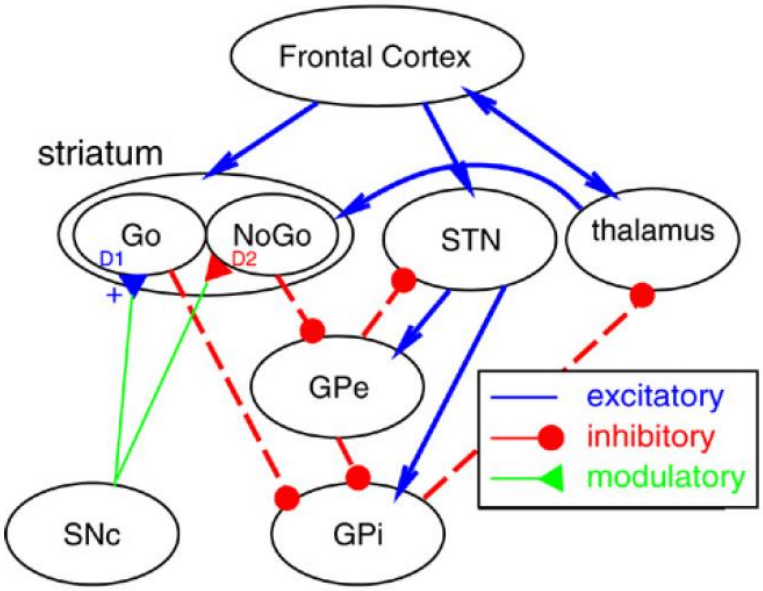
However, the mere fact that PEs are computed by DA neurons does not necessarily mean that these signals are utilised in a behaviourally relevant way during the learning of cue-action-outcome associations, as predicted by computational modelling. Evidence for a causal link between DA-mediated PE signals and associative learning has been provided by a number of animal experiments (Steinberg et al., 2013; Tsai et al., 2009; Witten et al., 2011). A particularly interesting example is a study showing that the optogenetic activation of DA neurons enables the association of new cues with fully predicted outcomes (thus eliminating the blocking effect). In this study, rats were conditioned to enter a port to receive a sucrose reward whenever a tone stimulus was presented. After initial learning had occurred, a light stimulus was displayed in addition to the tone before the reward was obtained. Crucially, in this phase, rats in the experimental group (but not those in the control group) received DA stimulation during reward receipt, simulating a PE signal. Following repeated pairings of the tone + light combination with the reward, the light was displayed on its own (not followed by any outcome) and the rats' tendency to enter the port in expectation of a reward was assessed. Notably, during the initial learning phase, the tone fully predicted the reward, which is why no DA-mediated PE signal occurred following the tone + light stimulus combination. Therefore, it was expected that control rats would not learn any associations between the light and the reward, thus demonstrating a blocking effect. By contrast, in the experimental group, the optogenetic DA neuron activation during reward receipt created the impression that a PE signal had occurred,

indicating the need for an update of the predictive value of the tone + light stimulus combination. Thus, rats in the experimental group were hypothesised to show learning of an association between the light and the rewarding outcome. In line with these expectations rats in the experimental group showed a higher tendency than controls to enter the reward port when only the light was presented (Steinberg et al., 2013). This study, as well as others (Tsai et al., 2009; Witten et al., 2011), suggests that DA-mediated PE signals appear to be causally involved in the learning of cue-action-outcome associations.

This raises the question of how this learning process is implemented; i.e. how dopaminergic PE representations are formed and propagated through the brain to initiate or inhibit actions. Evidence suggests that dopaminergic PE signals may originate in the midbrain where they are computed based on the integration of prediction and outcome information. Specifically, it has been suggested that, in the ventral tegmental area (VTA), the prediction signal may be encoded by sustained activity of gamma-aminobutyric acid (GABA) neurons, potentially based on inputs from the orbitofrontal cortex. This GABA signal may exert an inhibitory influence on reward-related DA activity if received rewards were expected, resulting in a PE signal (Cohen, Haesler, Vong, Lowell, & Uchida, 2012). In line with this suggestion, stimulating GABA neurons in the interval between cue presentation and outcome receipt results in reduced DA responses to the reward (as if it was more expected), while inhibiting GABA firing at this time leads to enhanced reward-related DA activity (as if the reward was less expected; Eshel et al., 2015). Similarly, GABAergic inhibition of DA neurons is thought to be involved in the negative PE signal following reward omission, with GABA neurons being excited by habenula neurons that are phasically activated by aversive outcomes (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Cohen et al., 2012). Thus, midbrain DA neurons seem to integrate excitatory reward information with inhibitory (GABA-mediated) prediction and aversion signals to ‘compute’ PE representations.

Moreover, the dopaminergic PE signal generated in the midbrain is thought to be propagated to other brain regions to be used for action initiation or inhibition in a decision-making context (see Frank, 2011 for a review of relevant models). The hypothesised trajectory of the PE signal though the brain has, for instance, been outlined in a computational model of the basal ganglia proposed by Frank, 2006 (see Figure 1). In this model, the dopaminergic PE signal is relayed from the midbrain to the dorsal striatum (DS). If this signal encodes a positive PE, associated with increased DA firing, a population of neurons responsible for 'go' responses in the DS is activated via DA binding to D1 receptors. In addition, a population of DS neurons responsible for 'no-go' responses is inhibited via DA binding to D2 receptors. The activation of the former population of neurons leads to the inhibition of neurons in the internal segment of the globus pallidus (GPi), which, in turn, disinhibits the inhibitory control this region exerts over the thalamus. The disinhibition of the thalamus, in turn, elicits the excitation of frontal cortical regions, such as the premotor area, and thereby facilitates action execution. Thus, positive dopaminergic PE signals, which may e.g. have resulted from a rewarding outcome that was received after a favourable choice, promote action (repetition). By contrast, if the dopaminergic PE signal relayed from the midbrain to the DS is negative, associated with a suppression of tonic DA firing, the abovementioned population of 'no-go' neurons in the DS is disinhibited via reduced DA binding to D2 receptors. This disinhibition in the DS leads to the inhibition of neurons in the *external* segment of the globus pallidus (GPe), which, in turn, elicits the disinhibition of neurons in the GPi. The latter, in turn, evokes increased inhibition of the thalamus and, thereby, decreases the excitation of frontal cortical regions such as the premotor area. Thus, negative dopaminergic PE signals, which may e.g. have resulted from an aversive outcome that was received after an unfavourable choice, inhibit action (repetition; Frank, 2006).

Figure 1*: Model of dopamine prediction error modulation of frontostriatal 'go' and 'no-go' pathways; from* Frank, 2006; *see text for details*



GPi: internal segment of globus pallidus; GPe: external segment of globus pallidus; SNc: substantia nigra pars compacta; STN: subthalamic nucleus

In line with the above model, animal studies have shown that the activation of D1 and D2 receptors in the dorsal striatum has differential effects, with the former resulting in increased behavioural preference and the latter in heightened avoidance. For instance, when provided with a choice between a touch trigger that has no effect and a touch trigger that induces optogenetic activation of D1 receptor expressing neurons in the dorsomedial striatum, mice express a preference for the D1-linked trigger. By contrast, when given a choice between an inactive trigger and a trigger leading to the optogenetic activation of striatal D2 receptor expressing neurons, mice avoided the D2-linked trigger (Kravitz, Tye, & Kreitzer, 2012). Similarly, in a task in which a cue is followed by a reward that is probabilistically delivered in a port on the left or on the right side, stimulation of D1 expressing neurons in the dorsal striatum biases mice towards choosing the port on the contralateral side to the stimulation. On the other hand, activation of striatal D2 expressing neurons biases mice towards avoiding the port contralateral to the stimulation side (thus inducing them to select the port on the ipsilateral side; Tai, Lee, Benavidez, Bonci, & Wilbrecht, 2012).

These findings (as well as the observations in humans described below) are consistent with the abovementioned model of the influence of dopaminergic midbrain PE signals on the basal ganglia. In addition, midbrain DA signals are also passed to other regions, such as the hippocampus, amygdala, hypothalamus, OFC and ACC, where they may impact the memory and emotional salience of unexpected outcomes (Bromberg-Martin et al., 2010).

1.3.1.2 Human Studies

The role of DA in learning has been further investigates by studies using DA manipulations in humans. Behavioural studies have found that low doses of D2 receptor *agonists* impair reward and enhance punishment learning in decision-making tasks (Frank & O'Reilly, 2006), while they reduce reward biases in signal detection paradigms (Pizzagalli, Evins, et al., 2008). By contrast, low doses of D2 receptor *antagonists* have been shown to increase reward and decrease punishment learning (Frank & O'Reilly, 2006; Jocham, Klein, & Ullsperger, 2011; Van Der Schaaf et al., 2014). The authors of the above studies argue that these (initially counterintuitive) findings are likely due to the binding of D2 agents to presynaptic autoreceptors when they are given in low doses, resulting in diminished or enhanced DA availability following the administration of D2 agonists or antagonists, respectively. Moreover, higher doses of D2 antagonists (presumably acting on postsynaptic receptors) have been found to evoke deficits in reward prediction and learning, as well as decreases in learning rates and increases in temperature parameters (indicating a tendency to make more exploratory choices; Diederen et al., 2017; Eisenegger et al., 2014).

Additionally, manipulations with more general (receptor unspecific) effects on DA functioning have yielded quite consistent results. For instance, enhancing DA levels with (meth-) amphetamines has been found to induce context conditioning, leading to the preference of a drug-paired over a placebo-paired location (Childs & de Wit, 2013; Mayo et al., 2013). Moreover, administration of the DA precursor levodopa has been shown to improve reward learning in both younger and older adults, as indicated by larger total wins and higher learning rates in decision-making paradigms (Chowdhury et al., 2013; Pessiglione, Seymour, Flandin,

Dolan, & Frith, 2006). Similarly, it has been found that Parkinson's Disease (PD) patients on, compared to off, levodopa (and D2 agonists) medication show enhanced learning from rewards, higher reward sensitivity and learning rates, and enhanced remembrance of reward contingencies (Coulthard et al., 2012; Frank, Seeberger, & O'Reilly, 2004; Rutledge et al., 2009). In addition, low levels of DA have been associated with improved punishment learning, both in PD patients off their medication and in healthy volunteers after DA precursor depletion (Cox et al., 2015; Frank et al., 2004; Robinson, Standing, Devito, Cools, & Sahakian, 2010).

Notably, the above findings of enhanced reward and punishment learning after increases and decreases in DA levels, respectively, are in line with the basal ganglia model of dopaminergic PE propagation described above (Frank, 2006). This is the case because high tonic DA levels result in a bias towards the excitation of the 'go' pathway (by reward-induced positive PEs), while low tonic DA levels lead to a bias towards the disinhibition of the 'no-go' pathway (by punishment-induced negative PEs – this mechanism has been formally confirmed with the use of computational modelling by Frank et al., 2004).

The basal ganglia model is further supported by findings from neuroimaging studies, with the most direct evidence coming from positron emission tomography (PET) research. For instance, older adults with reduced D1 binding potentials throughout the striatum have been found to demonstrate impaired reward learning, and D1 receptor availability in the striatum is positively correlated with reward learning performance (Cox et al., 2015; De Boer et al., 2017). In addition, fMRI studies have shown that enhancing DA levels with levodopa or low doses of D2 antagonists increases the encoding of reward PEs (and of unexpected rewards) in the striatum (Chowdhury et al., 2013; Jocham et al., 2011; Pessiglione et al., 2006; Van Der Schaaf et al., 2014). Conversely, lowering DA availability with DA precursor depletion has been found to decrease PE representations in the striatum, thalamus, and amygdala (Tobia et al., 2014). Thus, there appears to be a close relation between DA functioning and PE encoding (especially in the striatum).

With regards to prediction value representations, it has been observed that DA precursor depletion decreases reward prediction encoding in the striatum, thalamus, and midbrain (Tobia et al., 2014), while D2 antagonist administration enhances reward prediction representations in the ventromedial PFC (Jocham et al., 2011). The authors of the latter study argue that their findings may have resulted from a drug-induced shift to preferential D1 functioning in the frontal cortex, which has been found to lead to more stable stimulus representations than preferential D2 functioning (Jocham et al., 2011; Seamans & Yang, 2004). A similar argument has been put forth by a pattern classification study which observed that D2 antagonist administration, compared to placebo, resulted in a more accurate distinction between OFC activity patterns in response to reward-associated cues and reward-unrelated cues. The authors suggest that this effect may be due to reduced destabilisation of value representations after blocking of frontal D2 receptors (Kahnt, Weber, Haker, Robbins, & Tobler, 2015). Therefore, generally decreased DA levels and preferential D2 binding seems to be associated with reduced reward prediction value representations.

Contrary to the above findings, it has been reported that increasing DA levels via methamphetamine administration *reduces* PE and prediction encoding in the ventral striatum and vmPFC, respectively (Bernacer et al., 2013). The latter result is particularly surprising given that (somewhat) heightened levels of DA are thought to be associated with preferential D1 binding, which would be expected to *enhance* prefrontal prediction representations (Durstewitz & Seamans, 2008). A possible explanation for these inconsistencies is that the study may have included a participant sample with particularly high baseline levels of DA. Notably, the relation between DA levels and DA-related functioning is thought to follow an inverted U-shaped pattern, with both suboptimally low and suboptimally high levels of DA expected to result in impaired functioning (and preferential frontal D2 binding; Durstewitz & Seamans, 2008; see also below). This would explain the diminished prediction and PE encoding after methamphetamine administration, if participants had high baseline levels of DA.

Overall, the above studies demonstrate that (when starting from a 'normal/ average' baseline) higher levels of DA appear to facilitate reward learning, on both the behavioural and the neural level, while lower levels of DA seem to be associated with enhanced punishment learning.

1.3.2 Role of Serotonin in Learning

1.3.2.1 Mechanistic Considerations based on Animal Studies

Like DA, serotonin (5-hydroxytryptamine; 5-HT) is thought to be involved in learning. However, the mechanism underlying 5-HT's role in the learning process is much less well understood than that of DA (e.g. see reviews by Boureau & Dayan, 2011; Cools, Roberts, & Robbins, 2008). This is partly the case because it is difficult to target 5-HT neurons *in vivo,* which is why it has not been possible to examine the firing patterns of 5-HT neurons to the same extent as those of DA neurons (Cools, Nakamura, & Daw, 2011).

Nevertheless, theoretical accounts have proposed that 5-HT firing may encode *punishment* learning signals (Boureau & Dayan, 2011; Daw, Kakade, & Dayan, 2002), which may be relayed from the dorsal raphe nucleus to the amygdala, thalamus, hippocampus and the PFC (including the ACC; Moore, Halaris, & Jones, 1978). This suggestion is tentatively supported by a limited number of studies, if reward omission is regarded as an aversive event. For instance, during a saccade-based learning task, some dorsal raphe nucleus (DRN) neurons of rhesus monkeys show enhanced activity to cues that predict reward omission, as well as to the reward omission itself (Bromberg-Martin, Hikosaka, & Nakamura, 2010). Similarly, in a decision-making paradigm with probabilistic outcomes, some DRN neurons increase their firing rate when an expected reward is omitted (Ranade & Mainen, 2009), and, in a non-learning context, serotonergic DRN neurons respond to unexpected aversive events (Takase et al., 2004).

The above findings are consistent with the firing pattern that would be expected in neurons that encode punishment prediction and PE signals. However, it should be noted that the temporal trajectory of the firing was not assessed. Thus, it is not clear whether the neural

activity to the predictive cue increased and the (putative PE) response to the outcome decreased throughout the learning process, as would be expected from learning-related signals. Moreover, it is worth mentioning that not all recorded neurons in the above studies showed the same response pattern, and, importantly, in the former two studies it was not confirmed that the recorded neurons were serotonergic (although this is likely due to the large proportion of 5-HT neurons in the DRN; Moore et al., 1978).

While the above studies very tentatively support the notion that 5-HT neurons may encode a punishment prediction value, they leave open the behavioural relevance of this signal. Theoretical accounts have proposed that the 5-HT learning signal may, in interaction with DA, play a role in passive punishment avoidance, with some potential involvement in active escape behaviour. For instance, it has been proposed that serotonergic punishment prediction signals may result in the suppression of reward-seeking actions when there is a potential for aversive outcomes (which may be mediated by the inhibition of DA via 5-HT2C receptors; Dayan & Huys, 2009). This suggestion is in line with findings from reversal learning tasks in which animals are presented with a choice between two options and it is varied across time which of the options is more likely to yield a reward. Using this paradigm, a range of animal studies have reported that lower levels of 5-HT are associated with worse (reversal) learning performance (e.g. Brigman et al., 2010; Clarke, Walker, Dalley, Robbins, & Roberts, 2007; Izquierdo et al., 2012; Rygula et al., 2015; see below for human studies). More specifically, several studies have observed that 5-HT depletion (especially in the frontal cortex and amygdala) reduces punishment-induced behavioural suppression, leading to repeated choices of items that were initially rewarded but now result in (‘aversive’) reward omission (Clarke et al., 2007; Rygula et al., 2015). These findings may be taken to indicate that reducing serotonergic learning signals impairs the inhibition of reward-seeking behaviour in the presence of aversive outcomes (Dayan & Huys, 2009), which is consistent with a role of 5-HT in aversion prediction and passive avoidance.

Active avoidance, by contrast, has been argued to rely mainly on DA functioning, with only limited involvement of 5-HT. Specifically, while 5-HT firing may signal the prediction of an aversive outcome, the learning of active escape behaviour may be reinforced by a dopaminergic PE response which signals relief from (potential) aversion when an avoidant action was taken (Dayan & Huys, 2009). This suggestion is in line with observations demonstrating that passive, but not active, avoidance is affected by 5-HT manipulations (Lorens, 1978; Soubrié, 1986).

1.3.2.2 Human Studies

The role of 5-HT in learning and aversion prediction is further supported by human studies. For instance, it has been reported that 5-HT precursor depletion impairs punishment and reversal learning and increases the negative value of punishments in decision-making contexts (Rogers et al., 1999; Seymour, Daw, Roiser, Dayan, & Dolan, 2012; Tanaka et al., 2007). Similarly, acute doses of serotonergic antidepressants, which are thought to lower 5-HT levels due to increased 5-HT autoreceptor binding, have been shown to reduce reversal learning performance (Chamberlain et al., 2006; Skandali et al., 2018).

Moreover, in line with the animal literature, it has been found that 5-HT precursor depletion seems to specifically affect the passive prediction, but not the active avoidance, of punishments. This finding was obtained by presenting participants with differing proportions of blue and yellow squares and asking them to quickly indicate which colour was more prevalent. Crucially, in one condition, incorrect selections of one colour were punished, whereas incorrect choices of the other colour resulted in no outcome. In another condition, incorrect selections were never punished. While participants on placebo showed slower responses in the punishment condition than in the condition with no aversive outcomes, this difference was absent in the 5-HT depletion group. Notably, this effect was observed across all choices, rather than only being present when the punished colour was chosen. The authors argue that this finding indicates that 5-HT plays a role specifically in Pavlovian, rather than instrumental, punishment learning (i.e. in the formation of stimulus/state-outcome, rather than

stimulus-action-outcome, associations; Crockett, Clark, Apergis-Schoute, Morein-Zamir, & Robbins, 2012). This suggestion is consistent with the abovementioned proposal that 5-HT may be involved in the (passive Pavlovian) prediction of punishments, while DA may reinforce the (active instrumental) avoidance of potentially aversive outcomes (Dayan & Huys, 2009).

In line with the behavioural findings, neuroimaging studies have reported effects of 5-HT on neural aversion learning signals. Specifically, it has been found that 5-HT depletion results in reduced aversion prediction encoding in the OFC and amygdala in a Pavlovian conditioning paradigm (Hindi Attar, Finckh, & Büchel, 2012). Moreover, it has been observed that increased 5-HT functioning after repeated administration of serotonergic antidepressants is associated with stronger encoding of aversive (effort cost) PEs in the dorsal ACC (Scholl et al., 2017). These findings indicate that higher 5-HT functioning may be involved in the stronger representation of punishment learning signals.

However, it should be noted that not all findings are in agreement with the above notion. For instance, in a Pavlovian conditioning-based task in which participants were asked to predict whether a particular stimulus would be followed by a rewarding or an aversive outcome, 5-HT depletion has been found to *improve* punishment prediction (Cools, Robinson, & Sahakian, 2008; Robinson, Cools, & Sahakian, 2012). The authors initially argue that these results may have arisen because lower tonic levels of 5-HT after the depletion manipulation result in an enhanced signal-to-noise ratio, which, in turn, allows punishment PEs to have a stronger impact, leading to better punishment learning (Cools, Robinson, et al., 2008). However, the authors abandon this idea in a later paper, arguing instead that participants on placebo may make more errors during punishment prediction because they are more successful at inhibiting punishment-related thoughts than 5-HT depleted individuals (Robinson et al., 2012).

However, the above interpretations do not explain why previous studies have observed the opposite effect of 5-HT on punishment learning. A possible explanation of these inconsistencies is that the paradigms utilised in different studies may have differentially engaged 5-HT functioning. Notably, the task used by Robinson and colleagues could be

solved with a simple win-stay/ lose-switch strategy, while previous paradigms often involved probabilistic outcomes or other complexities that required learning in accordance with gradual (e.g. Rescorla-Wagner) reinforcement learning. Evidence from the animal literature suggests that these strategies may be differentially affected by 5-HT manipulations. For instance, it has been found that the optogenetic stimulation of 5-HT neurons in the dorsal raphe nucleus of mice increased the learning rate for a decision-making task condition that elicited gradual learning. By contrast, no effects of 5-HT stimulation were seen in a condition that induced win-stay/ lose-shift behaviour (Iigaya, Fonseca, Murakami, Mainen, & Dayan, 2018). Although these findings do not directly explain why punishment learning was observed to be *enhanced* after 5-HT depletion in the studies by Robinson and colleagues, they raise the possibility that varying tasks may differentially engage 5-HT functioning. This may explain the diverging results revealed by the deterministic task utilised by Robinson et al. compared to (mostly) probabilistic paradigms used in previous research (that observed a relation between decreased 5-HT levels and *reduced* punishment learning).

Besides playing a role in punishment learning, 5-HT has also been implicated in reward learning. For instance, it has been found that low levels of 5-HT after precursor depletion or short-term administration of serotonergic antidepressants result in reduced (reward) prediction value representations in the dorsolateral and ventromedial PFC, the ACC and the precuneus, as well as in diminished reward PE encoding in the rostral ACC, putamen, and hippocampus (Kumar et al., 2008; Seymour et al., 2012; Tobia et al., 2014). Conversely, increasing 5-HT functioning with longer-term administration of serotonergic antidepressants has been shown to enhance the encoding of reward PEs in the ACC, ventromedial PFC, parietal cortex and (marginally) in the striatum compared to placebo treatment (Scholl et al., 2017). Thus, 5-HT appears to facilitate the representation of reward learning signals. The involvement of 5-HT in both reward and aversion prediction PE encoding has led some authors to argue that 5-HT firing may represent unsigned (salience) learning signals (Matias, Lottem, Dugué, & Mainen,

2017). Others have suggested that the serotonergic modulation of reward learning may be due to 5-HT's excitatory effect on DA neurons via 5-HT2A receptors (Seymour et al., 2012).

All in all, behavioural and neuroimaging studies in humans indicate that 5-HT enhances punishment learning, with some findings suggesting a faciliatory effect of 5-HT on reward learning.

1.3.3 Summary

In summary, both DA and 5-HT are implicated in the learning process. Animal studies suggest that DA neurons appear to encode a reward prediction and PE signal which causally contributes to the learning of cue-action-outcome associations. These reward PE signals may be generated in the midbrain through an integration of DA responses to primary rewards and inhibitory GABAergic activity following reward-predicting cues. From the midbrain, the PE signals may be passed on to the (dorsal) striatum, where a cascade of inhibition and disinhibition is triggered that results in the facilitation or inhibition of actions by positive or negative dopaminergic PEs, respectively. Potentially through biasing these processes away from 'go' and towards 'no-go' responses, low levels of DA appear to be associated with diminished reward and enhanced punishment learning. This theoretical account is supported by a range of behavioural and neuroimaging findings in humans.

While the mechanism through which 5-HT affects learning is less well understood, it has been proposed that 5-HT firing may encode punishment predictions which, potentially through inhibition of DA responses, suppress reward-seeking behaviour when aversive outcomes are expected. In line with this suggestion, a number of behavioural and neuroimaging studies have observed that lower levels of 5-HT are associated with impaired reversal learning, punishment prediction and PE encoding, especially in the frontal cortex. Additionally, some studies show that reduced 5-HT availability results in deficits in reward learning (representations), which may be due to a reduction in the excitation of DA via 5-HT2A receptors. Thus, low levels of 5-HT seem to be linked to reduced reward and punishment learning. Yet, it should be noted that

it has been widely acknowledged that there are many complexities and inconsistencies in the literature on 5-HT's involvement in learning which are not (yet) fully understood (Boureau & Dayan, 2011; Cools et al., 2011; Dayan & Huys, 2009). Thus, further research is needed to elucidate the role of 5-HT in the learning process.

1.4 Research Objectives

1.4.1 Examining the Link between Depression, Social Processing, and Learning

The discussion in sections 1.1 and 1.2 has highlighted that depression is associated with deficits in both social functioning and learning. Moreover, it was pointed out that there is a potential link between these impairments. Specifically, it was suggested that decreased learning from social outcomes in depression may lead to suboptimal social behaviour, which, in turn, may result in the receipt of more negative feedback from other people. Additionally, impaired social learning may lead to enhanced uncertainty about social outcomes, which may give rise to the subjective perception of social situations as being more aversive. Importantly, the (subjective or objective) experience of more negative interpersonal encounters may contribute to social withdrawal, which is particularly problematic because social disengagement has been implicated in the onset and maintenance of depression.

As described above, a plethora of research has examined the impact of depression on social processing, social withdrawal and (non-social) learning in isolation. Yet, few attempts have been made to integrate these factors. That is to say, studies examining *social* learning in depression (and linking task-based measures to real-life social experiences) are lacking. It seems plausible that the core learning mechanisms (as posited by the abovementioned computational models; see section 1.2.2) underpin both social and non-social learning, and that these mechanisms may be altered in a similar manner for different outcome types in depressed subjects. Thus, based on the literature described in section 1.2, it would be expected that social and non-social *reward* learning is impaired in depression, *if* the utilised outcomes have a sufficiently high value (otherwise no group effects may be observed). This

deficit may be particularly pronounced when rewarding stimuli are paired/ interleaved with aversive stimuli, because (as discussed in section 1.1) depressed individuals display biases towards negative stimuli, which may impede reward learning by directing attentional processes away from positive outcomes.

At first sight, it appears plausible that the above mechanism may also enhance learning from negative outcomes in depression. Indeed, a negative attention bias may partly explain why previous studies have observed increased non-social punishment learning in depressed individuals (Beevers et al., 2013; Cooper et al., 2014). However, it is hypothesised here that a different process, namely rumination, may have a more dominant influence on *social* aversion learning. Given the strong link between negative interpersonal events and depression (as outlined in section 1.1), negative social stimuli may be particularly likely to induce rumination in depressed subjects (Watson & Andrews, 2002). This is likely to result in a distraction from the task, which may lead to *impaired* learning from negative social outcomes (Whitmer, Frank, & Gotlib, 2012).

In order to test the above hypotheses, and to examine how social learning relates to real-life social experiences, two studies were conducted. In ***study 1*** (reported in section 2), participants with high and low depression scores completed questionnaires about their everyday social interactions and performed a learning task with two other people. During the task, subjects repeatedly made choices between items for which they received positive, neutral, or negative feedback. In the social condition, participants were told that the feedback came from the other two people, whereas, in reality, it was computer-generated. A non-social condition with monetary outcomes was also added to assess the specificity of potential findings. A computational modelling approach was used to examine group differences in the mechanisms underlying the learning process, and model parameters were linked to real-life measures. It was hypothesised that, compared to controls, subjects with high depression scores would show impaired reward learning in the social and non-social conditions, while aversion learning was predicted to be enhanced (or unchanged) in the non-social condition

and reduced in the social condition (due to the abovementioned effect of rumination). In addition, it was expected that diminished social learning may be linked to decreases in the quality of real-life interpersonal encounters (based on the previous findings discussed in section 1.1.3).

These hypotheses were further investigated in ***study 2*** (reported in section 3) which extended the above approach to the neural level, with the aim of examining which neural processing abnormalities may underpin the social learning deficits observed in individuals with high depression scores in study 1. As part of study 2, participants with high and low depression scores completed a questionnaire about their everyday interpersonal experiences and performed a social learning task in the MRI scanner. During the task, name cues were presented followed by faces that probabilistically displayed happy, neutral, or fearful expressions. Subjects were asked to learn how likely it was that a given cue was followed by a positive or negative social outcome (/facial expression). A computational model was applied to the data to assess neural representations of social reward (happy faces) and aversion (fearful faces) prediction and prediction error signals. It was hypothesised that individuals with high depression scores would show impairments in behavioural and neural responses during social reward and aversion learning, and that these deficits would be linked to reduced social engagement in real life.

1.4.2 Examining the Link between Neurotransmitter Functioning and Social Learning

The observation of social learning deficits in individuals with high depression scores in studies 1 and 2 raised the question which pharmacological treatments may be suitable to alleviate these impairments. As discussed in section 1.3, two neurotransmitters that play a role in reward and punishment learning are dopamine (DA) and serotonin (5-HT). Crucially, these neurotransmitters have not only been implicated in learning, but also in the psychopathology of depression (Belujon & Grace, 2017; Nemeroff & Owens, 2009), as well as in social

processing (Kiser, Steemer, Branchi, & Homberg, 2012; Skuse & Gallagher, 2009; Steenbergen, Jongkees, Sellaro, & Colzato, 2016).

Study 3 (reported in section 4) therefore aimed to assess how altered DA or 5-HT functioning affects social learning, on both the behavioural and the neural level, to elucidate potential treatment targets for social learning deficits in depression. For this purpose, a dietary depletion manipulation was utilised which is a commonly used method to lower DA or 5-HT levels in healthy volunteers. This is achieved by giving participants a drink that contains a range of amino acids but is devoid of the precursor(s) of the neurotransmitter that is meant to be depleted (i.e. tyrosine and phenylalanine in case of DA, and tryptophan in case of 5-HT). Given that amino acids compete for uptake at the blood-brain-barrier, the consumption of this drink leads to decreased precursor availability, and thus to reduced DA or 5-HT synthesis, in the brain (Dingerkus et al., 2012). The efficacy of this procedure has been confirmed in animal and human positron emission tomography studies (McTavish et al., 1999; Montgomery et al., 2003; Nishizawa et al., 1997; Stancampiano et al., 1997).

As part of study 3, healthy volunteers were given one of the abovementioned dietary depletion drinks to lower DA or 5-HT levels (or they received a balanced placebo drink). After consumption of the drink, participants performed the same social learning task that was utilised in study 2 during MRI scanning. In the task, subjects were presented with name cues that were probabilistically followed by happy, neutral or fearful expressions and were asked to learn how likely it was that a given name was followed by one of the emotional expressions. Computational model-derived prediction and prediction error values were used as parametric modulators in the fMRI analysis to examine depletion effects on the encoding of social learning signals. It was hypothesised that on the behavioural and the neural level both depletion manipulations would impair learning from social reward (i.e. happy faces), while learning from social aversion (i.e. fearful faces) may be reduced after 5-HT depletion and enhanced following DA depletion.

2 Social Reinforcement Learning as a Predictor of Real-Life Experiences in Individuals with High and Low Depressive Symptomatology

[Study 1]

2.1 Abstract

Background: Several studies have reported impaired learning from *non-social* outcomes in depressed individuals (reviewed in Chen, Takahashi, Nakagawa, Inoue, & Kusumi, 2015); however, it is not clear how depression impacts learning from *social* feedback. Notably, mood disorders are commonly associated with deficits in social processing (Kupferberg et al., 2016; Rottenberg & Gotlib, 2008), which raises the possibility that potential impairments in social learning may negatively affect real-life social experiences in depressed subjects.

Methods: In the current study, 40 individuals with high (HD) and 52 subjects with low (LD) depression scores were tested. Participants performed a learning task during which they received monetary outcomes or social feedback (thumbs up/down) that they were told came from other people. Additionally, subjects answered several questions about their everyday social experiences. A computational model was applied to the task data and model parameters were related to social experience measures.

Results: HD subjects reported a reduced quality and quantity of social experiences compared to LD controls, including an increase in the amount of time spent in negatively perceived social situations. Moreover, HD subjects showed lower learning rates than LD individuals in the social (but not the monetary) condition of the task. Interestingly, across all participants, reduced social learning rates predicted higher amounts of time spent in negatively perceived social situations, even when depression scores were controlled for.

Conclusion: These findings suggest that HD subjects have an impaired ability to use social feedback to appropriately update future actions, which may be linked to their increased

reported experience of negative social situations. Specifically, social learning deficits in HD individuals may lead to suboptimal interpersonal behaviour, which, in turn, may evoke negative feedback from others. Additionally, impairments in social learning may increase HD subjects' uncertainty about what social outcomes to expect, which, if uncertainty is perceived as negative, may contribute to the report of more unpleasant social encounters.

2.2 Introduction

Major depressive disorder (MDD) is commonly associated with impairments in social functioning, including reductions in the quantity and quality of interpersonal interactions (Hirschfeld et al., 2000; Kupferberg et al., 2016; Rottenberg & Gotlib, 2008; Segrin, 2000; Segrin & Abramson, 1994). For instance, children who tend to withdraw from social situations have a heightened chance of developing depression as adults (Katz, Conway, Hammen, Brennan, & Najman, 2011), currently depressed individuals display impaired social skills and have fewer close relationships than controls (Brim et al., 1982; Gotlib & Lee, 1989; Lewinsohn, 1974; Segrin, 2000; Youngren & Lewinsohn, 1980), and deficits in social functioning persist even after recovery from MDD (Gotlib & Lee, 1989; Ladegaard, Videbech, Lysaker, & Larsen, 2016; Rhebergen et al., 2010). Conversely, high perceived emotional support and large social networks appear to have a protective effect against developing depression (Santini et al., 2015), and greater interpersonal support is associated with better responses to antidepressant treatment (Trivedi et al., 2005).

It has been proposed that depressed subjects may withdraw from social interactions, thus demonstrating a reduced *quantity* of social engagement, because they experience anhedonic or negatively biased responses to interpersonal encounters (Kupferberg et al., 2016; Rottenberg & Gotlib, 2008). In line with this suggestion, MDD patients have been found to derive less pleasure from peer approval than controls (Davey et al., 2011; Dedovic, Slavich, Muscatell, Irwin, & Eisenberger, 2016), and an association between heightened depression severity and diminished pleasure responses to social acceptance feedback has been

observed (Caouette & Guyer, 2016). Additionally, MDD symptoms have been related to increased expectancies of negative peer evaluation (Caouette & Guyer, 2016), as well as to the anticipation of weaker positive and stronger negative responses to social situations (Setterfield et al., 2016). Importantly, both elevated negative expectancies (Zimmer-Gembeck et al., 2016) and anhedonia (Silvia & Kwapil, 2011) have been linked to social withdrawal.

Besides displaying reductions in the *quantity* of social engagement, depressed subjects also demonstrate decreases in the *quality* of interpersonal interactions. For instance, experience sampling studies have shown that individuals with MDD symptoms encounter fewer positive (Bylsma, Taylor-Clift, & Rottenberg, 2011; Peeters, Nicolson, Berkhof, Delespaul, & De Vries, 2003; van Roekel et al., 2016) and more negative (Bylsma et al., 2011) social and non-social events than controls. It is obvious that anhedonic or negatively biased processing of pleasant and unpleasant social outcomes is likely to contribute to these findings. However, it is equally plausible that impaired learning from social feedback in MDD may play a role in the diminished quality of interpersonal encounters. Specifically, deficits in learning may diminish depressed subjects' ability to appropriately adjust their behaviour in response to social feedback, which, in turn, may bring about the experience of more unpleasant interpersonal encounters. Additionally, impaired learning may result in increased uncertainty about what social outcomes to expect, which, due to depressed subjects' tendency to regard uncertainty as negative (Carleton et al., 2012), may give rise to more negatively perceived social interactions.

Surprisingly, despite the importance of social stimuli in everyday life, research on learning from social outcomes in depression is lacking. One exception is a signal detection study which found a reduction in social reward biases in remitted MDD patients (Pechtel et al., 2013). However, in this study, subjects were aware that the 'social' outcomes – the words 'Well done!' displayed on the screen – were computer-generated. It is thus questionable whether this feedback can be regarded as truly social.

While there is little evidence regarding *social* learning in depression, a range of studies have examined learning from *non-social* feedback in MDD. For instance, in signal detection tasks with monetary outcomes, individuals with or at risk for depression fail to develop reward biases (e.g. Fletcher et al., 2015; Liu et al., 2016; Pechtel et al., 2013; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Vrieze et al., 2013). Moreover, depressed subjects demonstrate impaired reward maximisation, but, interestingly, enhanced punishment minimisation, in magnitude-based decision-making paradigms (Beevers et al., 2013; Blanco et al., 2013; Cooper, Arulpragasam, & Treadway, 2018; Maddox et al., 2012). Similarly, reward learning deficits have been observed in depressed individuals with the use of probabilistic and deterministic decision-making tasks that included interleaved positive and negative feedback (Herzallah et al., 2013; Kumar et al., 2018; Kunisato et al., 2012).

The above observations of altered learning in depression have been refined with the use of computational models, in which value representations of stimulus-action pairs are formed and updated using the difference between expected and actual outcomes (i.e. prediction errors). Fitting these models to participants' choice behaviour by adjusting model parameters allows for the assessment of group differences in various aspects of the learning process. Using this approach, it has been found that depressed individuals are less sensitive to rewarding outcomes (Huys et al., 2013) but more responsive to punishments (Byrne et al., 2016; Mkrtchian et al., 2017) than controls. Additionally, depression has been associated with alterations in learning rate (Beevers et al., 2013; Chase et al., 2010; Cooper et al., 2014; Dombrovski et al., 2010) and exploration (Beevers et al., 2013; Kunisato et al., 2012; Rupprechter et al., 2018) parameters, with results suggesting that depressed individuals' reward learning parameters are suboptimal.

The above findings indicate that depression is associated with altered learning from non-social outcomes. However, it is not clear whether these deficits extend to the social domain, and, if so, how they relate to everyday social experiences. The current study aimed to address this question. For this purpose, participants with high and low depression scores completed a

learning task with two other people. During the task, subjects made choices between party decoration items for which they received positive, neutral, or negative feedback. In the social condition, participants were told that the feedback came from the other two people, whereas, in reality, it was computer-generated. A non-social condition with monetary outcomes was also added to assess the specificity of potential findings. In both conditions, subjects' learning performance, as well as their negative expectancy biases, were measured. Additionally, participants completed questionnaires assessing their social anhedonia and depression severity and answered a number of questions about the quantity and quality of their daily interpersonal interactions. A computational modelling approach was used to examine group differences in the mechanisms underlying the learning process, and model parameters were linked to real-life measures.

It was hypothesised that, compared to controls, subjects with high depression scores would show deficits in learning from social (and non-social) outcomes. As described above, impaired social learning may lead to increased negatively-perceived uncertainty about social outcomes or to suboptimal interpersonal behaviour that elicits more negative feedback from others. Thus, it was predicted that, in the current study, impairments in social learning would be associated with decreases in the *quality* of real-life interpersonal encounters. Additionally, it was predicted that increased social anhedonia scores and negative social expectancy biases would be linked to reductions in the reported *quantity* of social engagement, based on the abovementioned relation between these constructs and social withdrawal.

2.3 Methods

2.3.1 Participants

The current study included 92 volunteers between the age of 18 and 45 years who scored below 8 (LD; N = 52) or above 16 (HD; N = 40) on the Beck Depression Inventory (Beck, Steer, & Brown, 1996). Some participants were tested at the university psychology department (N_{HD} = 20, N_{LD} = 30), while others performed the experiment online (N_{HD} = 20, N_{LD} = 22). This allowed for the collection of data from volunteers in different geographical locations with diverse backgrounds. The final sample consisted of participants living in the US (8%), Canada (7%) and the UK (85%). Of the HD subjects, 3% were Black, 20% Asian, and 78% Caucasian; 15% were employed, 30% unemployed, and 55% students in higher education. Of the LD participants, 8% were Black, 12% Asian, and 80% Caucasian; 31% were employed, 6% unemployed, and 63% students in higher education.

All participants were screened using an online version of the structured clinical interview for DSM-IV (SCID; adapted from First, Spitzer, Gibbon, & Williams, 1996). Given that the current study was focused more generally on individuals with depression symptoms, rather than specifically on those with clinical levels of MDD, the SCID was not used for diagnostic purposes, but merely to determine if any exclusion criteria were met. Specifically, LD volunteers were excluded if they reported a history of any Axis I disorder, and HD subjects were ineligible if they had ever experienced any Axis I disorder besides depression or low levels of anxiety (with anxiety symptoms being secondary to depression). Moreover, individuals in either group were excluded if they had taken any psychiatric medication in the past year or had used recreational drugs in the past three months.

Ethical approval for the study was obtained from the University of Reading Ethics Committee (2016-152-CM) and all participants provided informed consent. Subjects received £15 as reimbursement for their time.

2.3.2 Procedure

After completing the SCID, BDI, and a screening form, which assessed the general exclusion criteria listed above, eligible participants were asked to fill in the following questionnaires online: Temporal Experience of Pleasure Scale (TEPS, low scores indicate high anhedonia; Gard, Gard, Kring, & John, 2006), Revised Social Anhedonia Scale (RSAS, low scores represent low anhedonia; Eckblad, Chapman, Chapman, & Mishlove, 1982), Social Anxiety Questionnaire (SAQ, low scores signify low anxiety; Caballo, Salazar, Irurtia, Arias, & Hofmann, 2012) and a demographics form. Additionally, subjects answered a number of questions about their real-life social experiences, reporting how many friends they have, how close they feel to these friends, how much time they spend interacting with these friends, and how pleasant they find these interactions. Participants were also asked how difficult they find it to make new friends, and how much time they spend engaged in pleasant (e.g. going for dinner with friends or listening to music) and unpleasant (e.g. having a disagreement or doing chores) social and non-social activities.

Once participants had completed the above questionnaires, a testing session was scheduled. At the beginning of the session, all participants were asked to choose an avatar that would represent them during the task. Additionally, they were introduced to two other people with whom they would (purportedly) perform the task. These introductions included the other people's names, as well as some personal details, and took place online for the online participants and in person for those tested at the university. All participants then completed the task alone on an online platform.

Subjects were told that, as part of the task, they would be planning a party by making choices between party decoration items for which they would receive feedback. They were further instructed that, in the social condition, the feedback (thumbs up, horizontal, or down) was provided by the other people (in real time through the online platform), whereas, in the non-social condition, monetary feedback (wins, no change, or losses) was given by the computer.

In reality, the feedback in both conditions was computer-generated and, apart from the stimuli and feedback type, the social and non-social conditions were identical.

After each condition, participants were asked to rate how emotionally arousing they found the positive, neutral, and negative feedback. Moreover, at the end of the testing session, subjects indicated how sure they were that the feedback they received during the social condition came from other people (1 = very doubtful; 10 = very sure). Subsequently, participants were given a debrief sheet which clearly described and justified the deception involved in the study.

2.3.2.1 Learning Task

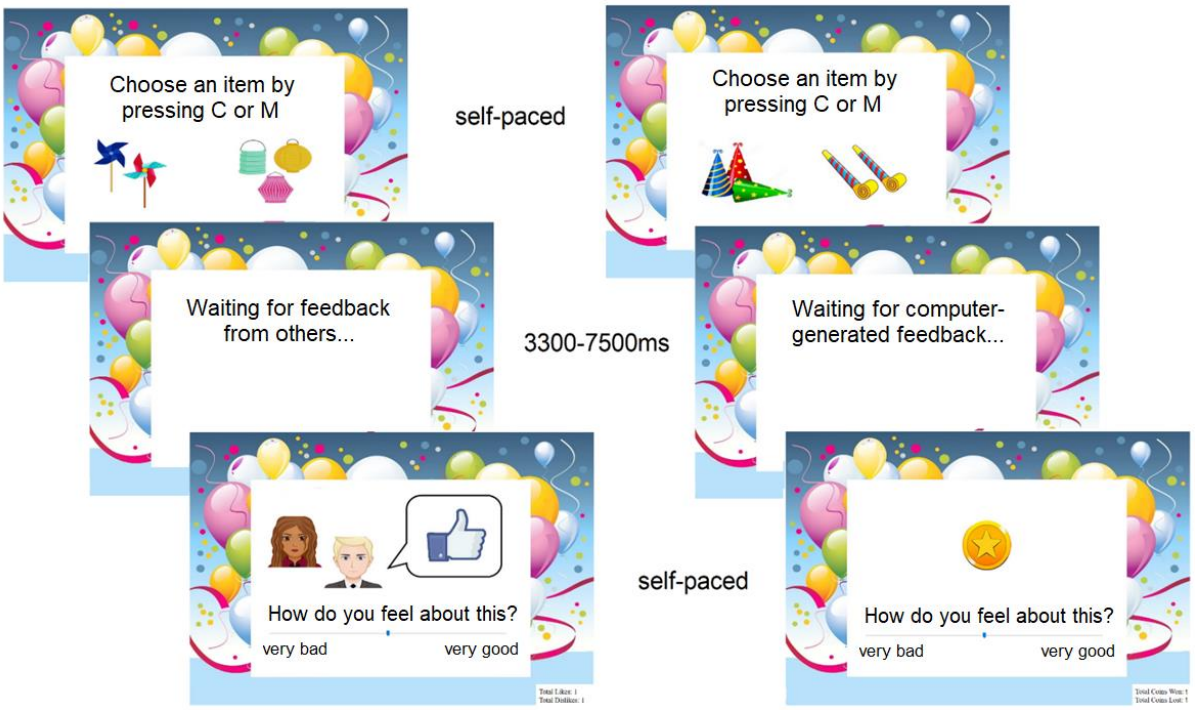
During the task, participants' aim was to make choices that maximised positive and minimised negative outcomes. At the beginning of each trial, subjects were shown two party decoration items side-by-side, and were asked to select one item by pressing the 'C' or 'M' key. The images were displayed until a selection was made, and after each choice the words 'waiting for feedback from others' or 'waiting for computer-generated feedback' were presented for between 3300ms and 7500ms. This relatively long and variable interval was chosen to give the impression that, in the social condition, the other people were truly selecting the feedback. Subsequently, participants were given positive, neutral or negative feedback, determined probabilistically as described below. Moreover, subjects were asked to rate how they felt about the outcome, using a visual analogue scale ranging from 'very bad' to 'very good' (0 to 100). The feedback stayed on the screen until the rating was submitted (see Figure 1).

The task consisted of a social and a non-social condition, which were completed in counterbalanced order. In the social condition, the feedback consisted of 'like' and 'dislike' signs as used on social media (thumb up or down), as well as neutral feedback in the form of a horizontal thumb. Participants were told that the feedback came from the other two people, with 'likes' or 'dislikes' indicating that both of the others approved or disapproved of their selection, respectively, and horizontal thumbs reflecting that one of the two others liked and the other disliked their choice. The latter outcome was chosen, rather than e.g. stating that no

ratings were available on neutral trials, because the outcomes would have seemed unrealistic if the other two people had always agreed on their feedback. Note that, in reality, all feedback was computer-generated. In the non-social condition, monetary feedback was provided in the form of winning 5 pence, no outcome, or losing 5 pence, represented by an image of a golden coin, a circle, or a crossed-out coin, respectively.

It may be argued that the horizontal thumb used in the social condition (as a representation of one 'like' and one 'dislike') is not an entirely neutral outcome, if the perceived pleasantness of 'likes' is stronger than the perceived unpleasantness of 'dislikes', or vice versa. However, it should be noted that, depending on a given participant's focus, receiving no monetary outcome could similarly have been be regarded as slightly positive ('not a loss') or slightly negative ('not a win'). Thus, the two conditions were matched in this regard, and the fact that 'neutral' outcomes were potentially not perceived as entirely neutral was taken into account in the computational modelling of the task data (see below).

Figure 1: *Illustration of the social (left) and non-social (right) conditions of the learning task*



Eight party decoration items were used as stimuli during the task (balloons, garlands, lanterns, pinwheels, party hats, party horns, candles, and confetti). For each participant, four items were randomly allocated to the social condition and the other four items to the non-social condition. Moreover, for each condition, each item was randomly assigned to one of the following outcome contingencies: 75% (item 1) or 25% (item 2) chance of yielding positive rather than neutral feedback, or 75% (item 3) or 25% (item 4) chance of yielding negative rather than neutral feedback.

Given that there were four items per condition, there were six possible pairings. Each of the pairings was repeated twelve times (six times with item A displayed on the left side of the screen and item B on the right side, and six times vice versa), yielding a total of 72 trials per condition.

During the task, participants' choices, their reaction times, and their ratings in response to the feedback were recorded. Additionally, explicit outcome expectancies were assessed by asking participants to rate each item twice: once on how likely they thought selecting this item would result in positive feedback, and once on how likely they thought choosing this item would result in negative feedback. Ratings were made on a visual analogue scale ranging from 'very unlikely - 0%' to 'very likely - 100%' and were collected in the middle and at the end of each condition.

2.3.3 Analysis

2.3.3.1 Behavioural Analysis

The questionnaire data were not normally distributed. Thus, non-parametric Mann-Whitney U tests were performed to assess group differences.

For the learning task, reaction time (RT) data were log transformed due to a positive skew. RTs were compared between groups and conditions using mixed-measure analyses of

covariance (ANCOVAs), in which the testing location (online or at the university) was added as a control variable.

Moreover, to examine participants' reward and 'punishment' learning performance, the frequencies of selecting the most rewarded item and of avoiding the most 'punished' item were calculated for the social and non-social conditions for each subject. Subsequently, a group by valence by condition mixed-measure ANCOVA (with the testing location as a covariate) was conducted. The data of one online LD participant were removed from all task analyses because their performance was substantially below chance, indicating that they may have misunderstood the task.

To assess participants' negative biases, negative outcome expectancy ratings from the middle and the end of the task were averaged for those items which never yielded negative feedback (items 1 and 2), while positive outcome expectancies were averaged for those items which never yielded positive feedback (items 3 and 4). The mean positive expectancy rating was then subtracted from the mean negative expectancy rating to obtain a negative bias score. This score indicates how much more negative than positive feedback participants expected to receive independently of the actually experienced outcomes (i.e. for choices that never yielded negative or positive outcomes, respectively). To account for the fact that participants' expectancy ratings for the individual items may be influenced by the *overall* amount of positive and negative outcomes they experienced throughout the task, relevant analyses were also run with the difference between the overall positive and negative feedback counts as a control variable.

In addition, group by condition by valence mixed-measure ANCOVAs were performed on the feedback pleasantness ratings, arousal ratings and negative expectancy bias scores. Where Mauchly's Test of Sphericity indicated that the sphericity assumption was not met, Greenhouse-Geisser corrected results are reported.

Moreover, to assess whether social anhedonia and negative biases contribute to social disengagement, a multiple regression analysis was conducted. Specifically, the amount of time spent with friends was predicted using RSAS and negative bias scores while controlling for BDI depression and SAQ anxiety measures. Given that for the raw data the assumption of normally distributed residuals was not met, the regression was performed on rank transformed data. As suggested by Thomas, Nelson, and Thomas (1999), F-statistics were thus converted to L-statistics (N-1* r^2), degrees of freedom were obtained by multiplying the number of independent variables with the number of dependent variables, and p-values were derived by evaluating the L-statistic on the χ^2 table. Some of the rank transformed predictor variables were weakly correlated; however, collinearity assumptions were not violated (all Variance Inflation Factors; VIFs < 2).

2.3.3.2 Computational Modelling

Q-learning models were fit separately to the data of the social and non-social condition. Q-values, which indicate the predicted value of choosing a given item, were initialised at 0 and updated on each trial (t) for the selected item (A) as follows:

$$Q_A(t+1) = Q_A(t) + \alpha_G * \max[0, r(t) - Q_A(t)] + \alpha_L * \min[0, r(t) - Q_A(t)]$$

where r(t) is the outcome value and αG and αL are the learning rates for positive and negative prediction errors, respectively. The outcome value was fit individually for each participant with the use of the free parameter *d* (as in Gold et al., 2012). Specifically, r(t) was set to 1-d for rewards, to -d for 'punishments', and to the midpoint between these values [i.e. $(1 - \mathrm{d}) - ((1 - \mathrm{d}) - (-\mathrm{d}))/2$] for 'neutral' outcomes (which provided a better fit than using d = 0). Note that, from a theoretical perspective, setting the value of 'neutral' outcomes to the midpoint between reward and punishment values is appropriate, particularly in the social condition in which 'neutral' outcomes represented receiving a 'like' from one person and a 'dislike' from the other person. It should further be noted that d values need to be interpreted relative to the initial Q-

value of 0. That is to say, the d parameter determines how large the impact of rewards and 'punishments' is in relation to the initial outcome expectation.

To account for the potential forgetting of the implicitly learned Q-values while making ratings in the middle of the task (after trial 36), all Q-values were decayed towards 0 for trial 37, with a free parameter (ω) determining the strength of this decay as follows (similar to Collins & Frank, 2012):

$$Q_i(37) = \ Q_i(37) \ + \ \omega \ * [0 - \ Q_i(37)]$$

Moreover, on every trial the probability of a given participant's choice (of item A over B) under the model was computed using a softmax function:

$$P_A(t) = \frac{e^{\frac{Q_A(t) + c_A(t) * \varphi}{\tau}}}{e^{\frac{Q_A(t) + c_A(t) * \varphi}{\tau}} + e^{\frac{Q_B(t) + c_B(t) * \varphi}{\tau}}}$$

where τ is the explore/ exploit temperature parameter, $c_A(t)$ is an indicator variable which is set to 1 if item A was chosen the last time it was presented and to $\gamma * c_A(t-1)$ otherwise (where γ is a decay parameter), and φ is the choice bias parameter representing how likely participants are to repeat an item choice *independently of the outcome it yields* (i.e., "sticky choice"; Schonberg, Daw, Joel, & O'Doherty, 2007).

Models containing different combinations of the free parameters (αG, αL, d, φ, γ, ω, τ; see Table 2) were fit to each participant's data by maximising the log likelihood estimate (LLE) of the participant's choices under the model across all trials, thus maximising:

$$LLE = \log\left(\prod_t P_{i,t}\right)$$

The model fitting was conducted in two hierarchical steps. In step 1, the maximum likelihood estimation (MLE) was conducted without a prior, as described above. In step 2, the MLE was re-run using a multivariate Gaussian prior on the parameter values. The prior was

parameterised with the mean and covariance (across *all* participants) of the parameter estimates from step 1. That is to say, each parameter value was evaluated on the abovementioned prior, and the log of this value was added to the LLE, thereby causing a higher increase in the LLE for parameter estimates that are more likely under the prior. This "shrinkage" procedure reduces the variance in the parameter estimates by bringing extreme values closer to the overall mean (Daw, 2011) and approximates hierarchical Bayesian estimation (although, unlike in Bayesian estimation, the same prior was applied to the data of *all* subjects, rather than using group-specific priors). Even though this approach does not implement the full Bayesian solution (i.e. it does not yield posterior distributions over parameters), our testing confirmed that this procedure improved the parameter recovery from data simulated based on the same task and trial number.

To assess the relative fit of the different models, Akaike's Information Criterion weights were computed (as outlined in Wagenmakers & Farrell, 2004). Two models (Q16 and Q4 in Table 2) were among the best fitting models for both the social and the non-social condition. For one of these models (Q16) the mean values of two of the parameters (learning rate and memory decay) were numerically similar for the two conditions. Thus, three further models were fit in which one or both parameters were shared for the social and non-social data fitting, while the other parameters could vary. AIC weights were used to compare the fit of the models with partly shared and entirely independent parameters.

Moreover, for the purpose of model validation, parameters from the best fitting model were used to simulate data. Subsequently, the generating model was fit back to the simulated data (using the two-step procedure described above) to assess if the parameters used in the simulation could be recovered. The latter was confirmed by running Spearman correlations between the initial and recovered parameters.

Additionally, the fit of the best model was compared to chance with the use of *pseudo-*R^2 values, which (as in Frank, Moustafa, Haughey, Curran, & Hutchison, 2007) were calculated as follows: *pseudo-*R^2 = ($LLE_{\text{learning model}}$ - $LLE_{\text{null model}}$) / $LLE_{\text{null model}}$, where $LLE_{\text{null model}}$ is the log

likelihood estimate of the data under a model that assumes random choices [i.e. $LLE_{null\ model}$ = number of trials * log(0.5)]. The data of one LD participant in the social condition and of five LD and five HD subjects in the non-social condition demonstrated a better fit for the null model than for the learning model. When data from these participants were excluded from the analyses, the same pattern of findings arose. Therefore, these data were included for the reported results.

Parameter values from the best fitting model were compared between groups using Mann-Whitney U tests. Additionally, to examine whether social learning deficits relate to the experience of positive or negative social outcomes in real life, a multiple regression analysis was performed. Specifically, the reported amount of time spent in pleasant and unpleasant social situations was predicted using social learning rate, outcome valuation, and temperature parameters (from model Q16; see Table 2 and below), as well as RSAS, SAQ and negative bias scores (while controlling for BDI depression scores). Again, the assumption of normally distributed residuals was violated for the raw data, which is why the regression was performed on rank transformed data using L-statistics as described above. Some of the predictor variables were moderately correlated; however, collinearity assumptions were not violated (all VIF < 5).

To confirm the robustness of our findings, the above analyses were also performed on the estimated parameters of a different model (Q4 in Table 2) which had an AIC weight close to that of the best fitting model. Given that the rank-transformed learning rate and temperature parameters were highly correlated in this model, the collinearity assumption was violated (VIF > 10). Notably, when conducting the regression analysis on the parameter estimates of model Q16 (as described above), the temperature and learning rate parameters did not show a significant predictive effect for the time spent in unpleasant and pleasant social situations, respectively. Thus, these parameters were removed from the respective regressions for the analysis related to model Q4.

2.4 Results

2.4.1 Demographic and Questionnaire Measures

Mann-Whitney U tests revealed no significant group differences in age (U = 941, p = 0.431), or consummatory TEPS scores (U = 1128, p = 0.167). As expected, BDI (U = 0, p < 0.001), social anhedonia RSAS (U = 510, p < 0.001), and social anxiety SAQ (U = 386, p < 0.001) scores were significantly higher for HD than for LD participants. Moreover, anticipatory TEPS scores were significantly lower in the HD than in LD group, indicating higher levels of anhedonia in HD subjects (U = 1390, p < 0.001; see Table 1).

Table 1: *Demographic data and questionnaire scores for individuals with low (LD) and high (HD) depressions scores.*

	LD (N = 52)		HD (N = 40)	
	Mean	SD	Mean	SD
Age (years)	24.02	6.59	25.33	7.59
N females/ males	41/ 11	-	31/ 9	-
BDI*	2.52	2.47	30.73	9.29
RSAS*	10.27	7.96	17.39	8.89
TEPS - A*	47.23	7.37	41.35	8.05
TEPS - C	37.29	7.10	35.59	6.64
SAQ*	95.56	20.17	120.63	19.65

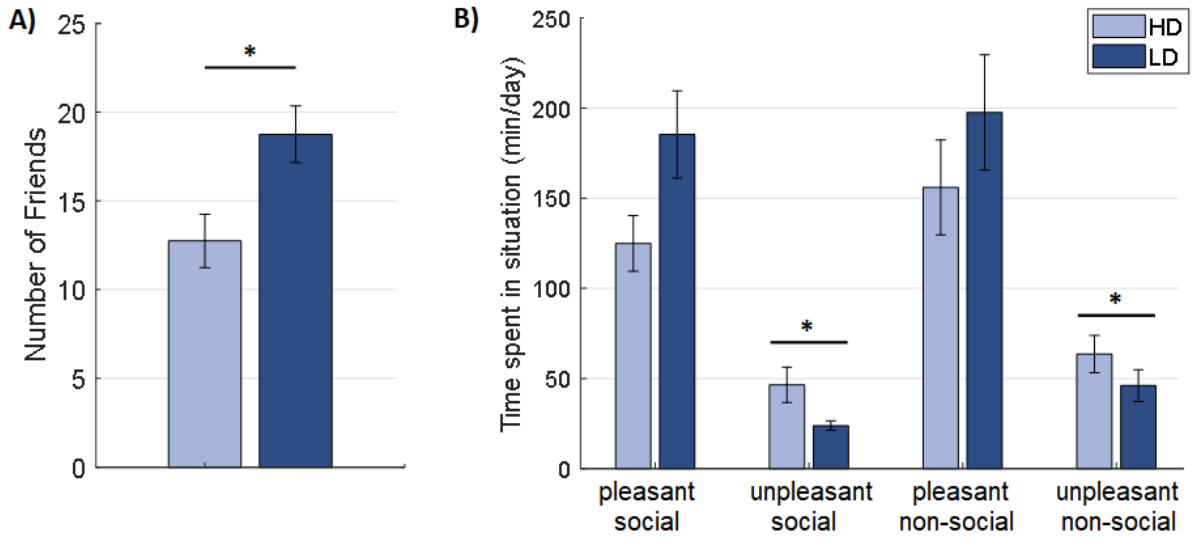
SD, standard deviation; BDI, Beck Depression Inventory; RSAS, Revised Social Anhedonia Scale; TEPS, Temporal Experience of Pleasure Scale (C, consummatory; A, anticipatory); SAQ, Social Anxiety Questionnaire; *asterisks indicates significant group differences

2.4.2 Real-Life Social Interactions

Mann-Whitney U tests demonstrated that, compared to LD controls, HD participants reported having significantly fewer friends (U = 1232, p = 0.007; see Figure 2A), finding it less pleasant to spend time with their friends (U = 1122, p = 0.042), feeling less close to their friends (U = 1169, p = 0.014), and finding it more difficult to form new friendships (U = 531, p = 0.001). When adjusted for the reported number of friends, the amount of time spent with friends did not differ between groups (U = 773, p = 0.293).

Additionally, compared to LD participants, HD individuals indicated spending significantly more time engaged in social (U = 486, p < 0.001) and non-social (U = 575, p = 0.005) situations that were regarded as unpleasant. By contrast, the reported amount of time spent in pleasantly perceived social (U = 1047, p = 0.173) or non-social (U = 998, p = 0.351) situations did not differ significantly between groups (see Figure 2B).

Figure 2: *A) Number of friends and B) reported time spent in pleasant and unpleasant social and non-social situations for individuals with high (HD) and low (LD) depressions scores.*



2.4.3 Learning Task Performance

A mixed measure ANCOVA (group x valence x condition, controlling for testing location) on participants' emotional responses to the positive, neutral and negative feedback showed the expected main effect of valence (F (1.21, 106.22) = 124.82, $p < 0.001$), with participants feeling better after receiving positive than after getting neutral ($t(90) = 16.22$, $p < 0.001$) or negative ($t(90) = 17.50$, $p < 0.001$) feedback and after receiving neutral than after getting negative feedback ($t(90) = 14.32$, $p < 0.001$) across the social and non-social conditions. No other significant main effects or interactions were observed (all $F < 0.4$).

In addition, a mixed measure ANCOVA (group x condition x valence, controlling for testing location) on participants' arousal ratings for positive, neutral and negative feedback demonstrated a significant main effect of condition ($F(1, 83) = 6.48$, $p = 0.013$), with higher reported arousal in the social than in the non-social condition. Additionally, a significant main effect of valence was found ($F(2, 166) = 33.48$, $p < 0.001$) due to higher arousal to positive feedback than to negative ($t(88) = 4.39$, $p < 0.001$) or neutral ($t(88) = 12.84$, $p < 0.001$) outcomes, as well as higher arousal to negative than to neutral feedback ($t(88) = 6.94$, $p < 0.001$). Moreover, a group by condition by valence interaction was observed ($F(2, 166) = 5.47$, $p = 0.005$). Follow-up one-way ANCOVAs showed that HD subjects reported significantly higher arousal than LD participants for negative social feedback ($F(1, 85) = 4.84$, $p = 0.030$), with no significant group differences for any other feedback type (all $F < 1.6$).

Furthermore, a mixed-measure ANCOVA (group x valence x condition, controlling for testing location) of the learning performance revealed a significant main effect of valence ($F(1, 88) = 4.13$, $p = 0.045$), with participants demonstrating better reward than punishment learning. Moreover, a trend for a group effect was observed ($F(1, 88) = 3.50$, $p = 0.065$), as HD individuals' learning performance tended to be worse than that of LD subjects. None of the other main effects or interactions were significant (all $F < 2.2$).

A mixed-measure ANCOVA (group x condition, controlling for testing location) on the log-transformed reaction time data found no significant main effects of group ($F(1, 88) = 0.40$, $p = 0.530$) or condition ($F(1, 88) = 0.20$, $p = 0.658$), nor a significant interaction ($F(1, 88) = 0.02$, $p = 0.877$).

To examine differences in negative feedback expectancy biases, a mixed measure ANCOVA (group x condition, controlling for testing location) was conducted. A significant main effect of group was found ($F(1, 88) = 5.33$, $p = 0.023$), as HD participants' bias scores were significantly higher than those of LD subjects across both social and non-social conditions. This group effect remained significant when controlling for the difference in the overall amounts of negative and positive feedback received throughout the task ($F(1, 88) = 5.70$, $p = 0.019$).

Moreover, a regression analysis revealed that negative expectancy biases ($\beta = -0.17$, $p = 0.063$) marginally, and RSAS social anhedonia scores ($\beta = -0.62$, $p < 0.001$) significantly, predicted the amount of time participants reported spending with their friends (while controlling for SAQ social anxiety, $\beta = 0.17$, $p = 0.127$, and BDI depression, $\beta = 0.13$, $p = 0.254$, scores; $L(4) = 25.70$, $p < 0.001$, $R^2 = 0.31$). It should be noted that it cannot be ruled out that the negative biases observed in the task were the result of a generalisation from negative social experiences in real life to the experimental setting (see discussion). It could therefore be the case that, in the regression analysis, the negative bias values act as a 'proxy' for an effect of negatively perceived interpersonal encounters on social withdrawal. Thus, the regression analysis was rerun with the reported amount of time spent in unpleasant social situations as an additional control variable. The observed pattern of results was similar, with both negative biases ($\beta = -0.19$, $p = 0.046$) and RSAS scores ($\beta = -0.61$, $p < 0.001$) contributing significantly to the prediction of the amount of time spent with friends. This indicates that, independent of how many negatively perceived social situations they encounter, individuals who are more anhedonic and who expect more negative social outcomes spend less time with their friends.

Finally, a Mann-Whitney U test was performed on participants ratings of how sure they were that the feedback in the social condition of the learning task came from other people. There were no group differences (U = 887, p = 0.909), with average ratings of around 5 out of 10 in both groups (M_{HD} = 5.08, SD_{HD} = 2.82; M_{LD} = 5.06, SD_{LD} = 3.03). Although this indicates that participants did not fully believe that the feedback was provided by other people, it should be noted that, as long as subjects thought there was a chance that the feedback came from the others, they are likely to have behaved as if it did. Moreover, the very question itself may have induced participants to be uncertain about the source of the feedback, and in response to a more open question ('Did you notice anything strange or unexpected during the task? If so, what?') only two participants expressed doubt over whether the feedback was provided by other people.

2.4.4 Computational Modelling

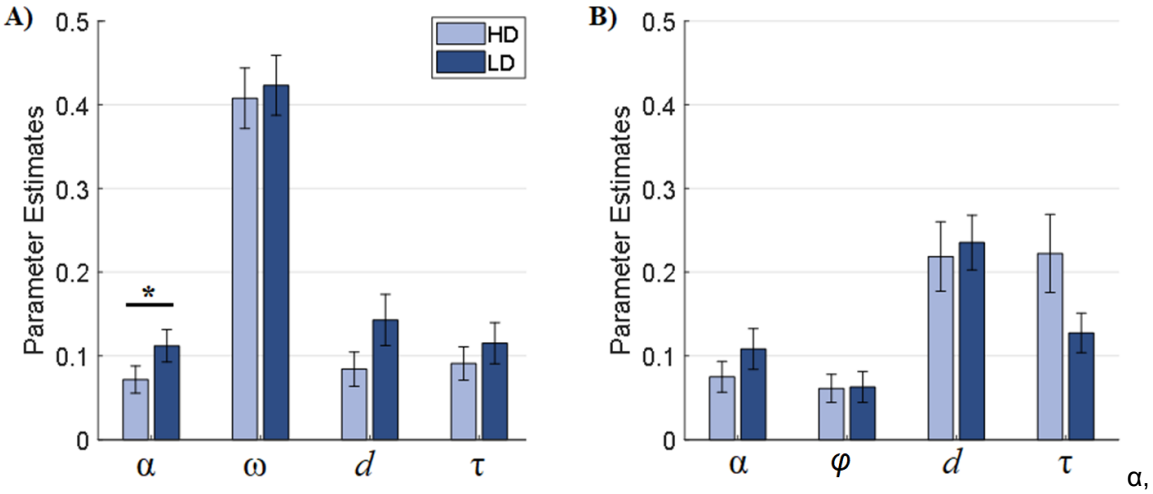
For the data from the social condition, the best fitting model for both groups included one learning rate (α; αG = αL), as well as the outcome valuation (d), memory decay (ω), and temperature parameters (τ; model Q16 in Table 2). For the data from the non-social condition, the best fitting model for both groups contained one learning rate, and the outcome valuation, choice bias (φ), and temperature parameters (model Q5 in Table 2). The involvement of a sticky choice bias parameter in the non-social but not the social condition may indicate that participants were more likely to find a strategy and stick with it in the non-social condition, potentially because they perceived the latter to be less volatile than the social condition.

It should be noted that model Q16 fit the non-social data similarly well as the best fitting model (Q5), and the numerical values of the mean learning rate and memory decay parameters for Q16 were similar for the social and non-social condition. Thus, three further models were fit in which either or both of the latter parameters were shared between the conditions. AIC weights indicated that the model in which all parameters varied between conditions provided the best fit (AIC weight = 0.293), closely followed by the model in which the memory decay parameter

was shared (AIC weight = 0.292). The models in which the learning rate (AIC weight = 0.190) or both learning rate and memory decay parameters (AIC weight = 0.226) were shared fit slightly less well. The analysis below thus focuses on model Q16 with no shared parameters (as well as on other well-fitting models, namely Q4 for the social condition, and Q5 and Q4 for the non-social condition).

Mann-Whitney U tests on parameters form the social condition found significantly lower learning rates (Q16: U = 1277, p = 0.040; Q4: U = 1314, p = 0.019) in HD subjects compared to LD controls. No group differences were observed for the outcome valuation (Q16: U = 1095, p = 0.549; Q4: U = 1157, p = 0.273), memory decay (Q16: U = 1047, p = 0.829; Q4: N/A), or temperature (Q16: U = 1099, p = 0.528; Q4: U = 1242, p = 0.076) parameters (see Figure 3A for parameters from model Q16). In the non-social condition, there were no significant group differences in the learning rate (Q5: U = 1025, p = 0.968; Q4: U = 1019, p = 0.994; Q16: U = 1017, p = 0.981), choice bias (Q5: U = 1105, p = 0.497; Q4 & Q16: N/A), outcome valuation (Q5: U = 1035, p = 0.905; Q4: U = 1094, p = 0.554; Q16: U = 1097, p = 0.538), or temperature (Q5: U = 885, p = 0.280; Q4: U = 876, p = 0.250; Q16: U = 854, p = 0.184) parameters (see Figure 3B for parameters from model Q5). Although the numerical group difference in the learning rate value went in the same direction for the social and non-social condition, the main effect of group (based on the average learning rate across conditions) did not reach significance (U = 1222, p = 0.106).

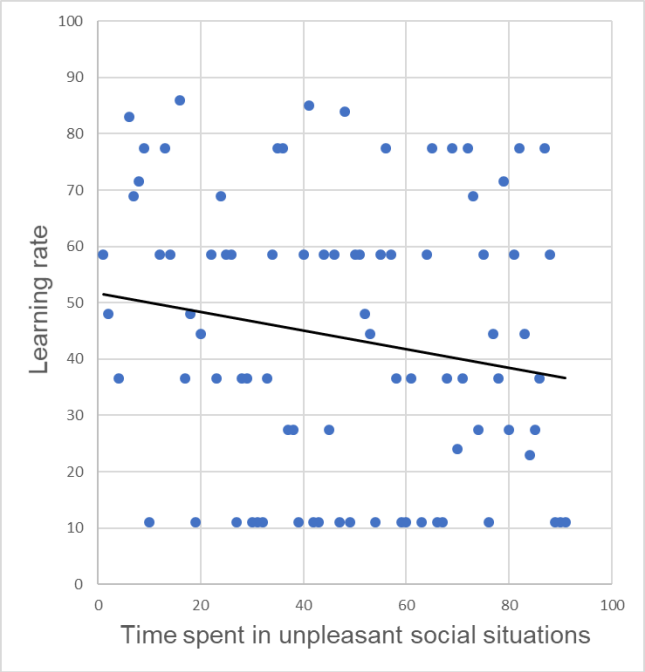
Figure 3: *Parameter estimates for the A) social (Q16) and B) non-social (Q5) condition for individuals with high (HD) and low (LD) depressions scores.*



α, learning rate; ω, memory decay; *d,* outcome valuation; *τ*; explore-exploit/ temperature; φ, choice bias

A regression analysis revealed a significant association of social model parameter values (and questionnaire measures) with the reported amount of time spent in unpleasantly perceived social situations (Q16: $L(6) = 16.21$, $p = 0.013$, $R^2 = 0.19$; Q4: $L(5) = 16.80$, $p = 0.005$, $R^2 = 0.20$). This predictive relation was driven by outcome valuation (Q16: β = 0.31, $p = 0.016$; Q4: β = 0.29, $p = 0.025$) and learning rate (Q16: β = -0.45, $p = 0.046$; Q4: β = -0.31, $p = 0.020$; see Figure 4) parameter values, as well as BDI depression scores (Q16: β = 0.28, $p = 0.018$; Q4: β = 0.28, $p = 0.017$). By contrast, SAQ social anxiety scores (Q16: β = 0.15, $p = 0.188$; Q4: β = 0.15, $p = 0.205$), negative biases (Q16: β = 0.03, $p = 0.949$; Q4: β = 0.09, $p = 0.374$), and temperature parameter values (Q16: β = 0.23, $p = 0.252$; Q4: N/A; removed due to collinearity) had no significant effect. Thus, individuals with higher outcome valuation parameters (i.e. with lower responsiveness to rewards and higher sensitivity to punishments), lower learning rates and higher BDI depression scores reported spending more time in unpleasantly perceived social situations. The highly similar results obtained when using parameters from models Q16 and Q4 provide evidence for the robustness of this effect.

Figure 4: *Association between learning rate parameters and time spent in unpleasant social situations (shown data is rank-transformed)*



In addition, the abovementioned measures also significantly predicted the reported amount of time spent in social situations that were regarded as pleasant (Q16: $L(5) = 18.06$, $p = 0.003$, $R^2 = 0.22$; Q4: $L(4) = 19.32$, $p = 0.001$, $R^2 = 0.23$). When utilising parameter estimates from model Q16, this association was driven by RSAS social anhedonia scores (β = -0.49, $p < 0.001$), with temperature parameters only marginally contributed to this relation (β = 0.34, $p = 0.065$). By contrast learning rate (β = -0.37, $p = 0.091$), outcome valuation parameters (β = 0.01, $p = 0.944$) and BDI depression scores (β = -0.01, $p = 0.896$) had no significant effect. When using parameters from model Q4, RSAS social anhedonia scores similarly had a significant predictive effect (β = -0.46, $p < 0.001$), but it was the outcome valuation parameters that additionally made a significant contribution (β = 0.24, $p = 0.030$), while temperature parameters (β = 0.10, $p = 0.377$), and BDI scores (β = 0.02, $p = 0.863$) had no significant effect. The same pattern of results was observed when learning rate values (β = 0.08, $p = 0.547$) were included as predictors instead of temperature parameters. The fact that the

regression results vary depending on which model parameters are used indicates that the findings are not robust and should thus be interpreted with caution.

In terms of model validation (based on models Q16 and Q5 for the social and non-social conditions, respectively), it can be seen from Figure 5 that the relative accuracy pattern of the two groups in the simulated data closely resembled that of the real data (although the overall accuracy was slightly overestimated). Additionally, *pseudo-R^2* values indicated that in both the social (*pseudo-R^2* = 0.34) and non-social (*pseudo-R^2* = 0.33) condition the model provided a relatively good fit for the data, and no group differences in *pseudo-R^2* values were observed in either condition (U = 1116, p = 0.443 and U = 1229, p = 0.095, respectively). Moreover, in both the social and non-social condition, participants' parameter values and the parameter estimates from the simulated data were significantly correlated (see Table 3), and, for the social condition, group differences in the learning rate could be recovered from the simulated data (U = 1349, p = 0.009).

Figure 5: *Percent of accurate choices in six bins of twelve trials for the participants' data in the A) social and C) non-social condition, as well as for the data simulated using parameters from the best fitting model in the B) social and D) non-social condition.*

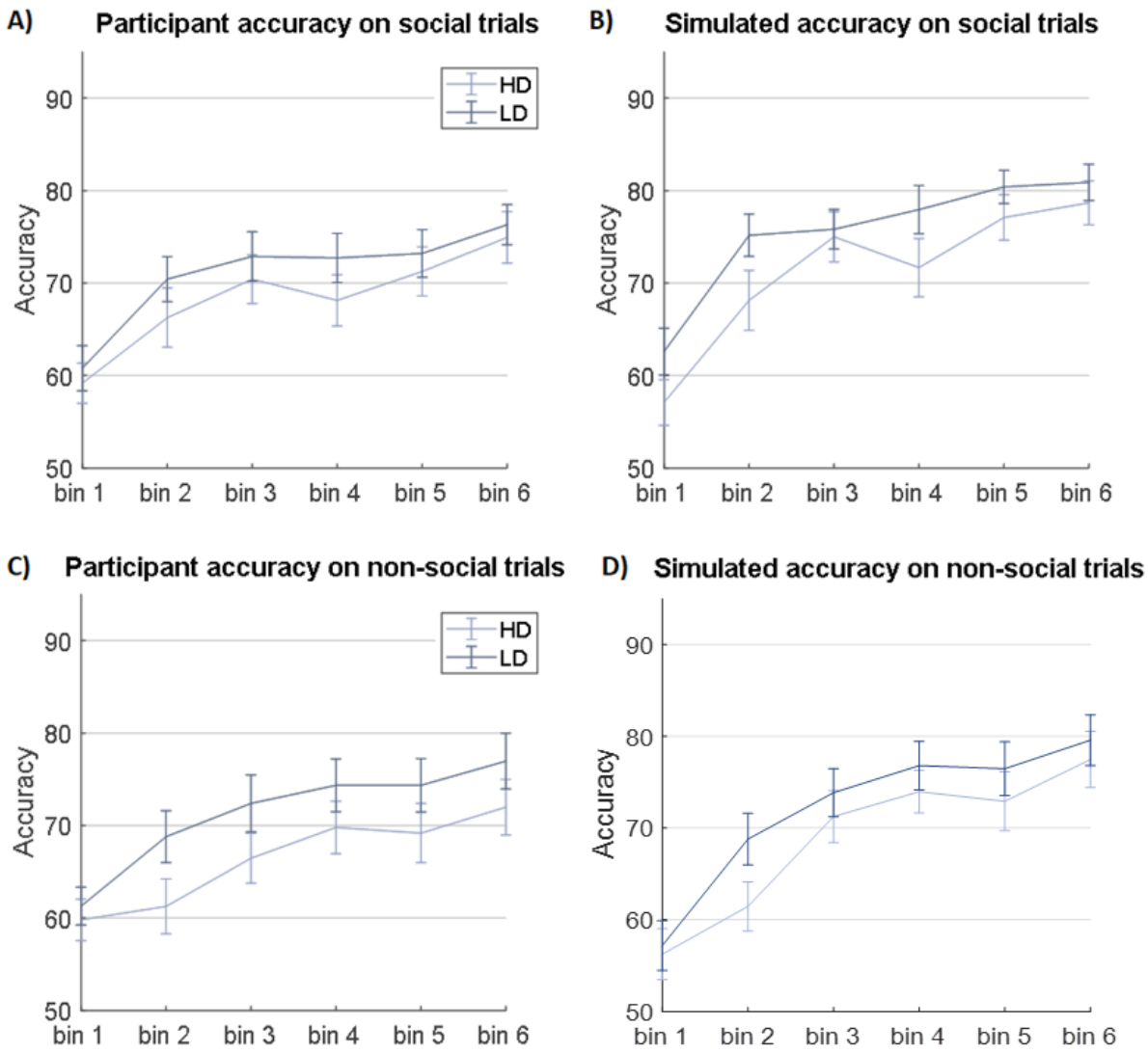


Table 2: *Overview of the models that were fit to the data and the associated Akaike's Information Criterion (AIC) weights for the social and non-social condition.*

Model	Learning rate (αG, αL)	Outcome valuation (d)	Choice bias (φ)	Choice bias decay (γ)	Memory decay (ω)	Tempe-rature (τ)	AIC weight social	AIC weight non-social
Q1	1					x	0.007	0.010
Q2	1		x			x	0.018	0.023
Q3	1		x	x		x	0.026	0.024
Q4	1	x				x	0.086	0.087
Q5	1	x	x			x	0.066	0.096
Q6	1	x	x	x		x	0.066	0.056
Q7	2					x	0.030	0.023
Q8	2		x			x	0.046	0.031
Q9	2		x	x		x	0.035	0.037
Q10	2	x				x	0.078	0.067
Q11	2	x	x			x	0.075	0.057
Q12	2	x	x	x		x	0.035	0.033
Q13	1				x	x	0.005	0.007
Q14	1		x		x	x	0.011	0.015
Q15	1		x	x	x	x	0.017	0.018
Q16	1	x			x	x	0.089	0.080
Q17	1	x	x		x	x	0.062	0.073
Q18	1	x	x	x	x	x	0.021	0.055
Q19	2				x	x	0.023	0.012
Q20	2		x		x	x	0.029	0.023
Q21	2		x	x	x	x	0.026	0.024
Q22	2	x			x	x	0.066	0.060
Q23	2	x	x		x	x	0.042	0.054
Q24	2	x	x	x	x	x	0.042	0.036

For models Q1 to Q6 and Q13 to Q18, the same learning rate was used for positive and negative prediction errors (i.e. αG = αL), while for the remaining models separate learning rates were utilised. An x indicates that the parameter was estimated in the model, while the other parameters were fixed at 0 (for choice bias and decay) or removed (for d, with r(t) being set to 1, 0, and -1 for positive, neutral, and negative outcomes, respectively). The dark grey shading highlights the best fitting models, and the light grey shading indicates similarly well-fitting models.

Table 3: *Correlations between participant parameters used for data simulation and parameters recovered from the simulated data for the social and non-social condition.*

	social		**non-social**	
	r_s value	*p value (one-tailed)*	*r_s value*	*p value (one-tailed)*
learning rate (α)	0.54	<0.001	0.39	<0.001
choice bias (φ)	N/A	N/A	0.52	<0.001
outcome valuation (d)	0.42	<0.001	0.45	<0.001
memory decay (ω)	0.32	0.001	N/A	N/A
temperature (τ)	0.53	<0.001	0.61	<0.001

2.5 Discussion

Addressing a lack of research on social learning in depression, the current study assessed the performance of individuals with high (HD) and low (LD) depression scores in a learning task with both social and non-social feedback. Additionally, measures of participants' everyday interpersonal interactions were collected, which allowed for the examination of how task-based social learning relates to real-life social experiences.

2.5.1 Learning from social feedback predicts the quality of social experiences

In the task, it was found that HD participants tended to demonstrate reduced learning across all trials compared to LD controls. Due to the lack of an interaction, it was not possible to ascertain whether this effect may have been driven by reward or 'punishment' learning deficits in the social or non-social condition. Nevertheless, the finding is consistent with previous reports of impaired learning in depression (Herzallah et al., 2013; Kumar et al., 2018; Kunisato et al., 2012; Maddox et al., 2012; Pechtel et al., 2013; Robinson, Cools, Carlisi, Sahakian, & Drevets, 2012).

To examine which learning *mechanisms* may be affected in HD individuals, computational modelling was performed. This approach revealed that, in the social (but not the non-social) condition of the task, HD subjects demonstrated significantly lower learning rates than LD participants. Hence, HD individuals made smaller updates to their outcome predictions based on social feedback than controls. This result is in line with previous observations of altered learning rates in depressed subjects (Beevers et al., 2013; Chase et al., 2010; Cooper et al., 2014; Dombrovski et al., 2010) and extends these findings to the social domain.

Interestingly, the present study further demonstrated that social learning model parameters were related to real-life interpersonal experiences. Specifically, it was found that, across all participants, higher outcome valuation parameters were associated with more time spent in unpleasantly perceived social situations. That is to say, individuals who showed enhanced

sensitivity to negative outcomes and diminished responsivity to positive feedback (relative to the initial expectation of an outcome value of zero) reported experiencing more negative social encounters. This is likely due to these subjects *subjectively* perceiving more social interactions as unpleasant, resulting in elevated reporting of negative encounters.

Moreover, an increased amount of time spent in unpleasant social situations was also associated with lower learning rate values. This may partly be the case because reduced updating of outcome predictions based on social feedback may give rise to enhanced uncertainty about what to expect from social interactions. Considering that uncertainty can be regarded as negative (e.g. in depressed individuals; Carleton et al., 2012), heightened uncertainty may result in more social encounters being *subjectively* perceived as unpleasant. Additionally, it is possible that individuals with low learning rates *objectively* experience more unpleasant social encounters, because their impaired ability to use social feedback to appropriately update future actions may lead to suboptimal interpersonal behaviour (see below).

The current study further showed that the reported amount of time spent in *pleasantly* perceived social situations was mainly predicted by social anhedonia scores. This finding could be a result of anhedonic individuals' reduced motivation to engage in social activities or due to their tendency to experience and categorise fewer social encounters as pleasant.

It is worth noting that, compared to controls, HD subjects showed heightened social anhedonia scores, as well as reduced learning rates, and reported spending numerically lower and significantly higher amounts of time in pleasantly and unpleasantly perceived social situations, respectively. Taken together with the above results, these findings suggest that HD individuals' increased levels of social anhedonia may reduce their experience of positively perceived social encounters. Moreover, the impaired ability to update outcome predictions based on social feedback may expose HD individuals to more negatively (perceived) interpersonal

experiences, potentially due to higher uncertainty about social outcomes, or due to an inability to appropriately adjust behaviours based on other people's responses.

The latter suggestion is in line with previous proposals that increased experience of negative social encounters in depression may be the result of an impaired (learned) ability to evoke pleasant responses from other people (Carvalho & Hopko, 2011; Lewinsohn et al., 1980). This notion is partly supported by findings that, compared to controls, depressed individuals show less appropriate behaviour during social interactions, as they make less eye contact, smile less, speak more monotonously, time their responses less fittingly, and are less likely to offer help to others (reviewed in Rottenberg & Gotlib, 2008 and Segrin, 2000; see also Setterfield et al., 2016). Importantly, inappropriate social behaviour has been shown to elicit fewer positive responses to, and even rejection of, depressed subjects by their interlocuters (Segrin & Abramson, 1994). Following on from the current results, it would therefore be interesting for future studies to investigate whether the relation between learning performance and the (objective) frequency of negative social encounters is mediated by individuals' (learned) social skills.

2.5.2 Responses to social feedback predict the quantity of social engagement

Contrary to expectations, no group differences were observed in participants' emotional responses to the feedback they received during the learning task. This finding is at odds with previous reports of associations between depression symptoms and reduced positive responses to social acceptance feedback (Caouette & Guyer, 2016; Davey et al., 2011). A possible explanation for this discrepancy is that in past research the relevant feedback indicated whether other people liked the participant or not, whereas in the present study the feedback was related to subjects' party planning choices. It may thus be the case that group differences in emotional responses to social outcomes are specific to more personal feedback.

Despite the absence of group differences in emotional responses to the task feedback, the current study observed that HD individuals reported heightened arousal to negative social

outcomes, as well as enhanced negative feedback expectancy biases, compared to controls. Notably, the latter group effect remained significant even when the amount of actually experienced positive and negative feedback was controlled for. It is possible that the elevated arousal experienced by HD subjects in response to negative social feedback may have made negative outcomes more salient than positive ones, which may have contributed to increases in negative expectancy biases. Alternatively, the latter may have been the consequence of a generalisation from heightened levels of (actual or perceived) negative experiences in real life to the experimental setting. That is to say, based on unpleasant social encounters in everyday life, HD subjects may have formed the belief that others often respond negatively to their actions, and this belief may have biased the expectancy ratings in the task. In either case, the current findings are in line with past observations that depression symptoms are associated with enhanced expectancies of negative evaluations from others (Caouette & Guyer, 2016), as well as with our own work showing that individuals with high levels of depressive symptomatology expect to experience more negative responses to social situations than controls (Setterfield et al., 2016).

The present study further found that higher social anhedonia scores and, marginally, negative social expectancy biases predicted a reduction in the quantity of social engagement (time spent with friends). Notably, HD subjects showed increased anhedonia and negative bias scores. Taken together, these findings suggest that HD individuals' reduced responsiveness to pleasant social interactions, as well as their increased expectancies of negative social outcomes, may result in withdrawal from close relationships. This disengagement, in turn, may prevent future exposure to positive social experiences, thereby sustaining anhedonia levels and maintaining (or further exacerbating) negatively biased expectancies in HD subjects.

2.5.3 Conclusion

All in all, the current study found that individuals with high depressions scores demonstrate deficits in learning from social feedback. Interestingly, this impairment was linked to more time spent in unpleasantly perceived social situations, potentially due to increased uncertainty about social outcomes or suboptimal interpersonal behaviour. Moreover, HD participants displayed increased negative feedback expectancy biases and higher levels of social anhedonia compared to controls, with both of these factors predicting decreased social engagement. These findings lend support to the suggestions that impaired social learning, diminished pleasure derived from social feedback, and negative expectancy biases contribute to the decreased quality and quantity of social interactions in depression (Kupferberg et al., 2016; Lewinsohn, 1974). In future studies, it would be of interest to examine the neural underpinnings of social learning deficits in depressed individuals.

3 Behavioural and Neural Responses during Social Learning in Individuals with High and Low Depressive Symptomatology

[Study 2]

3.1 Abstract

Background: Major depressive disorder is associated with altered social functioning and impaired (non-social) learning, on both the behavioural and the neural level (Chen et al., 2015; Kupferberg et al., 2016; Stuhrmann et al., 2011). These deficits are likely related, considering that successful social interactions require learning to accurately predict other people's emotional responses. Yet, there is little research examining this relation.

Methods: In the current study, 43 individuals with high (HD; N = 21) and low (LD; N = 22) Beck Depression Inventory scores answered questions regarding their real-life social experiences and performed a social learning task during fMRI scanning. As part of the task, name cues were presented followed by faces that probabilistically displayed happy, neutral, or fearful expressions. On each trial, subjects rated the likelihood of seeing a particular emotional expression after the name cue. Using computational modelling, behavioural and neural correlates of social learning were examined and related to measures of real-life social experiences.

Results: HD participants reported reduced motivation to engage in real-life social activities and demonstrated elevated uncertainty about social outcomes in their task likelihood ratings, compared to LD controls. On the neural level, HD subjects displayed reduced encoding of social reward (i.e. happy expression) predictions in the insula, temporal lobe and parietal lobe. Interestingly, across all subjects, higher task uncertainty (in interaction with the perceived negativity of uncertainty) and reduced parietal prediction encoding were associated with decreased motivation to engage in real-life social activities (even when depression scores were controlled for).

Conclusion: The results indicate that HD individuals show reduced social engagement motivation, as well as impaired learning from social outcomes, on both the behavioural and the neural level. Moreover, subjects who demonstrated greater uncertainty about social outcomes in the task, and who regarded uncertainty as negative, displayed lower motivation to engage in real-life social activities. Taken together, these findings suggest that reduced learning from social outcomes may impair depressed individuals' ability to predict other people's emotional responses in real life, which renders social situations uncertain. This negatively perceived uncertainty, in turn, may contribute to reduced social engagement in depression.

3.2 Introduction

Deficits in social functioning are commonly observed in major depressive disorder (MDD; Katz, Conway, Hammen, Brennan, & Najman, 2011; Rhebergen et al., 2010; Rottenberg & Gotlib, 2008). Compared to controls, depressed individuals have fewer friends (Brim et al., 1982; Frey, Frank, & McCabe, 2019; Youngren & Lewinsohn, 1980), fewer intimate relationships (Gotlib & Lee, 1989), and spend less time with people in their social circle (Youngren & Lewinsohn, 1980). Additionally, depressed subjects show inappropriate behaviour during social interactions (reviewed in Rottenberg & Gotlib, 2008; Segrin, 2000), which can result in the receipt of negative feedback from other people (Segrin & Abramson, 1994).

Successful interpersonal interactions require learning to predict other people's responses and to adjust one's own behaviour accordingly. Therefore, social functioning abnormalities in MDD may partly be linked to impaired learning from interpersonal outcomes. In line with this suggestion, we previously found that subjects with depression symptoms show deficits in learning from social feedback and demonstrate heightened negative feedback expectancy biases during a social decision-making task. Interestingly, impaired learning predicted the experience of more negatively perceived social encounters in real life, while negative biases, as well as social anhedonia, were associated with decreased amounts of time spent with

friends ([study 1]; Frey et al., 2019). Additionally, using a social conditioning paradigm, it has been observed that elevated depression scores are correlated with heightened arousal ratings in response to faces that were previously paired with negative statements about the participant. This effect was still seen three months after the conditioning phase, indicating that the learning of negative social associations may be stronger in individuals with higher levels of depressive symptomatology (Wiggert et al., 2017).

The above research provides limited evidence for changes in social learning in depressed individuals. Additionally, a range of studies have reported altered *non-social* learning in MDD. For instance, using decision-making tasks, it has been observed that depressed subjects display impaired reward learning (Blanco et al., 2013; Cooper et al., 2014; Herzallah et al., 2013; Kumar et al., 2018; Kunisato et al., 2012; Maddox et al., 2012; Pechtel et al., 2013; Robinson, Cools, Carlisi, et al., 2012), while their punishment learning is either enhanced (Beevers et al., 2013; Maddox et al., 2012) or unchanged (Herzallah et al., 2013; Kumar et al., 2018; Kunisato et al., 2012; Robinson, Cools, Carlisi, et al., 2012), when compared to controls. Moreover, in Pavlovian conditioning paradigms, depressed participants tend to demonstrate less accurate reward contingency predictions during or after the conditioning phase (Kumar et al., 2008; Robinson et al., 2012, although see Lawson et al., 2017 and Rupprechter, Stankevicius, Huys, Steele, & Seriès, 2018 for no group differences). By contrast, behavioural punishment conditioning does not seem to differ between depressed and control subjects when assessed with explicit measures (Lawson et al., 2017; Robinson et al., 2012; although neural group effects have been observed, see below).

The above behavioural research has been extended by neuroimaging studies which have examined neural learning signals with the use of computational models. In these models, the predictive value of a given cue is iteratively updated based on the difference between current outcomes and previous predictions. The latter difference, referred to as a prediction error (PE), as well as model-derived prediction values, have been used as parametric modulators in fMRI analyses.

Using this approach, it has been found that depressed individuals display reduced reward PE encoding in the midbrain, striatum, medial orbitofrontal cortex, dorsal anterior cingulate cortex, and hippocampus, compared to controls (Gradin et al., 2011; Kumar et al., 2018, 2008; Rothkirch et al., 2017). Notably, the magnitude of the striatal reward PE signal has been shown to moderate the relationship between real-life anticipatory and consummatory pleasure in depressed subjects (Bakker et al., 2018). Moreover, while some studies have observed attenuated habenula punishment PE representations in depression (Liu et al., 2017), others have found these representations to be unchanged in MDD (Rothkirch et al., 2017).

In addition, examinations of neural prediction encoding have found that depressed subjects display reduced reward prediction-related responses in the hippocampus and parahippocampus (Gradin et al., 2011), as well as decreased inverse correlations between reward prediction and PE signals in the ventral striatum (Greenberg et al., 2015), compared to controls. Additionally, depressed patients demonstrate reduced punishment prediction encoding in the habenula (when shocks are used as outcomes; Lawson et al., 2017).

The above findings suggest that depression is associated with learning deficits, both on the behavioural and the neural level, partly due to impaired generation and updating of outcome predictions. However, it should be noted that most previous studies assessing learning in MDD utilised non-social outcomes. Given the ubiquity of social stimuli in everyday life, it is important to further examine how far depressed subjects' learning impairments extend to the social domain, and whether these impairments are related to the abovementioned social functioning deficits in MDD. The current study aimed to address this question. For this purpose, a social learning task was developed in which name cues were presented followed by faces that probabilistically displayed happy, neutral, or fearful expressions. Participants with high and low depression scores completed the task during fMRI scanning and were asked to learn the average likelihood of seeing a particular emotional expression after a given name cue. Additionally, subjects answered a number of questions about their real-life social experiences. A computational model was applied to the learning task data and model-derived prediction

and PE values were used as parametric modulators in the fMRI analysis to assess the neural correlates of social learning. It was hypothesised that individuals with high depression scores would show impairments in the behavioural and neural prediction of social outcomes and that these deficits would be related to altered reports of real-life social engagement.

3.3 Methods

3.3.1 Participants

The current study included 43 right-handed volunteers between the age of 18 and 45 years who scored below 8 (LD; N = 21) or above 16 (HD; N = 22) on the Beck Depression Inventory (BDI, Beck, Steer, & Brown, 1996). Subjects were screened using the structured clinical interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996). LD volunteers were excluded if they had a history of any Axis I disorder or had ever taken any psychiatric medication. HD subjects were ineligible if they had ever experienced any Axis I disorder, apart from depression and moderate levels of secondary anxiety symptoms, or if they had taken any psychiatric medication in the past year. Additional exclusion criteria for volunteers in either group were the current use of any medications besides contraceptives, the use of recreational drugs in the past three months, smoking more than five cigarettes per week, or demonstrating any contraindications to MRI scanning.

The study received ethical approval from the University of Reading Ethics Committee (UREC-16/08). All subjects provided informed consent and received £30 for their participation.

3.3.2 Procedure

Before the testing session, potential participants attended a screening visit during which the SCID, as well as an l interview about past and current medical conditions, were conducted to ascertain that none of the exclusion criteria were met. Subsequently, eligible subjects completed the following online questionnaires at home: trait subscale of the State and Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), Revised

Social Anhedonia Scale (RSAS, Eckblad, Chapman, Chapman, & Mishlove, 1982), Uncertainty Intolerance Scale (UIS, Buhr & Dugas, 2002), and a demographics form.

In addition, subjects answered several questions about their everyday social interactions, indicating how many friends they have, how close they feel to these friends, and how difficult they find it to make new friends. Participants also rated their anticipatory, motivational and consummatory responses to social and non-social activities.

After the above questionnaires had been completed, a testing session was arranged. At the beginning of the session, participants filled in the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988). Subsequently, they performed a name learning test and some practice trials of the social learning task, as well as two other tasks not reported here, outside the MRI scanner. Following the practice, subjects completed the social learning task in the MRI scanner, and, after the scan, filled in a task feedback questionnaire.

3.3.2.1 Name Learning Test

Before completing the social learning task, subjects were asked to rate their familiarity and their positive and negative associations with a list of modified Scandinavian and Eastern European names (on a scale from 0 = 'no association/ familiarity' to 10 = 'strong association/ familiarity'). The names with which participants were least familiar, and with which they had the weakest associations, were chosen as cues for the social learning task on an individual basis.

As described below, the social learning task involved learning how likely it is that a given name cue is followed by a face with a happy, neutral or fearful expression, while the face *identity* that a particular name is paired with stayed constant. To ensure that participants were fully focused on learning the name-emotion associations during the task, subjects were asked to memorise the name-face identity pairings beforehand. For this purpose, participants were shown the selected names together with the (neutral) faces that were going to be used during the task (i.e. three male and three female faces from the Pictures of Facial Affect Series;

Ekman & Friesen, 1976). Subjects were given as much time as they needed to memorise the name-face identity pairings. Once they felt ready, participants completed a name learning test, during which the six faces were numbered and displayed in a random order together with *one* of the learned names. Subjects were instructed to select the number of the face that was associated with the presented name. After each choice, the words 'correct' or 'wrong – the correct face is:' were displayed for one second together with the correct face. The name test continued until participants had correctly matched each name with the corresponding face three times. The order in which the names were displayed was pseudo-random. Participants' memorising time, as well as their accuracy, reaction times, and number of trials needed to reach criterion were recorded.

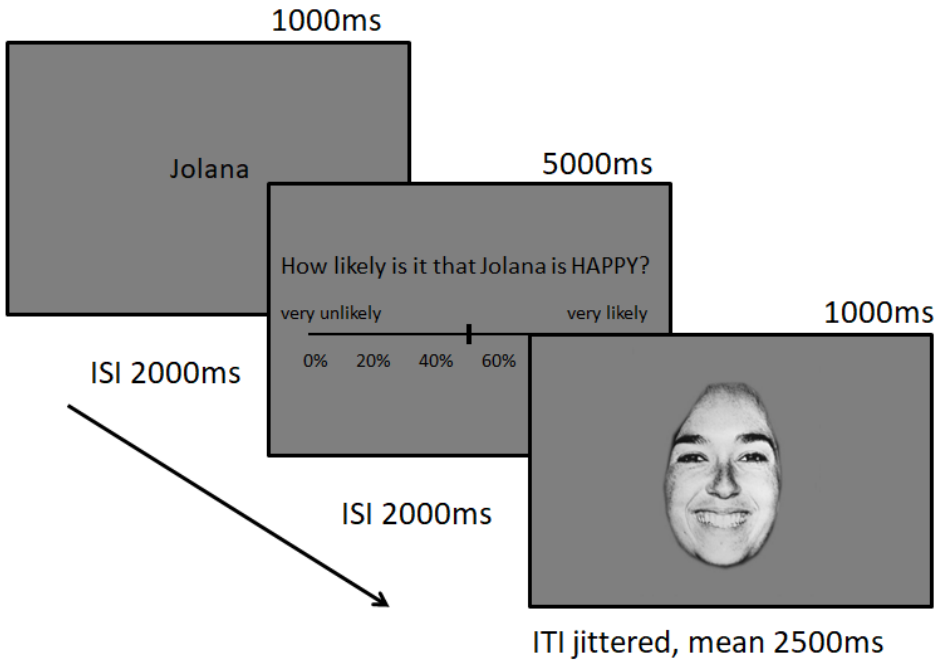
3.3.2.2 Social Learning Task

During the social learning task, participants' aim was to learn how likely it is that a given name cue is followed by a happy, neutral or fearful facial expression. At the beginning of each trial, subjects saw one of the six names that they had learned during the name test (1000ms), followed by a visual analogue rating scale (5000ms; see below). Subsequently, the face associated with the name was displayed (1000ms), showing either a neutral or an emotional expression, as determined by the probabilistic contingencies described below. The stimulus presentations were separated by a 2000ms inter-stimulus interval, and the inter-trial interval was jittered by drawing from an exponential distribution with a minimum of 2000ms and a mean of 2500ms (see Figure 1).

The task was divided into social reward and social aversion blocks which were performed in counterbalanced order. In the social reward block, three of the six faces were displayed, each of which had a different likelihood (25%, 50% or 75%) of showing a happy rather than a neutral expression. In the social aversion block, the other three faces were presented, each of which had a different likelihood (25%, 50% or 75%) of displaying a fearful rather than a neutral expression. The six faces were randomly assigned to the blocks and likelihoods for each participant and were presented in a pseudo-random order.

Subjects were asked to learn how likely it was, on average, that a given face displayed an emotional expression. They indicated this likelihood on a visual analogue scale, ranging from 0% to 100%, in response to the question 'How likely is it that [name] is [HAPPY / AFRAID]?'. Participants were told to start with a guess, and to subsequently base their ratings on the intuition or 'gut feeling' they derived from all the times they had seen a given name-face pairing before.

Figure 1: *Example of a social learning task trial (see main text for details).*



The task practice consisted of 8 repetitions of each name-face pair, resulting in 24 trials per block and 48 practice trials in total (which were performed outside the MRI scanner). The experimental phase (which was completed inside the MRI scanner) included 12 presentations of each name-face pair, resulting in 36 trials per block and 72 experimental trials in total.

3.3.2.3 fMRI Data Acquisition

A three-Tesla Siemens scanner (Siemens AG, Erlangen, Germany) with a 32-channel head coil was used to acquire blood oxygenation level dependent (BOLD) functional images. A GRAPPA multiband sequence was utilised with an acceleration factor of 6, a repetition time (TR) of 700ms, an echo time (TE) of 30ms, and a flip angle (FA) of 90°. The whole brain was covered by the field of view (FOV) with a voxel resolution of 2.4 x 2.4 x 2.4mm^3. Additionally, structural T1-weighted images were obtained with a magnetisation prepared rapid acquisition gradient echo sequence (TR = 2020ms, TE = 3.02ms, FA = 9°) with a FOV covering the whole brain and a voxel resolution of 1 x 1 x 1mm^3.

3.3.3 Analysis

3.3.3.1 Behavioural Analysis

Normality assumptions were not met for the questionnaire or name learning data. Group differences in these measures were therefore assessed using Mann-Whitney U tests.

Due to technical difficulties, the name test and social learning task *practice* data were lost for four HD and nine LD participants. The mixed-measure (group x valence x probability) ANOVA reported in the main text was performed on the likelihood ratings averaged across all available (practice and/or experimental) data for each participant. However, to ensure that the results were not biased by the missing data, the analysis was repeated using only the data from the experimental trials (which were available for all participants). The pattern of findings was almost identical for the two approaches (see supplement).

Moreover, to examine subjects' uncertainty regarding the task outcomes, likelihood ratings were converted into uncertainty scores. For this purpose, 50 (i.e. the value indicating maximal uncertainty) was subtracted from each likelihood rating of a given participant, separately for social reward and aversion blocks. The resulting values were transformed into absolutes and then averaged across probabilities (separately for the two blocks). This yielded two scores for

each subject, with lower scores indicating higher uncertainty about what outcomes to expect. To make the result interpretation more intuitive, scores were reversed by subtracting each value from the maximum score across all participants. Thus, the final uncertainty scores are high for high levels of uncertainty. A mixed-measure (group x valence) ANOVA was performed on the scores.

Additionally, to relate the task performance to real-life measures, uncertainty scores were entered into a regression analysis. Given that the scores for social reward and aversion blocks were highly correlated ($r = 0.57$; $p < 0.001$), they were averaged across the two blocks for the regression. The overall uncertainty score was then mean-centred and used to predict participants' motivation to engage in real-life social activities, together with BDI depression, RSAS, and mean-centred UIS negativity scores (calculated based on Sexton & Douglas 2009; note that very similar results were obtained when using the inhibitory subscale of the UIS, calculated based on Carlton Norton et al 2007; see supplement). An uncertainty score*UIS negativity interaction term was also included in the analysis, as it is likely that uncertainty about social outcomes primarily affects social engagement motivation when uncertainty is perceived as negative. STAI scores were not entered into the analysis, because this would have resulted in a violation of the multicollinearity assumption (Variance Inflation Factor > 10) due to a high correlation between STAI anxiety and BDI depression scores. This high correlation is in line with previous findings demonstrating that the STAI contains many items that map onto depression rather than specifically onto anxiety (Bados, Gómez-Benito, & Balaguer, 2010). However, it should be noted that STAI scores did not significantly contribute to the prediction of motivation when they were included in the regression model and BDI scores were removed.

3.3.3.2 Computational Modelling

A Rescorla-Wagner model (Rescorla & Wagner, 1972) was applied to the data, in which the prediction error (δ) for a given trial (t) is calculated as the difference between the predicted value (V) and the actual outcome (r):

$$\delta = r(t) - V(t).$$

Moreover, the predicted value for the next trial is updated by adding the prediction error, multiplied by a learning rate (α), to the previous prediction:

$$V(t+1) = V(t) + \alpha * \delta$$

The predicted value was (at first, see below) initialised at 0.5, which reflects the mean probability of encountering an emotional (rather than a neutral) expression, as well as the fact that it is reasonable for participants to initially rate the likelihood of seeing an emotional expression as 50% (expressing maximal uncertainty). Moreover, outcome values were set to 0 for neutral expressions and to 1 for happy or fearful faces, thus capturing the prediction of salient emotional outcomes. It should be noted that coding fearful faces as -1 (and initialising V at -0.5) simply leads to a change in sign of the prediction and prediction error values compared to coding fearful expressions as 1. The negative encoding of fear predictions can thus be assessed by examining negative covariations between prediction values and BOLD responses in the below parametric modulation fMRI analysis.

Given that the same stimuli and outcome contingencies were used during the practice and experimental phases of the social learning task, the computational model was fit to participants' data across both phases, but separately for social reward (happy) and aversion (fear) blocks. To account for the fact that forgetting was likely to occur between the practice and experimental trials, which were performed outside and inside the MRI scanner, respectively, prediction values were decayed towards the initial value of 0.5 for all stimuli after the 48 practice trials:

$$V(49) = V(49) + \gamma*(0.5-V(49))$$

where γ is the decay parameter determining the strength of the 'forgetting' effect. (Note that a similar method has been used by Collins & Frank, 2012 to capture the effects of working memory decay.)

The decay and learning rate parameters were estimated for each participant by minimising the sum of squared errors between the model prediction value (V*100) and the participant's likelihood ratings (similar to Hindi Attar, Finckh, & Büchel, 2012). Given that the practice data was missing for some participants, this fitting procedure was performed in two steps. Firstly, the model was fit to only the data of those participants for whom the practice data was available. Using the estimated parameters, the prediction values (V) for the first experimental trial of each stimulus were obtained for each included participant. These prediction values were then averaged across subjects. Subsequently, the model fitting was repeated for *all* participants for *only the experimental trials* (thus estimating only α and not γ), utilising the average prediction values from the first fitting step to initialise V (instead of using 0.5). In this way, the learning that occurred during the practice trials was taken into account for all subjects, without biasing the model fitting depending on whether or not practice data was available for a given participant (as V was initialised at the same value for *all* participants). Note that, for the participants for whom both practice and experimental data were available, the model fit and the parameter estimates were highly similar during the first and second step of this procedure, indicating that this approach does not seem to negatively affect the parameter estimation.

To assess group differences, Mann-Whitney U tests were conducted on the parameter estimates, as well as on the sum of squared error values which provide a measure of model fit.

3.3.3.3 fMRI Analysis

Preprocessing and analysis of the fMRI data was performed using the Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm). Functional images were realigned to the average position and motion parameters were saved for inclusion as regressors of no interest in the first-level analysis. Structural images were co-registered with the functional images and aligned to the SPM MNI space tissue probability map using segmentation. The resulting normalisation parameters were applied to the functional images which were subsequently smoothed with a Gaussian kernel of 6mm full-width at half-maximum.

Three first-level GLM analyses were run. GLM1 examined covariations between BOLD responses and values derived from the computational model described above. For this purpose, model-derived prediction values were entered as parametric modulators at the time of the cue, using separate regressors for the social reward and aversion blocks. In line with the previous literature, prediction values were calculated using average learning rate parameters across all participants (social reward block: $\alpha = 0.12$, social aversion block: $\alpha = 0.08$) to ensure that any group differences in the fMRI results were not due to the use of varying parameter values (Bakker et al., 2018; Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006; Daw, 2011; Pessiglione et al., 2006; Schonberg et al., 2007, 2010). However, for completeness, the above analysis was also run with individual learning rate values (GLM2), which yielded very similar results (see supplement).

As has been commonly reported in the previous literature (e.g. Behrens, Hunt, Woolrich, & Rushworth, 2009; Chowdhury et al., 2013; Rothkirch et al., 2017; Tobia et al., 2014), the outcome and prediction error (PE) values were highly correlated in the current study. It was, therefore, not feasible to unambiguously identify PE-related BOLD responses by using PE values as parametric modulators at the time of the outcome. Notably, brain responses encoding a canonical PE should, at the time of the outcome, covary positively with outcome values and negatively with prediction values. As in previous studies (e.g. Chowdhury et al.,

2013; Rothkirch et al., 2017; Rutledge et al., 2017), these two PE components were thus entered into the first-level analysis as separate parametric modulators at the time of the outcome (for the social reward and aversion block). Subsequently, MarsBar (Brett, Jean-Luc, Valabregue, & Poline, 2002) was used to extract average parameter estimates for outcome and inverse prediction encoding from a 6mm sphere around striatal coordinates that have been found to encode PEs in a previous meta-analysis (left ROI: -10 8 -6; right ROI: 10 8 -10; Chase et al., 2015). The extracted values were then compared between groups by conducting one-way ANOVAs.

Additionally, a third GLM analysis was performed (GLM3) to assess valence-dependent BOLD responses to the cues and outcomes. Onset timings of the following events were entered as regressors: name cues from the social aversion block, name cues from the social reward block, fearful faces, happy faces, and neutral faces. Subsequently, contrasts were run for social reward vs. aversion cues, fearful vs. neutral faces, and happy vs. neutral faces.

In all three GLM analyses, the regressors of interest, as well as their temporal derivatives, were convolved with the haemodynamic response function. Moreover, the six motion parameters from the realignment preprocessing step and a constant, as well as the onsets of the rating scale, were included as regressors of no interest.

On the second level, one-sample t-tests were performed on the data of the LD control group to assess main effects, and one-way ANOVAs were conducted for group comparisons. All results are reported at a voxelwise threshold of 0.01 (uncorrected) and are family wise error (FWE) corrected at $p<0.05$ at the cluster-level.

Finally, to relate the fMRI results to real-life measures, parameter estimates were extracted from the peak voxels of the prediction-related group comparison and were correlated with participants' reported motivation to engage in positive social interactions (similar to Gradin et al., 2011).

3.4 Results

3.4.1 Demographic and Questionnaire Measures

Mann-Whitney U tests revealed that there were no significant group differences in age (U = 219, p = 0.970). As expected, BDI (U = 0, p < 0.001), RSAS (U = 22, p < 0.001), STAI-T (U = 0, p < 0.001), UIS negativity (U = 17, p < 0.001), and PANAS Negative Affect Scale (U = 65, p < 0.001) scores were significantly higher in HD than in LD participants. Additionally, PANAS Positive Affect Scale scores were significantly lower in HD than in LD subjects (U = 349, p = 0.001; see Table 1).

Table 1: *Demographic data and questionnaire scores for individuals with high (HD) and low (LD) depression scores.*

	HD (N = 21)		LD (N = 22)	
	Mean	SD	Mean	SD
Age (years)	23.20	5.66	22.45	4.35
N females/ males	17/4	-	14/8	-
BDI*	26.05	9.63	1.36	1.84
RSAS*	18.57	6.43	5.77	4.31
STAI-T*	57.75	7.12	27.85	6.92
UIS - neg*	94.71	17.81	52.76	17.19
PANAS - pos*	24.38	5.71	31.52	6.57
PANAS - neg*	21.29	7.27	13.43	5.26

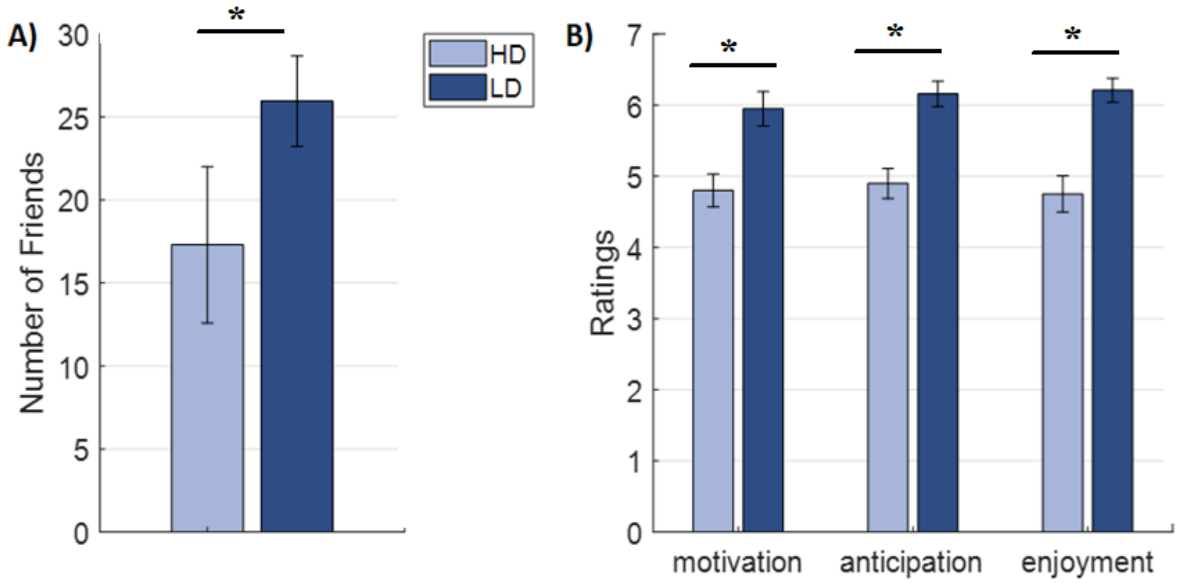
SD, standard deviation; BDI, Beck Depression Inventory; RSAS, Revised Social Anhedonia Scale; STAS-T, trait score of the State Trait Anxiety Inventory; UIS - neg, Uncertainty Intolerance Negativity Scale; PANAS-pos/neg, positive and negative mood scores of the Positive and Negative Affect Scale; * asterisks indicate significant group differences

3.4.2 Real-Life Social Interactions

Compared to LD subjects, HD participants indicated having significantly fewer friends (U = 320, p = 0.001; see Figure 2A), feeling less close to their friends (U = 364, p < 0.001), and finding it more difficult to form new friendships (U = 47, p < 0.001).

Moreover, HD individuals demonstrated significantly reduced motivation to engage in positive social activities (U = 294, p = 0.003), as well as significantly decreased anticipation (U = 316, p < 0.001) and enjoyment (U = 323, p < 0.001) of pleasant social activities, compared to LD controls (see Figure 2B). By contrast, no group differences were observed for anticipatory (U = 223, p = 0.365), motivational (U = 227, p = 0.309), or consummatory (U = 226, p = 0.322) responses to pleasant *non-social* activities.

Figure 2: *A) Number of friends and B) motivational, anticipatory, and enjoyment ratings for pleasant social activities in individuals with high (HD) and low (LD) depression scores.*



3.4.3 Name Learning Test Performance

For the name learning test, Mann-Whitney U tests showed no significant group differences in the memorising time (U = 86, p = 0.320), accuracy (U = 88, p = 0.363), reaction times (U = 135, p = 0.320), or number of trials needed to reach criterion (U = 126, p = 0.536). Thus, there was no indication that HD subjects displayed any *general* deficits in associative learning (between names and face identities).

3.4.4 Social Learning Task Performance

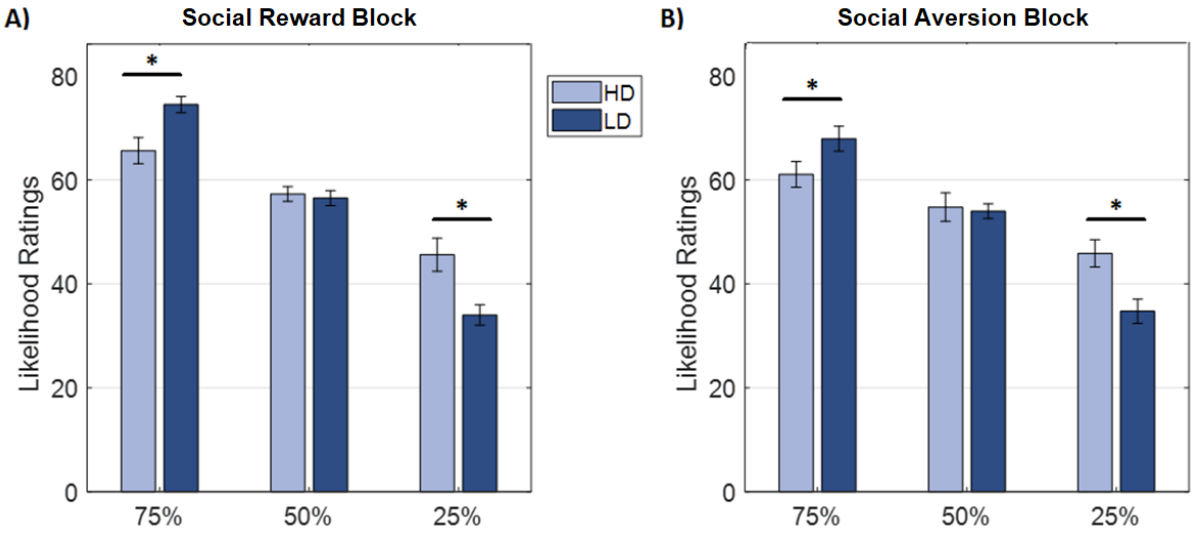
A mixed measure ANOVA (group x valence x probability) performed on participants' likelihood ratings revealed the expected main effect of probability (F(2, 82) = 94.95, p < 0.001), with participants rating the likelihood of seeing an emotional expression higher after cues that were more likely to be followed by an emotional face. Moreover, a main effect of valence was observed (F(1,41) = 8.30, p = 0.006) which indicated that participants rated the overall likelihood of seeing happy faces as higher than the likelihood of seeing fearful faces. Additionally, a group by probability interaction was found (F(2,82) = 11.77, p < 0.001) which was followed up as described below. All other main effects and interactions were not significant (all F < 2.3).

Follow-up one-way ANOVAs revealed that, compared to LD controls, HD participants' likelihood ratings were significantly *lower* on trials with a 75% chance of showing a happy (F(1,41) = 9.12, p = 0.004) or fearful (F(1,41) = 3.98, p = 0.053) expression. By contrast, HD subjects' ratings were significantly *higher* than those of controls on trials with a 25% chance of showing a happy (F(1,41) = 9.82, p = 0.003) or fearful (F(1,41) = 10.18, p = 0.003) face. No group differences were found on trials with a 50% chance of displaying a happy (F(1,41) = 0.15, p = 0.698) or fearful (F(1,41) = 0.07, p = 0.796) expression.

Visual inspection of the data revealed that the above group effects seemed to be due to HD participants' ratings being generally closer to 50% than those of controls, potentially indicating

increased uncertainty about what outcomes to expect (see Figure 3). To formally test this suggestion, a mixed-measure (group x valence) ANOVA was conducted on participants' uncertainty scores (which indicate the average difference between subjects' ratings and 50%; see Analysis section). This analysis revealed that HD subjects, indeed, tended to be more uncertain about the social task outcomes than controls ($F(1,41) = 3.67$, $p = 0.062$). Additionally, a significant main effect of valence indicated that subjects were more uncertain about aversive than about rewarding outcomes ($F(1,41) = 6.62$, $p = 0.014$). No significant interaction effect was observed ($F(1,41) = 0.160$, $p = 0.692$).

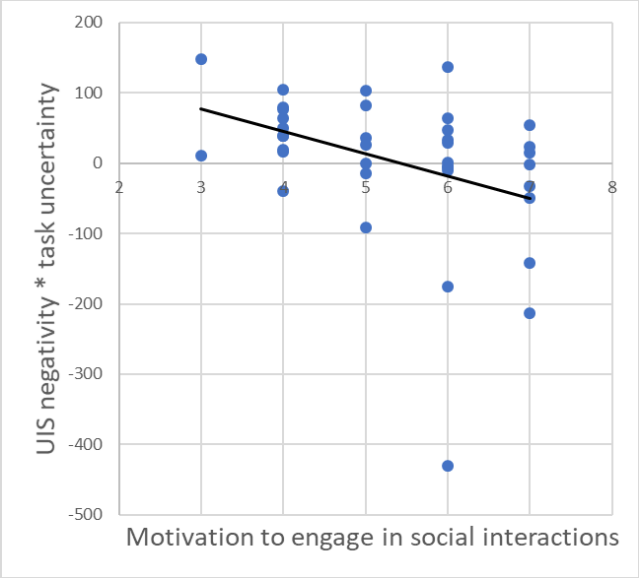
Figure 3: *Likelihood ratings by chance of seeing an emotional face for A) the social reward and B) the social aversion block in individuals with high (HD) and low (LD) depression scores.*



Moreover, a multiple regression analysis revealed that task uncertainty scores (averaged across blocks), together with questionnaire measures, predicted participants' motivation to engage in pleasant social activities ($F(5, 32) = 8.57$, $p < 0.001$, $R^2 = 0.51$). Predictors significantly contributing to this relation were the main effect of UIS negativity ($\beta = -0.55$, $p = 0.008$), the UIS negativity * task uncertainty interaction term ($\beta = -0.32$, $p = 0.015$; see Figure 4), and, marginally, RSAS social anhedonia scores ($\beta = -0.37$, $p = 0.061$). By contrast, the main effect of task uncertainty ($\beta = -0.21$, $p = 0.096$) and BDI depression scores ($\beta = 0.32$, $p = 0.149$) had no significant effect. Thus, the motivation to engage in pleasant social activities

was particularly reduced in individuals who were uncertain about what social outcomes to expect and who experienced uncertainty as negative.

Figure 4: *Scatter plot showing the association between motivation to engage in pleasant social activities and uncertainty intolerance (UIS) * task uncertainty interaction values.*



3.4.5 Task Feedback Questionnaire Responses

Finally, in a task feedback questionnaire, HD subjects demonstrated a tendency to show higher emotional responses to fearful expressions than controls (U = 142, p = 0.069), while their self-rated ability to remember happy faces was marginally decreased (U = 280, p = 0.065). No group differences were found for emotional responses to happy faces (U = 229, p = 0.615), or for the reported ability to remember fearful faces (U = 245, p = 0.363).

3.4.6 Computational Modelling

Mann-Whitney U tests on the model parameters revealed that learning rates were significantly lower in HD than in LD participants, both in the social reward (U = 351, p = 0.004) and in the social aversion (U = 355, p = 0.003) block. The model fit, as indicated by the sum of squared errors, did not differ significantly between groups in either the social reward (U = 171, p = 0.145; U = 169, p = 0.132) or aversion (U = 189, p = 0.308; U = 182, p = 0.234) block when using individual or averaged parameters (respectively).

3.4.7 fMRI Results

3.4.7.1 Neural Prediction Value Encoding

In the LD group, a significant covariation between BOLD responses and model-based social reward (i.e. happy expression) prediction values was observed in a right-lateralised cluster ranging from the superior to the inferior temporal lobe and the fusiform gyrus (see Table 2). No significant (positive or negative) covariations between BOLD responses and social aversion (i.e. fearful expression) prediction values were observed.

Group comparisons revealed reduced social reward prediction encoding in HD, compared to LD, subjects in the superior parietal lobe/ precuneus, as well as in a cluster including the right insula, supramarginal gyrus and superior temporal lobe (see Table 3 and Figure 5). No group differences were found for social aversion prediction encoding.

Across all subjects, correlation analyses revealed a significant positive correlation between participants' motivation to engage in pleasant social activities and parameter estimates extracted from the peak group comparison voxels in the parietal lobe (r = 0.49, p = 0.002) and insula (r = 0.36, p = 0.023). This relationship remained significant for the parietal lobe (r = 0.36, p = 0.027), but not the insula (r = 0.25, p = 0.137), when BDI depression scores and task uncertainty scores were controlled for (in a partial correlation).

3.4.7.2 Neural Prediction Error Encoding

One-way ANOVAs were conducted on the average parameter estimates extracted from the left and right striatal ROI for the encoding of outcome and inverse prediction values (i.e. the two PE components). This analysis revealed no significant group differences for either the social reward or the social aversion block (all F < 2.9).

Figure 5: *Clusters showing lower social reward prediction encoding in individuals with high (HD) than with low (LD) depression scores, as well as parameter estimates extracted from A) the right insula peak voxel and B) the parietal peak voxel.*

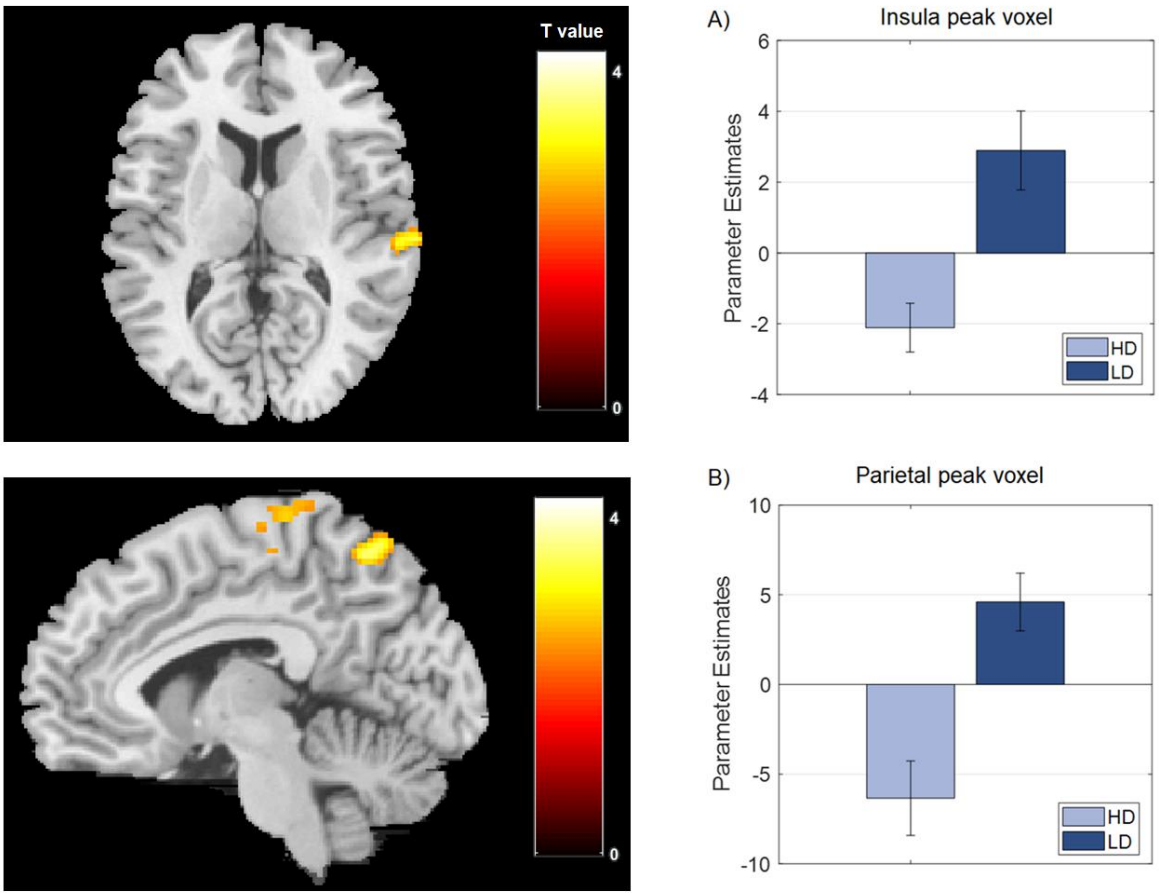


Table 2: *Parametric modulation results for social reward prediction encoding in control participants (LD) only.*

	MNI coordinates				
Brain Region	X	Y	Z	Z score	*p* value
Right Inferior Temporal Lobe	52	-36	-22	4.40	0.025
Right Superior Temporal Lobe	44	-24	-4	3.21	
Right Fusiform Gyrus	38	-34	-22	3.12	

Voxelwise thresholded at p<0.01; whole-brain cluster p values are family-wise error corrected at p < .05

Table 3. *Parametric modulation results for social reward prediction encoding in individuals with low (LD) vs. high (HD) depression scores.*

	MNI coordinates				
Brain Region	X	Y	Z	Z score	*p* value
LD > HD					
Superior Parietal Lobe/ Precuneus	-18	-58	68	3.80	0.001
Right Insula	48	-20	18	3.47	0.045
Right Supramarginal Gyrus	58	-32	24	3.28	
Right Superior Temporal Lobe	68	-22	12	3.17	

Voxelwise thresholded at p<0.01; whole-brain cluster p values are family-wise error corrected at p < .05

3.4.7.3 Neural Responses to Name Cues and Emotional Faces

None of the name cue or face contrasts resulted in any significant clusters in the LD group alone. Yet, group comparisons revealed significantly higher activation to fearful (vs. neutral) faces in HD compared to LD subjects in the bilateral supramarginal gyrus, right fusiform gyrus, bilateral inferior temporal lobe, dorsal anterior cingulate, and in a cluster ranging from the dorsolateral to the ventrolateral PFC and to the insula (see Table 4). No group differences were observed for the happy vs. neutral face contrast or for the social reward vs. social aversion name cue contrast.

Table 4: *Regions showing higher responses to fearful (vs. neutral) faces in individuals with high (HD) vs. low (LD) depression scores.*

	MNI coordinates				
Brain Region	X	Y	Z	Z score	*p* value
HD > LD					
Dorsal ACC/ MCC	-2	10	28	4.73	<0.001
Right Occipital Lobe	18	-92	-8	4.30	0.033
Right Fusiform Gyrus	34	-76	-18	3.56	
Right dlPFC (BA 8)	50	24	42	4.25	<0.001
Right vlPFC (BA 45)	54	32	10	3.50	
Right Insula	46	10	12	3.18	
Right Supramarginal Gyrus	36	-46	50	4.01	<0.001
Right Inferior Temporal Lobe	58	-54	-4	3.99	0.002
Left Inferior Temporal Lobe	-54	-58	-14	3.96	0.034
Left Supramarginal Gyrus	-28	-48	52	3.36	0.001

Voxelwise thresholded at p<0.01; whole-brain cluster p values family-wise error corrected at p < .05; ACC, anterior cingulate cortex; MCC, mid cingulate cortex; dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; BA, Brodmann Area

3.5 Discussion

3.5.1 Uncertainty about social outcomes predicts reduced social engagement motivation

The current study examined learning from social outcomes in individuals with high (HD) and low (LD) depression symptoms, linking task performance to measures of real-life social experiences.

It was found that HD participants reported having fewer friends and feeling less close to their friends than LD controls. Additionally, HD subjects showed reduced anticipatory, motivational and consummatory responses to pleasant social (but not non-social) activities. These results replicate our previous findings ([study 1]; Frey et al., 2019) and are in agreement with past observations of increased social anhedonia (Blanchard, Horan, & Brown, 2001; Szczepanik et al., 2017) and decreased social network sizes in depression (Brim et al., 1982; Gotlib & Lee, 1989; Youngren & Lewinsohn, 1980).

Moreover, in both the social reward and the social aversion block of our learning task, HD individuals *under*estimated the likelihood of being presented with emotional faces on *high* probability trials, while they *over*estimated this likelihood on *low* probability trials. In other words, HD subjects provided ratings close to 50% across all trial types, indicating a general uncertainty about what social outcomes to expect.

These findings are partly consistent with previous reports of impaired reward conditioning in depression (Kumar et al., 2008; Robinson et al., 2012; see also Chen et al., 2015). Yet, it may seem somewhat surprising that HD subjects demonstrated higher uncertainty (and thus decreased learning) in the social aversion block, considering that past studies have observed *enhanced* punishment learning in depression (Beevers et al., 2013; Maddox et al., 2012). A possible explanation of this finding is that the social stimuli used in the current study may have been particularly likely to induce rumination in HD individuals, which may have interfered with the aversion learning process (Whitmer et al., 2012). Moreover, it is worth noting that, unlike

previous tasks, the current paradigm required the *continuous* formation, updating and working memory maintenance of *explicit* outcome contingencies. This may have been particularly difficult for HD individuals (independent of the stimulus valence), which would explain the general learning deficit and increase in uncertainty observed in this group.

Notably, in everyday social cognition both implicit and explicit processes play a role (Frith & Frith, 2008). Thus, HD individuals' impaired ability to learn to explicitly predict other people's responses is likely to have an effect on real-life social functioning. In line with this suggestion, the current study found that task-based uncertainty, in interaction with the perceived negativity of uncertainty, significantly predicted participants' motivation to engage in positive social activities (even when depression scores were controlled for). That is to say, subjects who demonstrated more uncertainty about (and thus worse learning from) social outcomes in the task, and who were more averse to uncertainty in general, were less motivated to engage in pleasant social activities in real life. Importantly, HD subjects demonstrated high levels of task uncertainty, regarded uncertainty as negative, and displayed reduced social engagement motivation. Taken together, these findings suggest that deficits in learning from social outcomes may contribute to social withdrawal in depressed individuals. Social disengagement, in turn, may further increase depressed subjects' uncertainty regarding social encounters by reducing their exposure to situations in which social outcome contingencies can be learned.

The current findings are consistent with previous observations of increased intolerance of uncertainty in depression (Carleton et al., 2012). Moreover, past studies have reported a link between uncertainty intolerance and depressive rumination (Yook, Kim, Suh, & Lee, 2010), and it has been argued that uncertainty leads to behavioural inhibition when it is regarded as negative (Carleton, 2016). It may thus be the case that, in response to higher social outcome uncertainty, depressed individuals are prone to ruminate about possible negative outcomes, which reduces (/inhibits) their motivation to engage in social activities. This idea is supported by the supplementary analysis of the present study which shows that the interaction between

task uncertainty and *inhibitory* uncertainty intolerance predicts reduced social engagement motivation. In addition, the above suggestion is in line with our previous findings showing that increased negative social feedback expectancies are associated with social disengagement in individuals with high depressive symptomatology ([study 1]; Frey et al., 2019). It would be of interest for future studies to examine whether the relation between uncertainty and social withdrawal is indeed mediated by rumination-induced negative expectancies.

3.5.2 Neural predication of social rewards is impaired in HD subjects

Consistent with the behavioural findings, the current study found that HD individuals showed impaired learning signals on the neural level. Specifically, compared to controls, HD participants displayed lower covariation between social reward prediction values and BOLD responses in the superior parietal lobe, as well as in a cluster extending from the insula to the supramarginal gyrus and superior temporal lobe.

Given the superior parietal lobe's involvement in attentional processing (Behrmann, Geng, & Shomstein, 2004), this region may have been recruited after the repeated pairing of cues with happy expressions because this association made the cues a more salient target for active attentional processing. Moreover, the insula, supramarginal gyrus and temporal lobe have previously been implicated in the processing (Fusar-Poli et al., 2009) and working memory maintenance (Nichols, Kao, Verfaellie, & Gabrieli, 2006) of faces. Hence, the increased engagement of these regions by cues that were more frequently paired with task-relevant happy expressions may reflect a working memory mechanism that aids the learning processes.

Based on the above, the current findings of reduced social reward prediction encoding in HD individuals could be taken to indicate that the latter display deficits in neural attention and working memory processing during learning. However, it should be noted that BOLD responses were not simply reduced in HD subjects, but were instead reversed. That is to say, rather than being close to zero, parameter estimates extracted from the peak voxels of the

group contrast were significantly below zero in the HD group (and significantly above zero in the LD group; see supplement). This indicates that, in HD individuals, BOLD responses were higher the more frequently cues were associated with *neutral* faces. A possible explanation for this finding is that, due to negative processing biases, HD individuals perceived the ambiguous neutral faces as negative, especially when they were displayed amongst happy expressions. Such a negative perception may have made the neutral faces particularly salient, and may thus have led to the recruitment of attentional and working memory resources to represent and predict neutral rather than happy faces.

The above suggestion is consistent with previous behavioural observations showing that depressed individuals tend to perceive neutral expressions as negative (Bouhuys et al., 1999; Hale et al., 1998; Leppannen et al., 2004). Moreover, the increased salience of neutral faces may also have contributed to the behavioural findings of the current study. Specifically, the mismatch between task demands (of happy expression prediction) and neural processes (supporting neutral expressions prediction) may have given rise to the uncertainty reflected in HD participants' task ratings. Notably, a similar mechanism could play a role in real life, if automatic processing supports learning from negative social feedback and reflective processes are needed (but potentially unable) to accurately predict the positive value of engaging in social activities (along the lines of the dual process model of Beevers, 2005).

It thus seems plausible that the neural processes of HD subjects supported the prediction of negatively perceived neutral expressions rather than that of happy faces. Following on from this suggestion, it may have been expected that the neural response to happy vs. neutral faces would have differed between groups, due to increased (aversive) processing of neutral faces in HD participants. Yet, such a group effect was not observed. This may potentially be the case because the prediction of neutral expressions in HD subjects, after some learning had occurred, may have engaged preparatory downregulation processes resulting in similar neural responses to neutral faces in HD and LD individuals.

Interestingly, the current study further found that lower social reward prediction encoding in the parietal lobe was significantly correlated with reduced motivation to engage in positive social activities in real life, even when task uncertainty and depression scores were controlled for. Considering the abovementioned involvement of the parietal lobe in attentional processing (Behrmann et al., 2004), this may indicate that individuals who demonstrate diminished attentional processing of positive social feedback, or enhanced attentional processing of ambiguous and negative feedback, may be less motivated to engage in social activities (although the direction of this relation cannot be determined based on the present data). This may especially be the case in HD subjects, who displayed decreased parietal prediction encoding, as well as reduced motivation to engage in pleasant social activities.

With regards to social aversion processing, the current study found that HD individuals demonstrated increased responses to fearful (vs. neutral) faces in a range of areas, including the fusiform gyrus, insula, dorsal ACC, ventrolateral PFC and dorsolateral PFC. These regions have, among other functions, previously been implicated in the processing of fearful faces (Fusar-Poli et al., 2009), as well as in emotion regulation (Frank et al., 2014), and have been shown to be abnormally engaged during emotional processing in depression (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013). The increased responsiveness of these regions to fearful faces in HD individuals is consistent with the observed behavioural results of marginally stronger self-reported emotional responses to fearful faces in HD compared to LD participants.

3.5.3 Conclusion

All in all, the results of the current study suggest that individuals with high depression symptoms demonstrate impaired learning from social outcomes, on both the neural and the behavioural level. Importantly, this deficit is associated with reduced motivation to engage in real-life social activities, partly due to increased negatively-perceived uncertainty about what to expect from social situations. To identify potential treatment targets for these impairments, future studies are called for to examine how different neurotransmitters are involved in learning from social outcomes. It would be of particular interest to assess the contribution of dopamine and serotonin to the social learning process, given that these neurotransmitters have been implicated in the psychopathology of depression (Belujon & Grace, 2017; Nemeroff & Owens, 2009), social processing (Kiser et al., 2012; Skuse & Gallagher, 2009; Steenbergen et al., 2016), and learning from non-social outcomes (Boureau & Dayan, 2011; Cools et al., 2011; Homberg, 2012; Schultz, 2010).

4 Effects of Dopamine and Serotonin Depletion on Behavioural and Neural Responses during Social Learning

[Study 3]

4.1 Abstract

Background: In previous research, we have shown that individuals with high depression scores demonstrate impaired social learning, and that these deficits are associated with reduced motivation to engage in real-life social activities ([study 2]; Frey & McCabe, 2019). Given that depression has been linked to abnormal dopamine (DA) and serotonin (5-HT) functioning (Belujon & Grace, 2017; Nemeroff & Owens, 2009), the current study aimed to elucidate the role of these neurotransmitters in social learning with the use of a dietary depletion manipulation.

Methods: In a double-blind design, 70 healthy volunteers were randomly allocated to the 5-HT depletion (N = 24), DA depletion (N = 24), or placebo (N = 22) group. Participants performed a social learning task during fMRI scanning in which they were shown name cues followed by faces that probabilistically displayed happy, neutral, or fearful expressions. After each name cue, subjects were asked to rate the likelihood of seeing one of the emotional expressions. Using computational modelling, the behavioural and neural effects of the depletion manipulation on social learning were examined.

Results: Behaviourally, the likelihood ratings of 5-HT depleted subjects were indicative of reduced learning from social rewards (i.e. from happy expressions) compared to placebo controls, with a marginal effect in the same direction in the DA depletion group. On the neural level, whole brain analysis revealed that 5-HT depletion reduced social reward prediction encoding in the insula, temporal lobe, dorsal anterior cingulate, and lateral to medial prefrontal cortex compared to placebo. Moreover, DA depletion decreased the representation of social reward predictions in the dorsal anterior cingulate and medial prefrontal cortex.

Conclusion: These results indicate that 5-HT depletion impairs learning from social rewards, on both the behavioural and the neural level, possibly partly by increasing attentional and working memory processing of negatively interpreted neutral faces. DA depletion had a similar, although less pervasive, effect. Interestingly, the behavioural and neural responses observed after 5-HT depletion in the current study closely resemble our previous findings in individuals with high depression scores. It may thus be the case that decreased 5-HT levels contribute to deficits in social learning in depression.

4.2 Introduction

Being able to predict other people's responses is crucial for successful interpersonal interactions, and deficits in learning from social outcomes are likely to have far-reaching consequences. For instance, we have previously found that impaired (task-based) social learning is associated with diminished social engagement motivation and more frequent experiences of negative social encounters in real life ([studies 1 & 2]; Frey, Frank, & McCabe, 2019; Frey & McCabe, 2019). This association may be particularly relevant to the understanding of social deficits in major depressive disorder, as we have shown that individuals with depression symptoms demonstrate reduced learning from social feedback. Specifically, subjects with high depression scores displayed decreased updating of their behaviours in response to interpersonal feedback and were less certain about what social outcomes to expect compared to controls. Moreover, on the neural level, individuals with high depression scores demonstrated weaker social reward prediction encoding in the insula, temporal lobe, and parietal lobe compared to controls ([studies 1 & 2]; Frey et al., 2019; Frey & McCabe, 2019).

Given that social functioning deficits are thought to contribute to the onset and maintenance of depression (Kupferberg et al., 2016; Segrin, 2000), the abovementioned impairments may be potential targets for pharmacological treatments. It is thus important to gain a better understanding of which neurotransmitters may contribute to reduced social learning in

depression. Based on previous research, it seems likely that altered dopamine (DA) or serotonin (5-HT) functioning may play a role in these deficits, given that these neurotransmitters have been implicated in the psychopathology of depression (Belujon & Grace, 2017; Nemeroff & Owens, 2009), social processing (Kiser et al., 2012; Skuse & Gallagher, 2009; Steenbergen et al., 2016), and non-social learning (Boureau & Dayan, 2011; Cools et al., 2011; Homberg, 2012; Schultz, 2010).

While studies using DA or 5-HT manipulations in combination with *social* learning paradigms are lacking, there is extensive research on the effect of these neurotransmitters on learning from *non-social* outcomes. For instance, behavioural studies have found that high doses of D2 antagonists impair reward learning and prediction (Diederen et al., 2017; Eisenegger et al., 2014; Jocham, Klein, & Ullsperger, 2014), and low doses of D2 agonists reduce the acquisition of reward biases, potentially due to autoreceptor binding (Pizzagalli, Evins, et al., 2008). In addition, DA depletion has been shown to enhance punishment learning in probabilistic selection and reversal learning tasks (Cox et al., 2015; Robinson et al., 2010), whereas levodopa and (meth)amphetamine have been reported to improve reward-based decision-making and context conditioning, respectively (Childs & de Wit, 2013; Chowdhury et al., 2013; Coulthard et al., 2012; Frank et al., 2004; Mayo et al., 2013; Pessiglione et al., 2006). Interestingly, it has further been shown that higher reward-induced DA release in the striatum (as measured by positron emission tomography) is not only associated with better learning task performance, but also with more reward-oriented behaviour in real life (Kasanova et al., 2017).

Regarding the involvement of 5-HT in learning, it has been demonstrated that lowering 5-HT levels via tryptophan depletion impairs punishment- and reward-based decision-making and reversal learning (Crockett, Clark, Apergis-Schoute, Morein-Zamir, & Robbins, 2012; Rogers et al., 1999; Seymour, Daw, Roiser, Dayan, & Dolan, 2012; Tanaka et al., 2009; although enhanced prediction accuracy for negative outcomes has also been observed; Cools, Robinson, et al., 2008; Robinson, Cools, & Sahakian, 2012). Similarly, acute doses of

selective serotonin inhibitors (SSRIs), which are thought to lower 5-HT levels via autoreceptor effects, have been found to impair reversal learning (Chamberlain et al., 2006; Skandali et al., 2018), while increasing 5-HT functioning via chronic SSRI treatment has been reported to improve reward learning (Scholl et al., 2017).

On the neural level, animal studies have provided insights into the mechanistic role of DA and 5-HT in learning. Such studies have shown that midbrain DA neurons fire in the presence of cues that reliably predict rewards, as well as when unexpected rewards are encountered. Moreover, if expected rewards are omitted, tonic DA firing drops below baseline levels (Schultz et al., 1997). This activity pattern is thought to represent prediction error encoding during outcome receipt, indicating that DA neurons compute the discrepancy between predicted and actual rewards (e.g. Suri & Schultz, 1999). In addition, it has been proposed that 5-HT responses may have an analogous role to DA activity in punishment learning. That is to say, 5-HT neuron firing may represent the computation of punishment (Boureau & Dayan, 2011; or salience, Matias, Lottem, Dugué, & Mainen, 2017) prediction errors. However, partly due to difficulties with identifying 5-HT neurons *in vivo*, this suggestion is somewhat tentative (Cools et al., 2011).

The mechanistic roles of DA and 5-HT during the learning process have been formalised using computational models. In these models, the (presumed) pattern of phasic DA or 5-HT firing is represented numerically, as an outcome prediction value (at the time of the cue) and a prediction error value (PE; at the time of the outcome). Throughout the learning process, PEs are used to update prediction values, which results in increasingly accurate predictions and decreasing PEs over time.

Model-derived prediction and PE values have been used as parametric modulators in functional magnetic resonance imaging (fMRI) analyses to examine the encoding of neural learning signals in humans. Using this approach, it has been found that increasing DA levels with low doses of D2 antagonists enhances reward prediction and PE encoding in the ventromedial prefrontal cortex (PFC) and striatum, respectively (Jocham et al., 2011).

Similarly, levodopa administration has been shown to increase reward PE encoding in the ventral striatum and putamen (Chowdhury et al., 2013; Pessiglione et al., 2006). By contrasts, reducing DA functioning with high doses of D2 antagonists decreases striatal PE representations (Jocham et al., 2014), and lowering DA levels via tyrosine and phenylalanine depletion results in diminished prediction responses in the caudate, thalamus, and midbrain, as well as in reduced PE encoding in the caudate, thalamus, and amygdala (Tobia et al., 2014). Overall, low levels of DA thus appear to be associated with impaired reward prediction and PE encoding, while heightened DA functioning enhances the representation of these learning signals.

5-HT manipulations have similarly been shown to affect neural learning processes. Specifically, lowering 5-HT levels via tryptophan depletion has been found to reduce punishment prediction encoding in the orbitofrontal cortex and amygdala (Hindi Attar et al., 2012). In addition, tryptophan depletion has been reported to decrease reward prediction respresentations in the dorsolateral and ventromedial PFC, anterior cingulate cortex (ACC), insula and precuneus (Seymour et al., 2012; Tobia et al., 2014), while also diminishing reward PE responses in the putamen (Seymour et al., 2012). Moreover, acute SSRI administration has been shown to attenuate (inverse) reward PE encoding in ACC and hippocampus (Kumar et al., 2008), while longer-term SSRI treatment has been found to strengthen representations of reward PEs in the ACC, ventromedial PFC, parietal cortex and (marginally) in the striatum (Scholl et al., 2017).

The above findings demonstrate that 5-HT and DA play a role in behavioural and neural learning processes when *non-social* outcomes are used. However, it is less clear whether, or how, these neurotransmitters are involved in *social* learning. The current study examined this question by lowering DA or 5-HT levels in healthy volunteers using acute tyrosine/ phenylalanine or tryptophan depletion, respectively. After consumption of the depletion drink (or a placebo), participants performed a social learning task in the MRI scanner during which they learned associations between name cues and rewarding (happy faces) or aversive

(fearful faces) social outcomes. Computational modelling was applied to the data to assess depletion effects on the neural encoding of social learning signals. It was hypothesised that both depletion manipulations would impair social reward learning, while social aversion learning may be enhanced after DA depletion and reduced following 5-HT depletion.

4.3 Methods

4.3.1 Participants

Seventy healthy, right-handed individuals between the age of 18 and 45 years took part in the current study. Volunteers were screened using the structured clinical interview for DSM-IV (SCID; First et al., 1998), and were asked a number of questions about their medical history. Subjects were ineligible if they had a history of any Axis I disorder, a significant current or past medical condition, or any contraindications to MRI scanning. Further exclusion criteria were the current use of any medications besides contraceptives, the use of any psychotropic medications or recreational drugs within the past three months, and smoking more than five cigarettes per week.

In a double-blind, between-subject design, eligible participants were randomly allocated to the DA depletion (N=24), 5-HT depletion (N=24), or placebo (N = 22) group (see further details below).

The study was approved by the University of Reading Ethics Committee (UREC 15/61). All subjects provided written informed consent and received a reimbursement of £40.

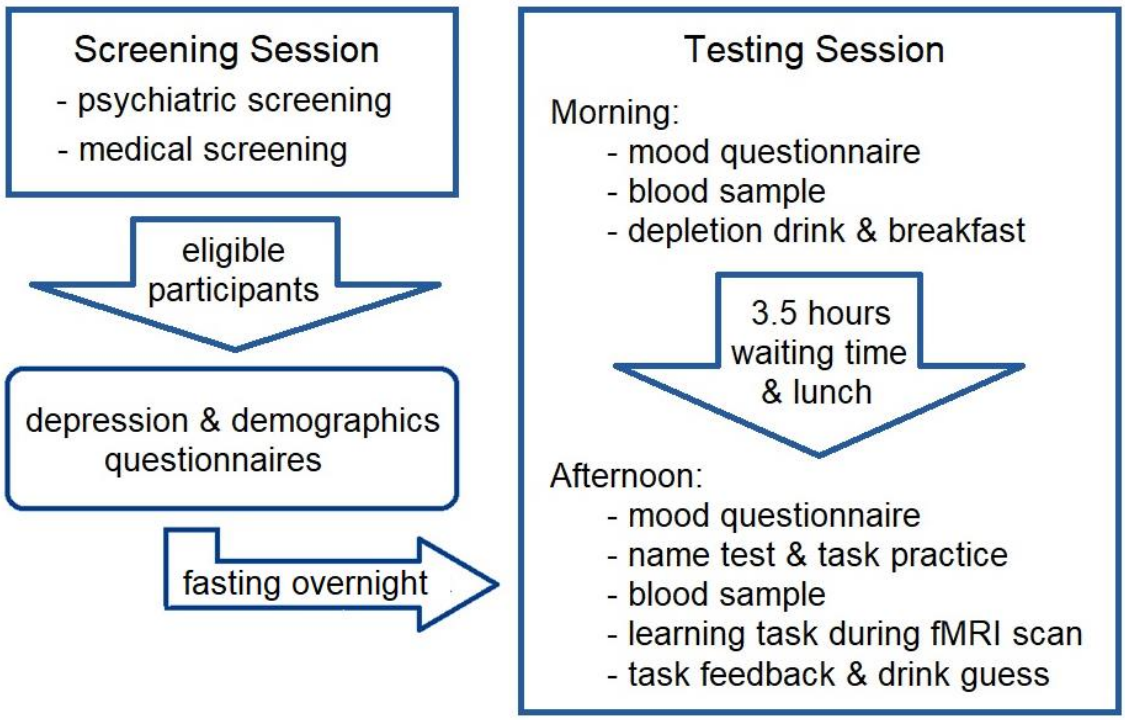
4.3.2 Procedure

Several days before the testing session, volunteers attended a screening visit during which the medical and SCID interviews were conducted to ensure that none of the exclusion criteria were met. Eligible participants were sent online versions of the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) and a demographics form to fill in at home.

Once the questionnaires had been completed, subjects were invited to attend the testing session. They were asked not to consume any food or drinks, besides water, after 10pm on the previous day, and to arrive at the study location at 9am on the testing day. At this point, participants completed the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegan, 1988) and gave a blood sample which was used to assess baseline amino acid levels. Subsequently, subjects consumed one of the three depletion drinks and were given a protein free breakfast bar. During the following 3.5 hours, participants occupied themselves in a waiting room, with lunch (protein free pasta with tomato sauce) being provided at 12 noon. This waiting period was chosen to ensure that the MRI scan took place 5 hours after consumption of the depletion drink, as the maximum depletion effect has been shown to occur around this time (Dougherty et al., 2008).

After the waiting period, subjects filled in the PANAS again, as well as a questionnaire assessing the potential experience of side effects. Subsequently, participants practiced the social learning task, as well as two other tasks not reported here, outside the MRI scanner. Additionally, subjects gave a second blood sample which was used to assess whether amino acid levels had been successfully depleted. Participants then performed the social learning task in the MRI scanner, and, after the scan, completed a task feedback questionnaire and guessed which drink they had consumed (see Figure 1 for an overview of the procedure).

Figure 1: *Flow chart of the study procedure; see main text for details.*



4.3.2.1 Amino Acid Depletion Drink

The *relative* amino acid amounts for the depletion drinks were based on previous 5-HT (Crockett, Clark, Smillie, & Robbins, 2012) and DA (Kelm & Boettiger, 2013) depletion studies. However, to reduce the experience of side effects, the *absolute* amounts were adjusted to each participant's body weight (which has been shown to lead to a reliable depletion effect with a slightly different mixture; see Dingerkus et al., 2012).

Specifically, the placebo drink contained the following amounts for a subject weighing 83.6kg (i.e. the average male weight in the UK), which were adjusted proportionally for lower or higher body weights: L-alanine, 4.1 g; L-arginine, 3.7 g; L-cystine, 2.0 g; glycine, 2.4 g; L-histidine, 2.4 g; L-isoleucine, 6 g; L-leucine, 10.1 g; L-lysine, 6.7 g; L-methionine, 2.3 g; L-proline, 9.2 g; L-phenylalanine, 4.3 g; L-serine, 5.2 g; and L-valine, 6.7 g; L-threonine, 4.9 g; L-tyrosine, 5.2 g; L-tryptophan; 3.0 g.

The depletion mixtures were identical to that of the placebo drink, except that the 5-HT depletion mixture did not contain tryptophan and the DA depletion mixture did not include tyrosine or phenylalanine.

The drinks were prepared by stirring the amino acids and a pinch of salt (to neutralise the bitter taste) into 120mL of tap water, 30mL of caramel syrup, and a tablespoon of oil (with liquid quantities being adjusted proportionally to the amino acid amounts).

4.3.2.2 Name Learning Test

Prior to performing the social learning task, participants completed a name selection and learning test, the procedure of which was identical to that reported in our previous study ([see method section of study 2]; Frey & McCabe, 2019). Briefly, participants rated a list of modified Scandinavian and Eastern European names regarding their familiarity and indicated the strength of any positive and negative associations they had with the names. The six lowest rated names were chosen as cues for the social learning task.

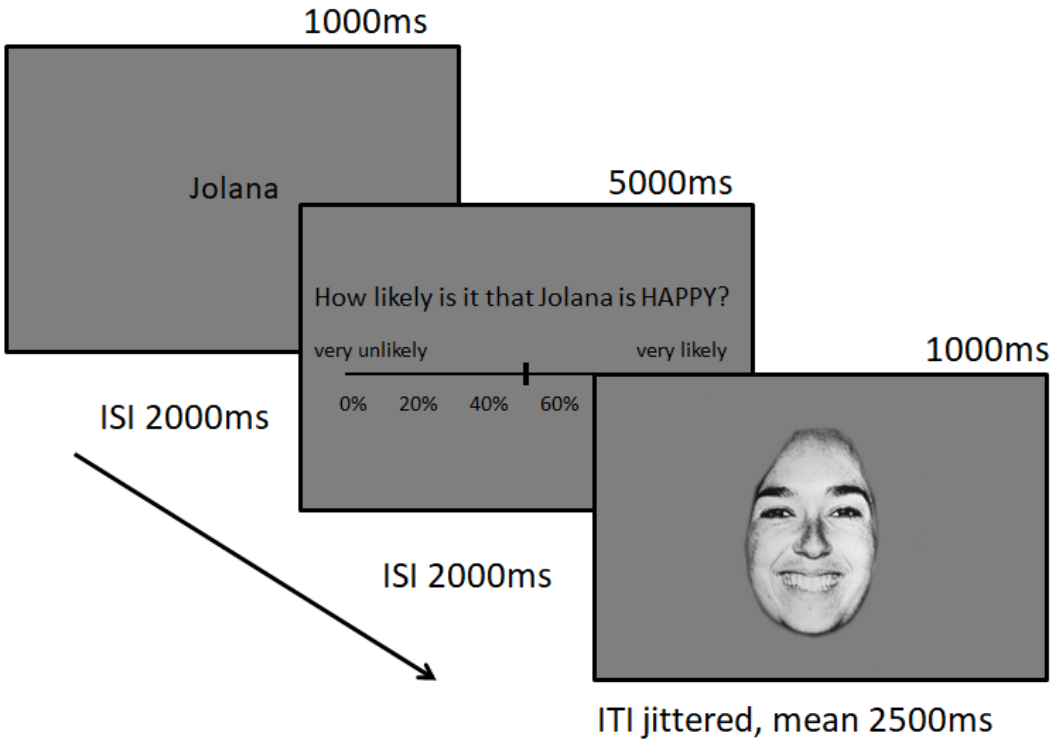
To familiarise participants with the name-face *identity* pairings, a name test was performed. During the test, the six selected names were coupled with three male and three female neutral faces from the Pictures of Facial Affect Series (Ekman & Friesen, 1976) and participants were asked to memorise the pairings. Subsequently, the names were replaced with numbers and only one name was shown at the top of the screen. Subjects were asked to select the number of the face that had been associated with the presented name. After their choice, participants were shown the correct face. The name test continued until subjects had completed three correct trials for each of the name-face pairings. Participants' memorising time, accuracy, reaction times and number of trials needed to reach criterion were recorded.

4.3.2.3 Social Learning Task

Participants' aim during the social learning task was to learn how likely it was that a given name cue was followed by a happy, neutral or fearful facial expression. Details of the task procedure can be found in our previous paper ([see methods section of study 2]; Frey &

McCabe, 2019). In brief, the task consisted of 48 practice and 72 experimental trials, which were divided into a social reward and a social aversion block. The blocks were performed in counterbalanced order and three name-face pairings were randomly allocated to each block. On a given trial, participants were presented with a name cue, followed by a rating scale (see below) and the face that had been paired with the name (see Figure 2). In the social reward block, each face had a different likelihood (25%, 50% or 75%) of displaying a happy rather than a neutral expression, while in the social aversion block each face had a different likelihood (25%, 50% or 75%) of showing a fearful rather than a neutral expression. Participants were asked to learn how likely it was that a given name was followed by an emotional face and to indicate this likelihood on a visual analogue scale (ranging from 0% to 100%). Subjects were instructed to start with a guess and to subsequently base their ratings on the intuition they gained from all the times they had seen the name-face pairing before.

Figure 2: *Example of a social learning task trial (see text for details).*



4.3.2.4 fMRI Data Acquisition

Blood oxygenation level dependent (BOLD) functional images were acquired using a three-Tesla Siemens scanner (Siemens AG, Erlangen, Germany) with a 32-channel head coil. During the social learning task, around 1500 volumes were obtained for each participant, using a multiband sequence with GRAPPA and an acceleration factor of 6. Other sequence parameters included a repetition time (TR) of 700ms, an echo time (TE) of 30ms, and a flip angle (FA) of 90°. The field of view (FOV) covered the whole brain with a voxel resolution of 2.4 x 2.4 x 2.4mm^3. Moreover, structural T1-weighted images were acquired utilising a magnetisation prepared rapid acquisition gradient echo sequence (TR = 2020ms, TE = 3.02ms, FA = 9°) with a FOV covering the whole brain and a voxel resolution of 1 x 1 x 1mm^3.

It should be noted that the MRI scanner was upgraded half-way through the study (from a MAGNETOM Trio to a MAGNETOM Prisma). However, scanning parameters were equivalent before and after the upgrade, and the groups were approximately matched before the upgrade (5-HT depletion N = 13; placebo N = 11; DA depletion N = 12). Moreover, a control variable indicating whether a given participant was scanned before or after the upgrade was included in the second-level fMRI analysis.

4.3.3 Analysis

4.3.3.1 Analysis of Amino Acid Plasma Levels

Blood samples (4mL) were taken using sodium heparin tubes and were centrifuged to obtain plasma, which was stored at -80C degrees. Before the biochemical analysis, plasma samples were deproteinised and filtered (using the procedure described by Prinsen et al., 2016). Relative amounts of tryptophan, tyrosine, phenylalanine and other large neutral amino acids (LNAA; leucine, isoleucine and valine) were determined using liquid chromatography. To assess the depletion effect, the ratio of each of the amino acids of interest (i.e. tryptophan, tyrosine, and phenylalanine) to the sum of the other LNAAs was calculated. This ratio is commonly used as a measure of the depletion effect (Evers et al., 2005; Hindi Attar et al.,

2012; Tobia et al., 2014), as the competition of the LNAAs at the blood brain barrier determines the uptake of the amino acids into the brain (Dingerkus et al., 2012; Oldendorf & Szabo, 1976). A group x time x amino acid mixed-measure analysis of variance (ANOVAs) was performed on the ratios to assess the depletion effects. As sphericity assumptions were not met, Greenhouse-Geisser corrected results are reported.

4.3.3.2 Behavioural Analysis

Where normality assumptions were met, questionnaire and task measures were analysed using one-way ANOVAs. Otherwise Kruskal-Wallis H tests were used. Additionally, chi-square tests were performed on categorical data.

Visual inspection of the learning task likelihood ratings revealed several clear outliers. Therefore, participants with values outside +/- 2 standard deviations of the mean were removed from the data set ($N_{5\text{-HT depletion}} = 3$, $N_{placebo} = 3$, $N_{DA\ depletion} = 4$). Subsequently, a group x valence x probability mixed-measure ANOVA was conducted, and interactions were followed up with one-way ANOVAs. As the sphericity assumption was violated for the probability factor, Greenhouse-Geisser corrected results are reported for the associated effects.

Moreover, to assess participants' uncertainty regarding the task outcomes, task likelihood ratings were converted into uncertainty scores, separately for social reward and aversion blocks (as in our previous study; see [study 2] Frey & McCabe, 2019). For this purpose, 50 (i.e. the value representing maximal uncertainty) was subtracted from the likelihood ratings of each subject. The resulting values were converted to absolutes and then averaged across probabilities (separately for the two blocks). This yielded two scores for each participant, with higher scores indicating lower uncertainty about what outcomes to expect. To make the result interpretation more intuitive, scores were reversed by subtracting each value from the maximum score across all participants. Thus, the final uncertainty scores are high for high levels of uncertainty.

4.3.3.3 Computational Modelling

As in our previous study using the same task ([see study 2]; Frey & McCabe, 2019), a Rescorla-Wagner model (Rescorla & Wagner, 1972) was applied to the data. In this model, prediction errors (δ) are computed for a given trial (t) by subtracting predicted (V) from actual (R) outcome values:

$$\delta = R(t) - V(t)$$

The prediction error, in turn, is multiplied by a learning rate (α) and added to the previous prediction to determine the prediction value for the subsequent trial:

$$V(t+1) = V(t) + \alpha*\delta$$

Given that, at the beginning of the task, is was reasonable for participants to guess that cues had a 50% chance of being followed by a neutral or an emotional expression, prediction values were initialised at 0.5. Moreover, outcome values were set to 0 for neutral expressions and to 1 for happy or fearful faces.

Considering that some forgetting of the likelihoods may have taken place between the performance of the practice and the experimental trials (which were completed outside and inside the MRI scanner, respectively), the prediction values for all stimuli were decayed towards the initial value of 0.5 after the 48 practice trials:

$$V(49) = V(49) + \gamma*(0.5-V(49))$$

The decay parameter, γ, indicates the strength of this forgetting effect (similar to the approach reported in Collins & Frank, 2012).

To estimate the learning rate and decay parameters, the model was fit to each participant's combined practice and experimental data (separately for social reward and aversion blocks) by minimising the mean squared error between the model prediction value (V*100) and the participant's likelihood ratings (as in Hindi Attar et al., 2012 and in our previous study [2], Frey & McCabe, 2019)

Kruskal-Wallis H tests were used to assess group differences in the parameter estimates, as well as in the model fit for individual and averaged parameters, with the latter being used in the fMRI analysis as described below.

4.3.3.4 fMRI Analysis

Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm) was used for the preprocessing and analysis of the fMRI data. Realignment to the average position and co-registration to the structural images was applied to the functional images. Additionally, the latter were moved into normalised space by aligning the structural images to the SPM MNI space tissue probability map using segmentation and applying the resulting transformation parameters to the functional images. Images were smoothed with a Gaussian kernel of 6mm full-width at half-maximum.

Three first level GLM analyses were run which were identical to those reported in our previous study ([see study 2]; Frey & McCabe, 2019). GLM1 assessed covariations between BOLD responses and model derived prediction values by using the latter as parametric modulators at the time of the cue (separately for the social reward and aversion blocks). The mean parameters across all participants were used to calculate the model-derived prediction values (social reward block: $\alpha = 0.14$, $\bar{\gamma} = 0.29$; social aversion block $\alpha = 0.12$, $\bar{\gamma} = 0.46$). This approach is commonly used and ensures that any observed group differences are not resulting from varying model parameters (Bakker et al., 2018; Daw et al., 2006; Daw, 2011; Pessiglione et al., 2006; Schonberg et al., 2007, 2010). Yet, for completeness, a second analysis (GLM2) was conducted in which prediction values were based on individual parameters, which yielded very similar results (see supplement).

The outcome and prediction error (PE) values in our data (as in many previous studies; e.g. Behrens et al., 2009; Chowdhury et al., 2013; Rothkirch et al., 2017; Tobia et al., 2014) were highly correlated. Thus, using PE values as parametric modulators at the time of the outcome would not have unambiguously identified PE-related BOLD responses. Therefore, the

approach outlined in our previous paper ([study 2] Frey & McCabe, 2019) was used to assess prediction error encoding. Briefly, the two PE components, i.e. inverse prediction values and outcome values, were used as parametric modulators at the time of the face presentation (separately for social reward and social aversion blocks). Subsequently, MarsBar (Brett et al., 2002) was used to extract average parameter estimates for the two components from a 6mm sphere around striatal coordinates that have been found to encode PEs in a previous meta-analysis (left ROI: -10 8 -6; right ROI: 10 8 -10; Chase et al., 2015). The extracted values were then compared between groups by conducting one-way ANOVAs.

To assess valence-dependent BOLD responses to the cues and outcomes, a third GLM analysis was performed (GLM3). For this purpose, the onsets of the following stimuli were included as regressors: name cues from the social aversion block, name cues from the social reward block, fearful faces, happy faces and neutral faces. Moreover, contrasts were run for social aversion vs. social reward cues, fearful vs. neutral faces, and happy vs. neutral faces.

In all three GLM analyses, the onsets of the rating scale, the six motion parameters from the realignment preprocessing step, and a constant were included, in addition to the regressors of interest and their temporal derivatives (convolved with the haemodynamic response function).

On the second level, main effects were examined by conducting one-sample t-tests on the placebo group data, and one-way ANOVAs were performed for group comparisons (placebo vs DA depletion, placebo vs 5-HT depletion, and DA vs 5-HT depletion). In the latter analysis, a covariate indicating whether a given participant was scanned before or after the scanner upgrade was included to control for any potential effects of the scanner upgrade. All results are reported at a voxelwise threshold of 0.005 (uncorrected) and are family wise error (FWE) corrected at $p<0.05$ at the cluster level.

4.4 Results

4.4.1 Questionnaires and Demographic Measures

No significant group differences were observed for age ($H(2) = 0.11$, $p = 0.949$), BDI scores ($H(2) = 1.11$, $p = 0.574$), or for the change in pre- to post-depletion PANAS ratings on the positive ($F(2, 66) = 1.38$, $p = 0.260$) or negative ($F(2, 66) = 0.57$, $p = 0.567$) mood subscales (see Table 1). Moreover, chi-square tests showed no significant group differences in gender ($\chi^2(2) = 0.41$, $p = 0.814$), drink guess ($\chi^2(2) = 0.86$, $p = 0.071$), or in the number of people who indicated experiencing side effects (such as mild nausea or tiredness; $\chi^2(2) = 1.56$, $p = 0.458$).

Table 1: *Questionnaire and demographic measures by group.*

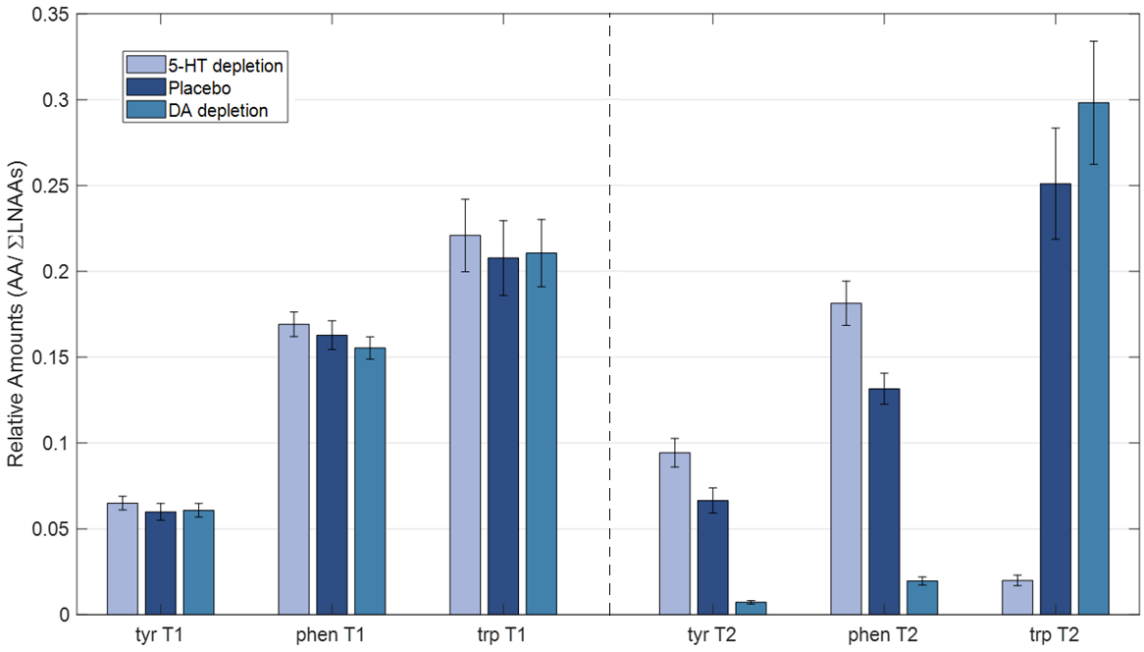
	5-HT Depletion (N = 24)		Placebo (N = 22)		DA depletion (N = 24)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
N female/ male	19/ 5	-	18/ 4	-	19/ 5	-
N reported side effects	2	-	4	-	5	-
N guessed drink correctly	6	-	8	-	6	-
Age (years)	21.50	3.52	21.95	4.18	21.70	4.53
BDI	2.13	2.29	2.32	2.59	3.26	3.84
PANAS dif – pos	-2.75	5.23	-1.23	4.82	-3.65	4.77
PANAS dif – neg	-1.63	3.10	-0.77	2.35	-1.09	2.68

SD, standard deviation; BDI, Beck Depression Inventory; PANAS dif – pos/neg, difference between pre- and post-depletion ratings on the positive and negative subscales of the Positive and Negative Affect Scale

4.4.2 Amino Acid Depletion Efficacy

A mixed-measure (group x time x amino acid) ANOVA on the ratio of the amino acids of interest to the sum of other LNAAs revealed a significant main effect of time ($F(1, 57) = 46.75$, $p < 0.001$) and amino acid ($F(1.16, 65.98) = 128.02$, $p < 0.001$), as well as time by amino acid ($F(1.34, 64.57) = 8.23$, $p < 0.001$), group by time ($F(2, 57) = 19.03$, $p < 0.001$), group by amino acid ($F(2.27, 64.57) = 8.66$, $p = 0.003$), and group by time by amino acid ($F(2.28, 64.96) = 82.13$, $p < 0.001$) interactions (see Figure 3).

Figure 3: *Ratios of tyrosine (tyr), phenylalanine (phen) and tryptophan (trp) to the sum of other large neutral amino acids (LNAAs) before (T1) and 5 hours after (T2) consumption of the depletion drinks.*



One-way ANOVAs conducted to follow up the interactions showed significant group effects for post-depletion tryptophan ($F(2, 57) = 35.00$, $p < 0.001$), tyrosine ($F(2, 57) = 47.12$, $p < 0.001$), and phenylalanine ($F(2, 57) = 75.76$, $p < 0.001$) ratios, but no group differences for pre-depletion levels (all $F < 1$). Post-hoc tests revealed that these differences were driven by significantly lower tyrosine and phenylalanine ratios after DA depletion than after 5-HT

depletion or placebo (all $p < 0.020$) and significantly lower tryptophan ratios after 5-HT depletion compared to DA depletion or placebo (all $p < 0.001$). Additionally, the 5-HT depletion group showed higher tyrosine and phenylalanine ratios compared to the placebo group (all $p < 0.001$).

4.4.3 Name Learning Test Performance

Independent-samples Kruskal-Wallis H tests conducted on the name test performance revealed no group differences in the memorising time ($H(2) = 0.365$, $p = 0.833$), accuracy ($H(2) = 1.79$, $p = 0.409$), the reaction times ($H(2) = 5.26$, $p = 0.072$), or in the number of trials needed to reach criterion ($H(2) = 1.54$, $p = 0.464$). These findings suggest that the depletion manipulations did not seem to result in *generally* impaired associative learning (between names and faces).

4.4.4 Social Learning Task Performance

As expected, the mixed measure ANOVA (group x valence x probability) of participants' likelihood ratings revealed a significant main effect of probability ($F(1.36, 77.65) = 209.71$, $p < 0.001$), as participants made higher ratings after names with a greater chance of being followed by an emotional face. Additionally, significant valence by probability ($F(1.92, 109.45) = 3.35$, $p = 0.040$), group by probability ($F(2.73, 77.65) = 4.42$, $p = 0.008$), and group by valence by probability ($F(3.84, 109.45) = 3.72$, $p = 0.008$) interactions were observed.

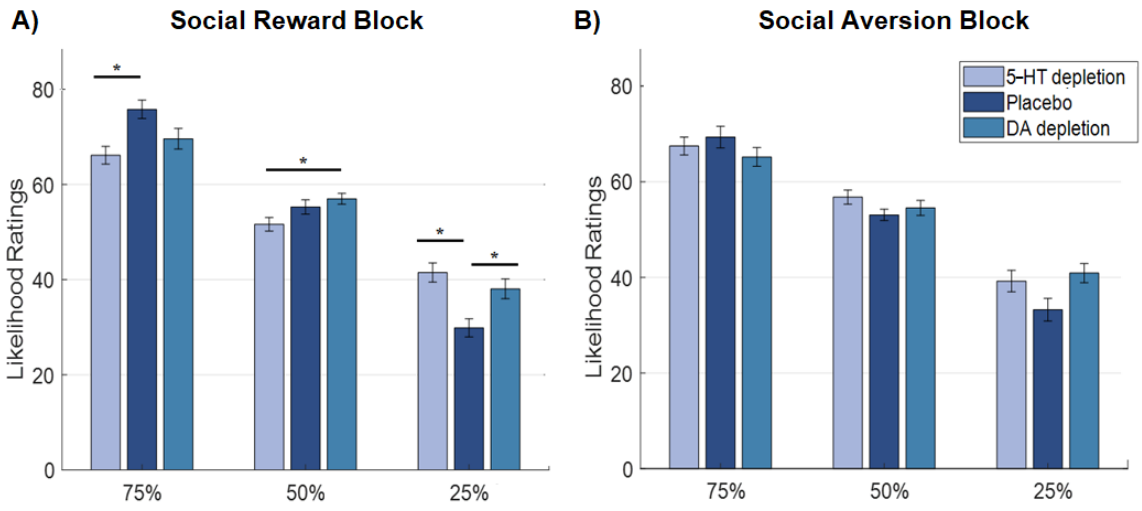
Follow-up one-way ANOVAs showed significant group differences in the 75% ($F(2, 57) = 4.81$, $p = 0.012$), 50% ($F(2, 57) = 3.29$, $p = 0.044$) and 25% ($F(2, 57) = 7.03$, $p = 0.002$) social reward conditions, with no group effect in any of the social aversion conditions (all $F < 2.65$). Bonferroni corrected post-hoc tests indicated that, compared to placebo, 5-HT-depleted subjects made significantly *lower* likelihood ratings on trials with a 75% chance of displaying a happy expression ($p = 0.010$), but made significantly *higher* ratings on trials with a 25% chance of showing a happy face ($p = 0.002$). Moreover, DA-depleted participants made

significantly higher ratings than placebo controls on 25% social reward trials (p = 0.040), as well as significantly higher ratings than 5-HT-depleted individuals on 50% social reward trials (p = 0.045;).

Visual inspection of the data revealed that the likelihood ratings of the depletion groups appeared to be generally closer to 50% than those of the placebo group, indicating higher uncertainty about social outcomes in the former groups (see Figure 4). To formally examine this observation, a mixed-measure (group x valence) ANOVA was performed on participants' uncertainty scores (which indicate the average difference between subjects' ratings and 50%; see Analysis section). This analysis revealed a main effect of valence (F(1, 72) = 5.41, p = 0.023), with subjects demonstrating higher uncertainty about aversive than about rewarding outcomes. The main effect of group did not reach significance (F(2, 72) = 1.20, p = 0.308). However, a significant group by valence interaction was found (F(2, 72) = 3.26, p = 0.044).

Follow-up one-way ANOVAs indicated that there were significant group differences in uncertainty scores for the social reward (F(2, 68) = 4.71, p = 0.012) but not for the social aversion (F(2, 70) = 0.40, p = 0.670) block. Bonferroni corrected post-hoc tests revealed that, in the social reward block, 5-HT depleted subjects were more uncertain about what outcomes to expect compared to the placebo group (p = 0.012), with a trend in the same direction for the DA depletion compared to the placebo group (p = 0.086). No significant differences in uncertainty were found between the DA and 5-HT depletion groups (p = 0.999).

Figure 4: *Likelihood ratings by group and probability in A) the social reward and B) the social aversion block*



4.4.5 Task Feedback Questionnaire Responses

Kruskal-Wallis H tests performed on task feedback questionnaire responses showed a significant group differences in participants' self-reported ability to remember happy faces (*H(2)* = 7.55, *p* = 0.023). Pairwise comparisons revealed that this effect was driven by significantly lower remembrance ratings in the 5-HT depletion compared to the placebo group (p = 0.023). No group differences were found for reported emotional responses to the happy (*H(2)* = 1.08, *p* = 0.583) or fearful (*H(2)* = 1.74, *p* = 0.419) faces, or for the indicated ability to remember fearful faces (*H(2)* = 2.58, *p* = 0.275).

4.4.6 Computational Modelling

There were no significant group differences in the learning rate (social reward block: $H(2)$ = 1.89, p = 0.389; social aversion block: $H(2)$ = 0.80, p = 0.672), or decay (reward block: $H(2)$ = 3.37, p = 0.185; aversion block: $H(2)$ = 1.56, p = 0.459) parameters. Similarly, no significant group effects were observed for the model fit, as indicated by mean squared errors, when using individual (reward block: $H(2)$ = 2.77, p = 0.250; aversion block: $H(2)$ = 1.14, p = 0.565) or averaged (reward block: $H(2)$ = 2.35, p = 0.309; aversion block: $H(2)$ = 1.81; p = 0.406) parameters.

4.4.7 fMRI Results

4.4.7.1 Neural Prediction Value Encoding

Parametric modulation analyses revealed significantly reduced social reward prediction encoding in 5-HT depleted subjects, compared to placebo controls, in the dorsal anterior cingulate cortex (ACC)/ dorsomedial prefrontal cortex (PFC), premotor cortex/ dorsolateral PFC, bilateral temporal lobe/ fusiform gyrus, and the in the right insula (see Figure 5A and 5B). Moreover, social reward prediction representations were significantly weaker in the DA depletion than in the placebo group in the dorsal ACC and dorsomedial PFC/ pre-supplementary motor area (see Table 2 and Figure 5C). Contrasts between the depletion groups and main effects for the placebo group did not reveal any significant clusters.

In the social aversion condition, no significant main effects of placebo were found, either for the ‘positive’ or for the ‘negative’ encoding of aversion prediction values (based on the coding of aversive outcomes as 1 or -1 in the computational model, respectively). 5-HT depleted subjects demonstrated stronger (‘positive’) prediction encoding than DA depleted individuals and placebo controls in the precentral gyrus and in the thalamus, respectively (see Table 2). All other group contrasts revealed no significant clusters.

Figure 5: *Clusters showing lower social reward prediction encoding in 5-HT depleted (A & B) or DA depleted (C) subjects than in placebo controls, as well as parameter estimates extracted from the peak voxel of the group contrasts in the insula (A) and the dorsal anterior cingulate cortex (dACC; B & C).*

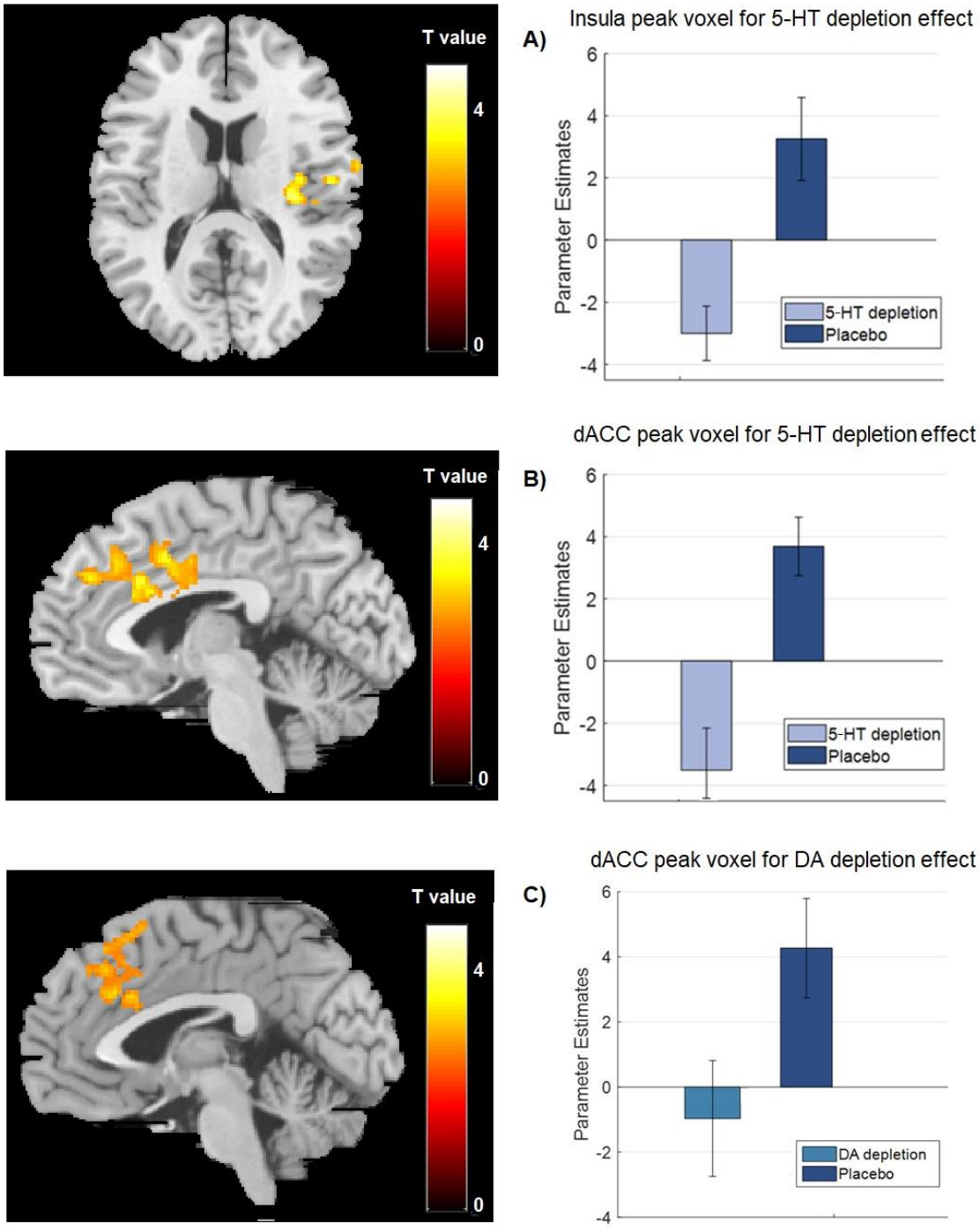


Table 2. *Parametric modulation results for prediction encoding.*

	MNI coordinates				
Brain Region	X	Y	Z	Z score	*p* value
Social Reward Prediction Encoding					
Placebo > 5-HT Depletion					
Premotor (BA 6) extending to	-26	6	48	4.35	<0.001
Dorsolateral PFC (BA 8)					
Dorsal ACC	8	20	30	3.67	
Dorsomedial PFC	-8	48	34	3.64	
Left Superior Temporal Lobe	-44	-44	16	4.20	0.015
Right Middle Temporal Lobe	54	-40	4	4.03	<0.001
Right Lingual/ Fusiform Gyrus	22	-72	-2	3.86	
Right Insula	40	-10	-10	4.13	0.004
Left Fusiform Gyrus	-32	-66	-12	3.89	<0.001
Placebo > DA Depletion					
Pre-Supplementary Motor Area/	-10	10	60	3.66	0.005
Dorsomedial PFC					
Dorsal ACC	8	22	26	3.07	
Social Aversion Prediction Encoding					
5-HT Depletion > Placebo					
Right Thalamus	28	-30	8	4.70	0.012
5-HT Depletion > DA Depletion					
Precentral Gyrus	22	-8	52	3.80	0.001

Voxelwise thresholded at p<0.005; whole-brain cluster p values family-wise error corrected at p < .05; ACC, anterior cingulate cortex, PFC, prefrontal cortex; BA, Brodmann Area

4.4.7.2 Neural Prediction Error Encoding

One-way ANOVAs were conducted on the average parameter estimates extracted from a left and a right striatal ROI for the encoding of outcome and inverse prediction values (i.e. the two PE components). This analysis revealed no significant group differences for either the social reward or the social aversion block (all $F < 0.8$).

4.4.7.3 Neural Responses to Names Cues and Emotional Faces

In the placebo group, the fearful vs. neutral face contrast revealed activation in the right dorsolateral to medial PFC, as well as in the pregenual ACC extending to the vmPFC. No significant responses were observed for the happy vs. neutral face or social aversion vs reward name cue contrasts.

In the fearful vs neutral face contrast, the placebo group displayed higher BOLD activity than the 5-HT depletion group in the vmPFC. Moreover, in the social aversion vs. reward name cue contrast 5-HT depleted subjects demonstrated higher responses than DA depleted individuals in a cluster ranging from the inferior parietal lobe to the insula, as well as in a cluster encompassing the mid- to anterior cingulate cortex and the dlPFC (see Table 3). All other comparisons yielded no significant clusters.

Table 3: *Name cue and facial expression contrasts*

	MNI coordinates				
Brain Region	X	Y	Z	Z score	*p* value
Fearful Face > Neutral Face					
Placebo					
Right Dorsolateral PFC	34	44	16	4.12	0.003
Dorsomedial PFC	10	42	26	3.21	
Pregenual ACC	-2	28	12	3.92	0.002
Ventromedial PFC	-16	46	14	3.73	
Placebo > 5-HT Depletion					
Ventromedial PFC	18	42	14	4.23	0.032
Social Aversion Name Cue > Social Reward Name Cue					
5-HT Depletion > DA Depletion					
Inferior Parietal Lobe	40	-36	30	4.05	<0.001
Right Insula	48	-26	22	3.79	
Mid-/Anterior Cingulate Cortex	-12	10	42	3.68	0.005
Dorsolateral PFC	36	14	40	3.30	<0.001

Voxelwise thresholded at p<0.005 whole-brain cluster p values family-wise error corrected at p < .05; PFC, prefrontal cortex; ACC, anterior cingulate cortex

4.5 Discussion

4.5.1 Effects of 5-HT depletion on behavioural social learning

The current study aimed to examine the effects of 5-HT and DA depletion on learning from social outcomes. The behavioural results revealed that 5-HT depletion impaired participants' ability to learn from social rewards. Specifically, in a social learning task, 5-HT depleted subjects *under*estimated the likelihood of being presented with happy faces on *high* probability trials, while they *over*estimated this likelihood on *low* probability trials. This effect was due to 5-HT depleted participants providing ratings closer to 50% than placebo controls across all trial types, thus expressing more uncertainty about what social outcomes to expect. Interestingly, this pattern of results is similar to our previous findings in individuals with high depression scores, who, in the same task, likewise tended to make ratings closer to 50% compared to healthy controls ([study 2]; Frey & McCabe, 2019). Given that low 5-HT functioning is strongly implicated in the psychopathology of depression (Nemeroff & Owens, 2009), it is therefore possible that reduced learning (and thus increased uncertainty) about social outcomes in depression may be linked to low levels of 5-HT.

The current findings of impaired learning after 5-HT depletion are in line with previous observations of deficits in decision-making and reversal learning performance following reductions in 5-HT functioning in humans (Chamberlain et al., 2006; Crockett, Clark, Apergis-Schoute, et al., 2012; Rogers et al., 1999; Seymour et al., 2012; Skandali et al., 2018; Tanaka et al., 2007). Moreover, contrasting findings of past conditioning studies, which have observed *improved* (punishment) learning after 5-HT depletion (Cools, Robinson, et al., 2008; Robinson, Cools, & Sahakian, 2012), may be the result of task characteristics. Specifically, in previous paradigms participants made *binary* predictions regarding whether they expected positive or negative outcomes following a cue, while in our task *continuous* outcome predictions needed to be formed, updated, and maintained in working memory. Notably, the previously-used binary learning task could be solved with a simple win-stay/ lose-switch strategy, while our

task required learning in line with a standard (e.g. Rescorla-Wagner) reinforcement learning model. Evidence from the animal literature suggests that these strategies may be differentially affected by 5-HT manipulations. For instance, it has been found that the optogenetic stimulation of 5-HT neurons in the dorsal raphe nucleus of mice increased the learning rate for a decision-making task condition that elicited gradual learning. By contrast, no effects of 5-HT stimulation were seen in a condition that induced win-stay/ lose-shift behaviour (Iigaya et al., 2018). Although these findings do not directly explain why punishment learning was observed to be *enhanced* after 5-HT depletion in the studies by Robinson and colleagues, they raise the possibility that varying tasks may differentially engage 5-HT functioning. This may explain the diverging results revealed by the probabilistic paradigm used in the current study (and in most previous research) compared to the deterministic task utilised by Robinson and colleagues.

4.5.2 Effects of DA depletion on behavioural social learning

The current study further found that DA depleted participants, similar to 5-HT depleted subjects, showed a tendency to be less certain about what social rewards to expect compared to placebo controls, although these findings were at trend level. The absence of a strong effect of DA depletion on learning in the present study stands in contrast with previous findings showing that lowering DA levels via DA depletion or high doses of D2 antagonists impairs reward and improves punishment learning (Cox et al., 2015; Diederen et al., 2017; Eisenegger et al., 2014; Jocham et al., 2014; Robinson et al., 2010), while increasing DA functioning with levodopa, methamphetamine or low doses of D2 antagonists enhances reward learning (Chowdhury et al., 2013; Coulthard et al., 2012; Frank et al., 2004; Jocham et al., 2011; Mayo et al., 2013; Pessiglione et al., 2006). Again, task characteristics may have contributed to these discrepancies. For instance, it is possible that the stimuli used in the current study (happy faces of strangers) were not salient or rewarding enough to elicit a robust DA response. As a result, the influence of DA on behavioural performance in our task may have been rather

subtle, although the (potentially more sensitive) fMRI analysis did reveal an effect of DA depletion on the neural encoding of learning signals (see below).

4.5.3 Effects of 5-HT depletion on neural prediction and PE encoding

Consistent with the behavioural findings, 5-HT depletion had an effect on neural learning processes. Specifically, 5-HT depleted subjects demonstrated a decreased covariation between social reward prediction values and BOLD responses in the dorsal ACC, dorsolateral and dorsomedial PFC, the insula, and the temporal lobe compared to placebo controls. These findings are in line with previous observations of reduced reward prediction signals in the ACC, PFC, and insula after 5-HT depletion (Seymour et al., 2012; Tobia et al., 2014).

The engagement of the insula and temporal lobe by cues that were more frequently paired with happy expressions may be explained by the role of these regions in the working memory maintenance of faces (Nichols et al., 2006), which may aid the learning process. Moreover, the dorsolateral PFC may have played a role in directing attentional resources toward cues that were more salient due their repeated pairing with happy faces (Kane & Engle, 2002), or directly in the prediction of future states (as suggested by Tanaka et al., 2006). Similarly, the involvement of the dorsal ACC may have resulted from this region's contribution to cue value computations (Amiez, Joseph, & Procyk, 2006; Kennerley, Behrens, & Wallis, 2011) and is in line with previous findings of prediction-related ACC activity during a social learning task in healthy volunteers (Jones et al., 2011).

At first sight, the above may be taken to suggest that 5-HT depleted subjects displayed reduced prediction encoding in the abovementioned regions due to reduced working memory and attentional processing. However, it should be noted that 5-HT depletion not merely lowered, but instead reversed, the neural prediction signal. That is to say, prediction-related parameter estimates were significantly *above* zero in the placebo group, while they were significantly *below* zero in the 5-HT depletion group. Moreover, on the whole-brain level, several regions were found to encoded *inverse* social reward prediction values in 5-HT

depleted subjects, while no such effects were seen in placebo controls (or in DA depleted participants; see supplement). This indicates that, instead of tracking the prediction of happy faces (as in individuals on placebo), brain responses of 5-HT depleted subjects seemed to track the prediction of *neutral* faces.

A possible explanation for this finding is that 5-HT depletion may have given rise to negative biases (Harmer, 2008), which may have led to the perception of ambiguous neutral faces as negative. This may have made the latter more salient, resulting in the recruitment of attentional and working memory processes to support the prediction of neural faces. Interestingly, using the same task, we previously found a similar pattern of reversed social reward prediction encoding in the insula and temporal lobe in individuals with high depression scores ([study 2]; Frey & McCabe, 2019). Taken together, these findings suggest that low levels of 5-HT may contribute to impaired social reward learning in depression by biasing learning towards negatively perceived stimuli.

Following the above interpretation, it may seem surprising that no group differences were found in the happy vs. neutral expression contrast. However, it is possible that the increased engagement of the PFC in anticipation of neutral faces may have led to a preparatory downregulation of limbic regions in 5-HT depleted subjects. This preparatory response may have equalised the otherwise potentially stronger activation to neutral faces in the 5-HT depletion compared to the placebo group.

4.5.4 Effects of DA depletion on neural prediction and PE encoding

Again paralleling the behavioural findings, DA depletion affected neural learning signals, but to a lesser extent than 5-HT depletion. Specifically, DA depleted subjects showed a decreased covariation of BOLD responses with social reward prediction values in the dorsomedial PFC and dorsal ACC compared to placebo controls. A possible explanation of this finding is that DA depletion may have reduced the stability of prefrontal prediction representations. More concretely, it is thought that the strength of input representations in the frontal cortex is

influenced by the balance between D1 and D2 binding. Moreover, low DA levels induce preferential D2 (rather than D1) binding, which is associated with weak input representations that are prone to interference by distractors (Seamans & Yang, 2004). Therefore, it is possible that DA depletion may have impaired the stability of prediction representations in the frontal cortex, especially for more strongly represented cues with a higher probability of being followed by a happy face. This interpretation is in line with that of Jocham and colleagues (Jocham et al., 2011), who found that the D2 receptor antagonist amisulpride increased predictive value signals in the vmPFC, which the authors argue may have resulted from a shift to more stable D1- (rather than D2-) mediated value representations.

4.5.5 Conclusion

Taken together, the results of the current study indicate that 5-HT depletion impairs social reward prediction on both the behavioural and the neural level, possibly partly by increasing attentional and working memory processing of negatively perceived neutral faces. DA depletion had a similar, although less pervasive, effect. Interestingly, the behavioural and neural responses observed after 5-HT depletion in the current study closely resemble our previous findings in individuals with high depression scores. It may thus be the case that decreased 5-HT levels contribute to deficits in social learning in depression.

5 General Discussion

5.1 Summary of Findings

The overall aim of this work was to gain an insight into the behavioural and neural mechanisms of social learning in depression. Specifically, studies 1 and 2 assessed to what extent individuals with high depressive symptomatology (HD) display impairments in social learning compared to controls (LD), and how these deficits impact real-life social experiences. Moreover, studies 2 and 3 investigated the neural underpinnings of social learning in HD subjects, as well as in healthy individuals after the depletion of dopamine or serotonin (precursors), which are implicated in the psychopathology of depression (Belujon & Grace, 2017; Nemeroff & Owens, 2009). As part of the studies, participants answered questions about their real-life social interactions (studies 1 and 2) and performed social learning tasks behaviourally (study 1) or during functional magnetic resonance imaging (fMRI; studies 2 and 3).

It was found that HD individuals demonstrated impairments in social learning, which were associated with increased experience of negative social encounters (study 1) and reduced social engagement motivation (study 2) in everyday life. Additionally, HD subjects displayed altered neural encoding of social reward predictions in the insula, temporal lobe and parietal lobe (study 2). Notably, the latter alterations closely resembled those observed in healthy individuals after serotonin depletion, while prediction-related dopamine depletion effects were mainly seen in other (frontal lobe) areas (study 3).

These findings suggest that depression symptoms are associated with social learning deficits, on both the behavioural and the neural level, which may be linked to real-life social withdrawal and may be underpinned by altered serotonin functioning.

5.2 Integration of Findings

When considering the study findings in conjunction, it is notable that studies 1 and 2 yielded very consistent results. For instance, HD subjects in both studies indicated having fewer friends, feeling less close to their friends, and finding it more difficult to form new friendships than controls. These findings are in line with previous research reporting that depressed individuals have smaller social networks than healthy volunteers (Brim et al., 1982; Gotlib & Lee, 1989; Rottenberg & Gotlib, 2008; Youngren & Lewinsohn, 1980).

Moreover, both studies 1 and 2 observed that HD subjects displayed impairments in learning from social outcomes which were associated with deficits in real-life social interactions. Specifically, taken together, the results of study 1 indicated that HD individuals' tendency to spend increased amounts of time in negatively perceived social situations may be related to their diminished updating of social outcome predictions based on interpersonal feedback. This may partly be the case because HD subjects' impaired ability to adjust their behaviour based on social feedback may result in suboptimal social behaviour which may lead to more negative social interactions. Additionally, it is possible that HD participants' reduced learning from social outcomes may make social interactions appear more uncertain, which, if uncertainty is regarded as negative, may lead to the perception of more social situations as unpleasant. Notably, the findings of study 2 were in line with the latter suggestion, demonstrating that HD subjects showed higher uncertainty about social outcomes and perceived uncertainty as more negative than LD participants. Moreover, this (negatively perceived) social outcome uncertainty was associated with reduced motivation to engage in pleasant social interactions. Thus, studies 1 and 2 provide consistent, novel evidence that social learning deficits in depression may contribute to a reduced quality and quantity of social encounters, potentially through increased uncertainty about social outcomes.

The neuroimaging findings of study 2 parallel the above behavioural observations, with HD subjects displaying reduced social outcome prediction encoding in the insula, temporal lobe and parietal lobe. Notably, a very similar pattern of results was observed in healthy volunteers

after 5-HT depletion (in study 3), who showed decreased social outcome prediction representations in the insula, temporal lobe, dorsal ACC, and dorsal PFC (as well as reduced behavioural social reward learning). This raises the possibility that reduced 5-HT functioning may be involved in social learning deficits in depression. By contrast, the potential role of DA in these impairments is less clear, as the effects of DA depletion on social learning were at trend level behaviourally, and neural alterations were observed only in frontal regions, which were not differentially engaged in HD and LD subjects in study 2 (although see below).

Interestingly, in both HD and 5-HT depleted subjects the encoding of social reward predictions was not merely reduced but instead reversed compared to controls, indicating that neural responses in these groups appeared to track the occurrence of neutral (rather than happy) faces. This may be the case because negative biases in these groups may have led to the perception of neutral faces as negative, which may have resulted in the allocation of neural attentional, working memory and valuation resources to the prediction of (the more salient) neutral faces. This suggestion seems particularly plausible given that it is thought that negative biases in depression are partly linked to reduced 5-HT levels, with selective serotonin reuptake inhibitor treatment alleviating negatively biased processing (Harmer, 2008).

The findings of studies 1, 2 and 3 were thus largely consistent. Nevertheless, some divergence was seen for the results of studies 2 and 3, as HD and 5-HT depleted (healthy) subjects displayed altered prediction encoding in the parietal and frontal lobe, respectively. Notably, however, these regions are thought to be part of the same cognitive control network which supports executive function across domains (such as working memory and flexibility) and engages attentional processing according to task demands (Niendam et al., 2012). It is thus possible that *functionally* both HD and 5-HT depleted participants displayed very similar deficits, but that these alterations were apparent to varying extents (e.g. at sub- or suprathreshold level) in different parts of the cognitive control network in the two groups. Indeed, using a slightly different analysis in study 3 (with individual parameters in the computational model; see chapter 4 supplement) revealed reduced social reward prediction

encoding in 5-HT depleted subjects in a similar parietal region as observed in HD participants in study 2. This finding supports the idea that 5-HT depletion had an effect on parietal prediction representations, and that this effect may have been present at a subthreshold level in the main analysis. Additionally, it should be noted that depression is associated with a range of non-serotonergic neurobiological abnormalities (Willner, Scheel-Krüger, & Belzung, 2013) and that *acute* lowering of 5-HT levels with the depletion manipulation is likely to have differential effects from *chronic* reductions of 5-HT functioning in MDD. These factors will likely have contributed to the partly divergent results of studies 2 and 3.

5.3 Critical Discussion

5.3.1 General Strengths

A major strength of the current work was the use of *social* learning paradigms. Social stimuli are of high importance in everyday life, and, as outlined in the general introduction, there is a close link between deficits in social processing and the onset and maintenance of depression (Kupferberg et al., 2016; Rottenberg & Gotlib, 2008; Segrin, 2000). Given that successful social interactions require learning to predict other people's responses and to adjust one's behaviour accordingly, it is particularly vital to understand the relation between learning and social functioning in depression. There are many studies examining depressed individuals' responses to social stimuli, either in the lab *or* in real life (Bourke et al., 2010; Kupferberg et al., 2016; Rottenberg & Gotlib, 2008; Segrin, 2000; Stuhrmann et al., 2011), as well as a range of research assessing *non-social* learning performance in depression (reviewed in Chen, Takahashi, Nakagawa, Inoue, & Kusumi, 2015). However, there appears to be a disconnect between these research areas, with surprisingly few studies attempting to examine the relation between these aspects. A particular strength of the current work was, therefore, that it included *social* learning paradigms and linked the performance in these tasks to measures of real-life social experiences.

Another strength of the present work was the examination of social learning with the use of a variety of methodologies, including computational modelling (studies 1, 2 and 3), neuroimaging (studies 2 and 3) and neurotransmitter depletion (study 3). The integration of findings across studies provides deeper insights than the separate studies in isolation. For instance, as discussed above, the similarity of the findings in HD individuals in study 2 and 5-HT depleted subjects in study 3 suggests (although not conclusively, see below) that 5-HT deficits may be involved in impaired social learning in depression. This evidence is strengthened by the inclusion of DA depletion as an active 'control' condition which exerted weaker effects on learning compared to 5-HT depletion. Moreover, the use of computational modelling provided a (tentative) link between the observed behavioural and neuroimaging findings and potential underlying neural mechanisms.

5.3.2 General Limitations

Besides the above strengths, the current work had several limitations. For instance, the studies contained a relatively small sample size, which means that some group effects which are present in the population may not have reached significance due to a lack of power. As a result of practical difficulties with recruitment (especially given the strict exclusion criteria), issues with equipment, and time constraints, it was not possible to recruit a larger number of participants. Given the small sample size, as well as the novelty of the utilised tasks, the findings of the current work should thus be considered with caution, and replication studies with larger samples are called for.

Moreover, in all three studies, more female than male participants were tested. As depression is about twice as common in females than in males (Piccinelli & Wilkinson, 2000), examining social learning in female subjects is of particular importance. Nevertheless, future studies should aim for a more gender balanced sample to allow for better generalisability of the findings and for the assessment of gender effects in the collected measures.

Another potential issue with studies 1 and 2 was that HD subjects were included on the basis of high Beck Depression Inventory scores, rather than based on a clinical diagnosis of depression. This had the advantage that participants did not received any pharmacological treatments, which could have confounded the study results. Moreover, given that social processing deficits are not only implicated in acute depression, but are also a risk factor for depression onset (Caspi et al., 1996; Ollendick et al., 1990), it is important to consider the link between learning and social experiences across individuals with a range of depression symptom levels, independent of their diagnosis status. Nevertheless, it needs to be kept in mind that depressed individuals who receive a clinical diagnosis as a result of seeking treatment may differ from those who do not seek medical help. For instance, the former group may have more (severe) symptoms that interfere with their everyday life. This should be taken into account when considering the clinical implications of the current findings (see section 5.4).

In addition, testing individuals with high depression scores without a clinical assessment does not make it possible to distinguish whether the observed effects are a precursor (/trait marker) or a consequence (/state marker) of clinical depression, as some volunteers may have met MDD diagnosis criteria while others may not. However, in either case, the reported social learning deficits could be a treatment target for MDD. Specifically, the results tentatively suggest that improving social learning may reduce negative social encounters and enhance social engagement motivation (although further research is needed to confirm the directionality of this effect). The experience of more positive social feedback may, in turn, improve depression symptoms (Lewinsohn, 1974; see section 5.4.1 for more details). It is possible that this mechanism may also contribute to the prevention of depression onset, *if* social learning is a trait marker for MDD (which the current work did not address). Thus, it would be informative for future longitudinal research to assess whether early impairments in social learning are associated with an increased risk of demonstrating social withdrawal and (clinical) depression later in life.

Furthermore, it is worth noting that HD individuals in studies 1 and 2 were not only experiencing depression symptoms, but also moderate levels of anxiety. During the screening process, it was attempted to ensure that anxiety symptoms were secondary to depression symptomatology in included HD subjects (e.g. by asking participants if they felt the former or the latter had a larger impact on their everyday life). Moreover, the potential confounding effects of anxiety symptoms were partly controlled for in the statistical analysis by including anxiety measures as a control variable. Nevertheless, it cannot be ruled out that some of the observed effects were related to anxiety symptomatology. Yet, this does not detract from the importance of the present findings, especially given the high comorbidity of anxiety and depression in the general population (Kessler et al., 2008). Still, in future studies it would be of interest to examine the specificity of the current observations, not only in subgroups of depression patients (e.g. with and without anxiety symptoms), but also across disorders, given that other conditions such as schizophrenia have also been linked to deficits in social functioning and cognition (Green, Horan, & Lee, 2015).

Finally, when considering the findings of all three studies, it should be kept in mind that, although learning is functionally well-defined by computational models, it is a complex construct which relies on many cognitive processes, including attention, working memory, and (when using emotional stimuli) emotion regulation. While these components are considered in the interpretations of the study findings, their involvement is difficult to dissociate and is often derived from reverse inferences based on the engaged brain regions and their supposed functions. This approach is problematic, not merely because brain regions are often implicated in several functions, but specifically because the social learning paradigm used in the current work may engage several cognitive processes that may be supported by the same brain region (Hutzler, 2014; Poldrack, 2006). As a result, the interpretations of the neuroimaging results of studies 2 and 3 should be regarded as tentative suggestions rather than conclusive statements regarding the underlying cognitive functions. Future studies would benefit from including measures of the subcomponents of the learning construct, such as working memory (e.g. n-

back) and attention (e.g. continuous performance) tasks, in addition to a learning paradigm, to get a better understanding of what particular cognitive impairments may contribute to deficits in social learning. Additionally, a non-social control condition (which was included in study 1 but not in studies 2 and 3) should be used to assess whether potential findings are specific to the social domain.

5.3.3 Critical Discussion of Chapter 2

5.3.3.1 Potential Biases in Social Experience Reports

In study 1, participants were asked to retrospectively report how much time they spent in positive and negative social situations. Such reports are likely prone to interference by memory biases, which is particularly problematic when testing individuals with depression symptoms, who demonstrate a bias towards preferentially accessing negative autobiographical memories (Dalgleish & Werner-Seidler, 2014). This bias may have led HD individuals to report spending more time in negative situations than they objectively did. However, it should be noted that all interpretations of the findings of study 1 carefully distinguished between potential effects relating to increased subjective vs. objective experiences of negative events. Moreover, study 2 somewhat improved on the measures of study 1 by using inherently subjective questions (e.g. 'How motivated are you to engage in social activities?'), which are not affected by memory biases and remove the ambiguity between objective events and their subjective experience.

Nevertheless, future studies would benefit from including additional or alternative measures of real-life social experiences, such as ecological momentary assessments which prompt participants to rate their current experiences several times a day (Myin-Germeys et al., 2018). A potential criticism that could be levelled against these measures is that they may be affected by experiential interpretation biases in HD individuals. That is to say, the experience of the same situation may be interpreted, and thus reported, as more negative by HD than by LD

subjects. However, this is not a substantial concern, given that it is the *subjective* perception of a given social situations that is behaviourally relevant.

5.3.3.2 Variability of Social Learning Task Feedback

Another potential issue with study 1 was the use of probabilistic outcomes in the social learning task. As a result of this setup, it appeared as if the other people, who were purportedly providing the feedback, occasionally changed their mind about whether they liked the participant's choice or not, which could have seemed unrealistic. It should, however, be noted that a given item could only yield positive and neutral *or* negative and neutral (never positive and negative) feedback. Thus, it could only seem as if *one* (not both) of the other people revised their feedback. It seems plausible that this could have occurred if real people had provided the feedback. For instance, if person A had no strong opinion about a particular choice, they may have provided somewhat random feedback for that option, or they could have been induced to change their mind by seeing the feedback of person B.

This process was not made explicit to the participants, as any elaboration on the potential reasoning of the other people would likely have cast doubt on the veracity of the feedback source. Thus, it is possible that the variable feedback appeared unusual to some participants. Indeed, in the task feedback questionnaire, some subjects mentioned this aspect in response to the question 'Did you notice anything strange or unexpected during the task? If so, what?'. Yet, the phrasing of the responses implied that the outcome variability did not seem to make participants suspicious about the source of the feedback. For instance, some subjects stated that they found it bothersome that *the other people* sometimes changed their mind, but (apart from two participants) they did not mention that it seemed to them as if the feedback was not provided by other people. Thus, the probabilistic outcomes do not seem to have interfered substantially with the believability of the task setup.

5.3.3.3 Monetary Outcomes and Specificity of Findings

A further consideration regarding study 1 was the use of low magnitude monetary outcomes in the non-social control condition. The discussion of previous research in the general introduction revealed that studies that observed group differences in reward learning between healthy and depressed subjects overwhelmingly used high magnitude outcomes, while studies utilising low magnitude feedback mostly found no group effects (Bakker et al., 2018; Beevers et al., 2013; Blanco et al., 2013; Chase et al., 2010; Cooper et al., 2014; Gradin et al., 2011; Herzallah et al., 2013; Johnston et al., 2015; Kumar et al., 2008; Maddox & Markman, 2010; Rothkirch et al., 2017). In study 1, it was nevertheless decided to use small monetary outcomes (5p) in the non-social condition of the learning task. This decision was made to match the social and non-social conditions as closely as possible, by attempting to use monetary and social outcomes with a similar value. While the exact value of social outcomes likely depends on the specific stimuli and task setup, previous research showed that social feedback (in form of a genuine smile) received during a learning task was regarded as having a worth of about 0.4 pence (Shore & Heerey, 2011). Using only a fraction of a pence as an outcome in study 1 would likely not have provided enough incentive, thus a slightly higher, but still relatively low, magnitude outcome was used to match the assumed value of the social feedback. This also ensured that there was no 'carry over' effect for participants who performed the non-social condition first, who might have been substantially less motivated in the social condition if the monetary outcome had been disproportionally large.

Nevertheless, it should be kept in mind that group differences in the non-social learning condition might have been observed if a larger monetary outcome had been used. Thus, no claims can be made with regards to the specificity of the findings of study 1 to social outcomes. It would, therefore, be advisable for future studies to further investigate whether some of the observed learning deficits are specific to social feedback. However, it should be noted that this issue does not detract from study 1's findings in the social condition, as the association between real-life social functioning deficits and learning impairments in depression is an

important observation, no matter whether the learning impairments are specific to social feedback or not.

5.3.4 Critical Discussion of Chapter 3 (partly applicable to chapter 4)

5.3.4.1 Use of Fearful Faces in the Social Aversion Block

A question that arises when considering the use of emotional faces as outcomes in study 2 (and 3) is whether fearful faces were the most appropriate choice. Fearful faces are thought to evoke negative emotional responses by signalling the presence of a threat in the environment which may or may not be social (Hooker, 2006). It could thus be argued that it may have been better to utilise angry or disappointed faces which are more unambiguously social and are potentially more relevant to depression symptoms such as guilt, worry, and lack of self-esteem. However, using these expressions would have been similarly problematic: anger may evoke varying responses, as it could trigger either anxiety and submissive withdrawal or counter-aggression in different individuals (Honk & Schutter, 2007). This would have introduced additional variability in the data and may have made it more difficult to detect group differences. Moreover, disappointment is not a basic emotion and may, therefore, have been difficult to recognise. This may have been especially the case for depressed subjects, given that depression is associated with impaired emotion recognition (Kohler, Hoffman, Eastman, Healey, & Moberg, 2011), which could have confounded the results. Another alternative would have been to utilise sad expressions; however, this appears similarly problematic as sad faces may evoke a more self-focused or other-focused response in HD and LD individuals, respectively (Likowski et al., 2011).

Thus, while using fearful faces in the social aversion block may not have been ideal, there are, similarly, drawbacks to using alternative emotional expressions. Additionally, many previous studies assessing social processing in depression (as well as in response to 5-HT depletion) have included fearful faces (Daly et al., 2010; Kroes et al., 2014; Marsh et al., 2006; Sheline et al., 2001; Van Der Veen, Evers, Deutz, & Schmitt, 2007; Zhong et al., 2011). Given that the

social learning task was newly developed specifically for study 2 (and 3), it seemed advisable to at least keep the utilised stimuli in line with previous studies to make results more comparable, thus enabling a better integration of the study's findings with the previous literature. It would be of interest for future studies to further examine the neural underpinnings of social learning in depression with a range of different stimuli, including alternative emotional facial expressions, 'like' and 'dislike' signs purportedly provided by other people (as in study 1), and more personal stimuli such as images of friends (vs. strangers).

5.3.4.2 fMRI Analysis Thresholding

Another potential criticism of study 2 (and 3) is the use of a somewhat lenient voxelwise threshold in the fMRI analysis. Current recommendations suggest the use of a voxelwise threshold of $p = 0.001$ with family wise error or false discovery rate correction at the cluster level (or using nonparametric permutation tests; Eklund, Nichols, & Knutsson, 2016; Woo, Krishnan, & Wager, 2014; Yeung, 2018). The use of more lenient voxelwise thresholds in study 2 (and 3) could thus be regarded as problematic, due to an increased likelihood of false positive findings (i.e. type I errors). However, it has been acknowledged that overly stringent thresholds would require a very large sample (of over 200 participants) to detect effects of moderate size (around 0.6), and that using such conservative thresholds for small samples increases the likelihood of false negatives (i.e. type II errors; Carter, Lesh, & Barch, 2016). Based on these points, it has been suggested that the use of somewhat more lenient thresholds is acceptable, especially when the precise localisation of significant effects (e.g. in very small brain regions) is not necessary (Carter et al., 2016). Using a more lenient threshold in study 2 (and 3) thus provided a balance between the likelihood of type I and type II errors given the relatively small sample size.

Moreover, the consistency of the results between different analyses and studies provides some support for the legitimacy of the results. Firstly, neural responses during social learning in study 2 (and 3) were observed in regions which have been commonly reported to be engaged in the previous learning literature. Secondly, using somewhat different analysis

methods (e.g. utilising individual or averaged parameters in the computational model) yielded highly similar results. Thirdly, the brain areas that showed differential responses in HD and LD subjects in study 2 were largely similar to (or in the same functional network as) regions that displayed differential responses in 5-HT depleted subjects and placebo controls in study 3. It seems unlikely that these consistencies would have been observed if the effects had been false positives. Thus, while caution with drawing conclusions from the findings is advised, it seems likely that the observed effects are genuine. Nevertheless, the current results should be regarded as preliminary and are in need of replication in larger samples.

5.3.4.3 Computational Modelling Parameters for fMRI Analyses

Another noteworthy point regarding study 2 (and 3) is that similar results were obtained when using individual or averaged parameters in the computational model to calculate the prediction values for the parametric modulation analysis. There is some controversy in the literature regarding the methodology used to derive these values. On the one hand, it has been argued that using individual parameters introduces additional variability into the fMRI analysis which can result in noisy fMRI regression weights, thereby obscuring group differences. Moreover, using averaged model parameters (across all subjects) ensures that any observed fMRI group effects are not due to differences in the model parameters (Daw, 2011; Schonberg et al., 2010). On the other hand, it could be argued that using individual parameters (as in several previous studies; see Chase, Kumar, Eickhoff, & Dombrovski, 2015 for a review) provides a closer link between behavioural and brain responses, and using average parameters may induce group differences in the (behavioural) model fit. It is thus not immediately clear which approach is more advantageous.

Interestingly, a relatively recent meta-analysis compared the two approaches and found higher prediction error (PE) related activation in the ventral striatum, frontal operculum and occipital lobe/ fusiform gyrus in studies using individual compared to averaged/ fixed learning rate parameters. Additionally, the reverse contrast yielded higher midbrain and thalamus activity, while both approaches revealed putamen responses (Chase et al., 2016). The authors argue

that the different brain regions that are observed to encode PEs when individual or average parameters are used may be part of different learning systems. Specifically, they suggest that activity in the medial striatum may represent a variable learning signal reflected in trial-by-trial choices (and thus found when using individual parameters), while the midbrain may encode a slower learning signal that is not strongly linked to task performance (and thus observed when using averaged parameters; Chase et al., 2016).

The above proposal is generally plausible, especially considering that several authors have provided detailed descriptions and justifications of different learning systems in the brain (e.g. Frank et al., 2007; Niv, 2009; see below). However, for the above suggestion to be convincing, it requires additional elaboration regarding the roles of the slow and the fast learning system, how the learning systems interact (over time), and why the particular brain regions would be involved. Moreover, the findings of the meta-analysis were obtained across studies using individual or averaged parameters in combination with different paradigms (e.g. Pavlovian learning or decision-making), with a variety of outcome types (e.g. liquid, social, monetary etc.), and with different computational models (e.g. Rescorla-Wagner or temporal difference learning). Thus, it is difficult to determine whether the observed differences were indeed due to the use of individual vs. averaged parameter values, or if they were the result of the use of varying tasks and analysis methodologies.

The fact that study 2 (and 3) of the current work obtained similar results when using individual or average parameters (applied to data from the same task) indicates that, at least in some cases, these approaches do not reveal separate learning systems. This is in line with a previous systematic exploration of the effect of model parameter values on fMRI results, which revealed that parametric modulation results for prediction and PE values did not differ substantially as learning rates were varied (Wilson & Niv, 2015).

It should, however, be noted that the observation of only one learning system with different analysis techniques in study 2 (and 3) could also partly be due to a higher dependence of the social learning task on only one learning system compared to other paradigms. It has been

suggested that learning ordinarily engages a working memory-based and a habitual learning system, both of which are involved throughout the learning process but to differing extents (Frank et al., 2007). Specifically, the PFC has been hypothesised to support working memory-related processes that are heavily implicated in learning during early trials. By contrast, during later trials, when responses to cues get more automated, the influence of the PFC-mediated working memory system decays, while the habitual basal ganglia system starts to dominate the learning process (Frank et al., 2007). Given the necessity of making *explicit continuous* likelihood ratings, the social learning task in study 2 (and 3) may have remained more dependent on the working memory system, rather than deferring control to the habitual system (especially since the task did not include a large number of trials). This may partly be why only one (prediction encoding) learning system seemed to be revealed with the use of individual and average parameters. Additionally, this may also explain why many of the regions that were differentially engaged in the HD and LD (and the 5-HT depletion and placebo) groups were areas implicated in working memory processing.

5.3.5 Critical Discussion of Chapter 4

5.3.5.1 Mechanistic Roles of 5-HT and DA in Learning

As discussed in the general introduction, dopamine (DA) firing is thought to encode reward predictions and PEs (Schultz, 2016), while serotonin (5-HT) activity may represent punishment learning signals (Boureau & Dayan, 2011; Daw et al., 2002). In addition, it has been proposed that 5-HT firing may be involved in reward learning, either directly (thus encoding *unsigned* prediction errors; Matias et al., 2017), or through 5-HT's excitatory effect on DA neurons via 5-HT2A receptors (Seymour et al., 2012). However, somewhat surprisingly, no effects of DA or 5-HT depletion on reward PE representations were found.

The lack of 5-HT depletion related findings may have been due to the examination of PEs in only a striatal region of interest. It is possible that 5-HT depletion effects would have been observed if other areas had been considered. By contrast, it is less clear why no effects of DA

depletion were found. Based on the computational basal ganglia model outlined in the introduction, it may have been expected that DA depletion would affect PE responses in the dorsal striatum. Specifically, the model posits that positive and negative dopaminergic PE signals are propagated from the midbrain to the dorsal striatum to facilitate 'go' or 'no-go' responses, respectively, via globus pallidas – thalamus – frontal cortex pathways (Frank, 2006). At first sight, it may seem doubtful whether this mechanism would have been involved in the social learning task utilised in study 3, as the paradigm did not include action-dependent outcomes. Moreover, as mentioned above, learning in the task was likely heavily dependent on working memory processing, especially due to the need for explicit continuous representations of outcome contingencies. However, it appears plausible that basal ganglia-mediated habitual learning may at least have *supported* this process, using task outcomes (facial expressions) to update future actions (e.g. pressing button 1 or 2 to move the rating indicator to the left or right of 50%).

Yet, as mentioned above, DA depletion, unexpectedly, did not significantly affect reward PE encoding in the dorsal striatum. A potential explanation for the absence of a DA depletion effect may be that the utilised stimuli (happy faces of strangers) may not have been rewarding enough to elicit a strong dopaminergic PE response, which is why the depletion effect may have been relatively weak. At first sight, this reasoning may seem questionable considering that DA depletion did have an effect on frontal reward prediction encoding. However, it is possible that dopaminergic PE representations may be more localised than prediction-related activity, potentially making the former more difficult to detect than the latter when (differences in) DA responses are weak. This explanation is speculative and future studies are needed to assess whether more rewarding social stimuli (such as positive pictures of close friends, partners or family members) may elicit more robust PE responses that can be significantly modulated with dopaminergic manipulations.

5.3.5.2 Effect of Dietary Precursor Depletion on Neurotransmitter Release

A question arising when considering the methodology of study 3 is how (far) the depletion of the 5-HT and DA precursors tryptophan and tyrosine/ phenylalanine, respectively, impacts neurotransmitter functioning. In study 3, as in previous research, the efficacy of the depletion manipulation was assessed based on precursor levels in collected plasma samples, which is an indirect measure of the assumed changes in DA and 5-HT functioning in the brain. Indeed, the effect of precursor depletion on neurotransmitter release is somewhat controversial. While positron emission tomography studies have shown that depletion procedures influence central DA and 5-HT *synthesis* in humans (Nishizawa et al., 1997), they do not provide specific information about the *release* of these neurotransmitters (Van Donkelaar et al., 2011). Surprisingly, some animal studies have found that tryptophan depletion had no effect on 5-HT release in the prefrontal cortex or raphe nucleus, despite decreased tryptophan plasma levels or diminished 5-HT metabolite amounts (Trulson, 1985; Van Der Plasse, Meerkerk, Lieben, Blokland, & Feenstra, 2007). Based on these studies, it has been argued that tryptophan depletion may not affect 5-HT release, potentially because neurons can 'recycle' 5-HT back into the presynaptic cell (Van Donkelaar et al., 2011).

However, the above view has been challenged. Specifically, it has been argued that the cited animal studies have only taken measures of 5-HT release at baseline and in a limited number of brain regions. This leaves open the possibility that tryptophan depletion may have an effect on 5-HT release when the latter is stimulated or when baseline levels in other brain areas are assessed (Crockett et al., 2013). This suggestion is supported by findings showing that tryptophan depletion decreases 5-HT release in the hippocampus following 5-HT stimulation (Stancampiano et al., 1997). Similarly, tyrosine depletion has been found to diminish DA release after amphetamine-induced stimulation, while leaving basal DA functioning unaffected (McTavish et al., 1999). Thus, depletion procedures do appear to decrease neurotransmitter release, although potentially only when relevant neurons are stimulated (i.e. when the neurotransmitters' utilisation is higher than their synthesis; Feenstra & van der Plasse, 2010).

Notably, study 3 assessed depletion effects using a task that is assumed to stimulate DA and 5-HT activity, and tested participants in the unfamiliar environment of the MRI scanner, which likely led to increased arousal and novelty related 5-HT and DA release (Young, 2013). Thus, even if it is assumed that depletion effects are only seen when the release of the relevant neurotransmitters is stimulated, it seems plausible that these effects were present in study 3.

5.3.5.3 Depletion-related Effects on Other Neurotransmitters

Another point to note about the depletion procedure is that it may have had an impact on other neural mechanisms besides DA and 5-HT release. For instance, tyrosine and phenylalanine depletion does not only affect DA functioning, but also lowers norepinephrine (NE) levels, as the latter is synthesised from DA (Fernstrom & Fernstrom, 2007). It is, therefore, possible that some of the observed effects in study 3 were due to decreases in NE rather than DA levels. However, upon closer inspection this seems unlikely for two reasons: firstly, while tyrosine depletion has been found to significantly decrease (amphetamine-induced) DA release, no effects on NE release have been observed (McTavish et al., 1999). Secondly, NE appears to be involved in the processing of *unexpected* uncertainty (i.e. variations in the probabilistic contingencies across a task; Yu & Dayan, 2005), while DA functioning is thought to be linked to *expected* uncertainty (i.e. outcome probabilities which stay stable throughout a task; Fiorillo, Tobler, & Schultz, 2003). Give that study 3 utilised a task involving *expected* uncertainty, it is reasonable to assume that DA functioning played an important role in the observed effects.

Regarding tryptophan depletion, it has similarly been argued that other neural effects besides lowered 5-HT functioning may play a role in reported findings. Based on evidence from animal studies, it has been proposed that tryptophan depletion may decrease nitric oxide levels in the hippocampus, which could affect cognitive functioning in a 5-HT independent manner (Van Donkelaar et al., 2011). However, evidence for this suggestion appears rather indirect and the exact mechanism through which tryptophan depletion is thought to affect nitric oxide is uncertain (Young, 2013). Moreover, the depletion procedures used in the cited animal studies

differed substantially from those utilised in humans. Thus, it is not clear if the effect of tryptophan depletion on nitric oxide is robust and applicable to human depletion studies (Young, 2013). Additionally, it has been argued that the notion that tryptophan depletion affects cognitive functions via lowered 5-HT functioning (rather than a different mechanism) is supported by its parsimony, as well as by the consistency between findings of depletion studies and research utilising other pharmacological 5-HT manipulations (Crockett et al., 2013). Thus, it seems likely that the findings of study 3 were a result of reduced 5-HT functioning.

It should, however, be noted that the findings observed in study 3 could also have been influenced by interactions between neurotransmitters. As no neurotransmitter system functions in isolation, this is the case for any pharmacological manipulation. However, of particular note in the current context is that the 5-HT and DA systems interact, which means that caution needs to be applied when considering the specificity of the findings of study 3. While there is little evidence for an influence of DA on 5-HT functioning, the reverse effect is well documented (De Deurwaerdère & Di Giovanni, 2017). Specifically, 5-HT2C receptors seem to tonically inhibit DA functioning, whereas other 5-HT receptor subtypes appear to enhance DA activity when 5-HT release is stimulated (Alex & Pehek, 2007). Notably, in study 3, both DA and 5-HT depletion reduced social reward prediction-related responses in the dACC/ dmPFC. It can thus not be ruled out that 5-HT depletion led to reduced DA activity in the frontal cortex, and that decreased DA rather than 5-HT functioning played a crucial role in the observed PFC effects. However, even if this was the case, other findings of study 3 (e.g. in the temporal lobe and insula) were more unambiguously 5-HT related, as they were present only under 5-HT and not under DA depletion. Importantly, it was these findings (and not those observed in the PFC) that were highly similar between 5-HT depleted subjects in study 3 and HD individuals in study 2. Thus, the main conclusions drawn from integrating the results of studies 2 and 3 remain unaffected by the potential interactions of 5-HT and DA.

5.4 Broader Implications

5.4.1 Psychotherapeutic Interventions for Depression

The findings of study 1 indicate that social learning deficits in depression are associated with increased amounts of time spent in negative social interactions. This may be the case because HD subjects' impaired ability to use social feedback to appropriately update future actions may lead to suboptimal interpersonal behaviour, thus resulting in negative responses from others. This suggestion is in line with findings that depressed individuals show less appropriate behaviour during social interactions (reviewed in Rottenberg & Gotlib, 2008 and Segrin, 2000; see also Setterfield et al., 2016), which may lead to the rejection of depressed subjects by their interlocuters (Segrin & Abramson, 1994). Along these lines, the results of study 1 may be taken to indicate that it is important to incorporate a social skills training component into psychological therapies for depression. Indeed, a meta-analysis of psychotherapeutic interventions (Barth et al., 2013) has shown that both interpersonal therapy (Klerman, Weissman, Rounsaville, & Chevron, 1984) and social skills training (Becker, Heimberg, & Bellack, 1987) are effective in treating depression.

However, it should be noted that training depressed individuals on how to behave appropriately in social situations potentially does not address the root of the social functioning impairments. Specifically, the results of study 1 tentatively suggest that potential social skills deficits in depressed subjects (which may have been the source of the reported negative social encounters) may partly be due to reduced social learning. Providing social skills training, although important, may therefore merely addresses the manifestation, but not the cause, of social functioning deficits in depression. That is to say, depressed subjects may be able to learn to improve their social skills during highly structured training sessions that include clear instructions and explicit feedback. This may eventually result in more optimal social behaviour and in the receipt of more positive feedback from other people in real life. However, depressed individuals may not be able to *fully* benefit from these improvements if learning deficits prevent

them from using the (more subtle, real-life) positive social feedback to update their predictions about future social encounters. This issue was further highlighted in study 2, which showed that depressed subjects demonstrated increased uncertainty in their social outcome predictions (/likelihood ratings), with this uncertainty contributing to reduced social engagement motivation.

Thus, the findings of studies 1 and 2 suggest that it may be beneficial for psychotherapeutic depression treatments to include not only a social skills training component, but also an element that is aimed at enhancing social learning. It should, however, be kept in mind that the participants of studies 1 and 2 did not have a clinical diagnosis of depression. Due to the abovementioned potential differences between depressed individuals who do and do not seek treatment, the above suggestion should be considered with caution and replications of the current findings in a clinical sample are needed. Nevertheless, it is interesting to note that a previous study has found that attention training towards positive outcomes abolished depressed individuals' deficits in non-social reward learning (Cooper et al., 2014). If similar findings were obtained in relation to social learning (in a clinical sample), this may suggest that training depressed individuals to attend to positive social outcomes as part of psychotherapeutic interventions may improve their social reward learning, which, in turn, may enhance their social engagement motivation.

At first sight, the above approach may seem problematic, because selectively enhancing attention to positive outcomes could result in reduced learning from negative feedback, therefore increasing aversion-related uncertainty. This may have negative consequences on social functioning, especially given the link between high *valence-unspecific* uncertainty and reduced social engagement motivation observed in study 2. However, as mentioned above, the reduced learning from, and thus the enhanced uncertainty about, social aversion in HD subjects may have been partly due to increased rumination in response to negative outcomes, which may have interfered with the learning process (Whitmer et al., 2012). Notably, it has been suggested that rumination may be linked to a narrowed attentional scope induced by

negative mood (Whitmer & Gotlib, 2013). Moreover, attentional bias modification training has been shown to alleviate depression symptoms (Jonassen et al., 2018; Wells & Beevers, 2010). Thus, attention training towards positive social outcomes may lead to more positive affect (possibly partly due to increased learning from and experience of pleasant social encounters), which may result in a widening of the attentional scope, thereby decreasing ruminative tendencies. Reduced rumination, in turn, may lead to 'normalised' aversion learning (and thus lower uncertainty) due to decreased interference of intrusive thoughts with the learning process.

The above tentatively suggests that integrating social attentional bias modification into psychotherapeutic treatments for depression may improve social learning, thereby reducing uncertainty about social outcomes and potentially enhancing social engagement motivation. It would be of interest for future studies to examine this hypothesised effect of attentional bias modification on social learning and real-life social functioning (especially in a clinical sample).

5.4.2 Pharmacological Interventions for Depression

Regarding pharmacological interventions, the findings of studies 2 and 3 tentatively suggest that medications enhancing 5-HT functioning, such as selective serotonin reuptake inhibitors (SSRIs), may be particularly effective in treating social learning deficits in depression. By contrast, dopaminergic drugs may potentially be less well suited to address these impairments, although replication studies with larger sample sizes and more rewarding social stimuli are needed to provide more conclusive evidence for this proposal.

It should be noted that the above suggestion is based on the similarities between the findings of studies 2 and 3, and the assumption that SSRI medication will have the opposite effect to 5-HT depletion. This does not take into account the differences between specific 5-HT functioning deficits after depletion in healthy volunteers and potentially much more global neural abnormalities in depressed individuals, nor the differential effects of acute vs. chronic 5-HT manipulations (Burghardt & Bauer, 2013), or the fact that treatment-seeking depressed

individuals may potentially display different (neural) deficits than those who do not seek help. Nevertheless, it is noteworthy that SSRIs have been found to improve some aspects of social functioning in clinical depression (Dubini, Bosc, & Polin, 1997). Considering the plethora of evidence indicating that serotonergic medication may abolish negative biases (often in relation to social stimuli such as facial expressions, Harmer, 2008), it seems likely that SSRIs may improve social functioning by providing depressed subjects with a more positive outlook on social encounters. That is to say, SSRI treatment may shift the attentional focus from negative (or negatively perceived ambiguous) towards positive social cues (Browning, Reid, Cowen, Goodwin, & Harmer, 2007), which may improve learning from positive social feedback, and, thereby, increase social engagement motivation. Future studies are needed to examine this suggestion, and to assess whether chronic SSRI treatment in depressed subjects can eliminate the social learning deficits observed in study 2. It would also be interesting to examine if early improvements in social learning with SSRIs predict later enhancements of real-life social engagement.

In addition, it is noteworthy that impaired social learning is not the only factor influencing social engagement in depression. For instance, the findings of study 1 indicate that heightened social anhedonia, i.e. the reduced pleasure and interest in social interactions, also contributes to social withdrawal. Notably, motivational anhedonia in depression has been linked to DA functioning (Argyropoulos & Nutt, 2013, although a relation between social motivation and norepinephrine has also been described; Briley & Moret, 2010). Thus, it is possible that DA functioning may influence social processing through other mechanisms besides social learning, such as by impacting social anhedonia tendencies. This gives rise to the interesting possibility that social functioning deficits may arise through different mechanisms in specific subgroups of depressed individuals with distinct underling neurotransmitter deficits. Future studies could examine if it is indeed the case that in some (clinically) depressed individuals social learning impairments contribute most strongly to social functioning deficits, while in others social anhedonia may play a more important role. Additionally, it could be investigated

if the former group responds better to 5-HT medication, while the latter is more responsive to DA (or NE) treatments. If there is indeed a dissociation between, for instance, 5-HT-mediated social learning deficits and DA-mediated social anhedonia, this would call for a personalised treatment approach in which different depression patient subgroups are treated with medications that are targeting their specific symptom profiles.

5.5 Conclusion

All in all, the current work provides evidence that depression symptoms are associated with impaired learning from social feedback, which, in turn, may contribute to negative social experiences and reduced social engagement motivation. These deficits may be associated with abnormal serotonin functioning and may result from preferential attention to negatively perceived (rather than positive) social outcomes. Thus, serotonergic medication, as well as psychotherapeutic interventions focused on improving attention to positive social outcomes, may be particularly effective in treating social learning impairments and social functioning deficits in depression.

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7 Appendices

7.1 Supplement for Chapter 3

7.1.1 *Supplementary Behavioural Results*

7.1.1.1 Prediction of Social Engagement Motivation with Inhibitory Uncertainty Intolerance

Inhibitory uncertainty intolerance (UI) scores were significantly higher in HD than in LD participants (U = 31.5, p < 0.001; HD: M = 17.00, SD = 4.34; LD: M = 8.18, SD = 3.19).

Moreover, similar results were obtained when predicting social engagement motivation using inhibitory UI than when utilising UIS negativity scores (as in the main paper). Specifically, a multiple regression analysis revealed that task-based uncertainty scores and questionnaire measures predicted participants' motivation to engage in pleasant social activities (F(5, 33) = 9.35, p < 0.001, R^2 = 0.52). Predictors significantly contributing to the relation were the main effect of inhibitory UI (β = -0.53, p = 0.005), the inhibitory UI* task uncertainty interaction term (β = -0.32, p = 0.011), and RSAS social anhedonia scores (β = -0.40, p = 0.036). By contrast the main effect of task uncertainty (β = -0.17, p = 0.161) and BDI scores (β = 0.31, p = 0.143) had no significant effect. Thus, the motivation to engage in pleasant social activities was particularly reduced in individuals who were uncertain about what social outcomes to expect and for whom uncertainty had an inhibitory effect.

7.1.1.2 Prediction Task Performance – Experimental Data Only

When only using the data from the experimental phase to assess prediction task performance, a very similar pattern of results emerged than when including both practice and experimental data (where available; see main paper). Specifically, a mixed measure ANOVA (group x valence x probability) performed on participants' likelihood ratings revealed the expected main effect of probability ($F(2, 82) = 82.39$, $p < 0.001$), as participants rated the likelihood of seeing an emotional expression higher after cues that were more likely to be followed by an emotional face. Moreover, a main effect of valence was observed ($F(1,41) = 4.35$, $p = 0.043$) which indicated that participants rated the overall likelihood of seeing happy faces as higher than the likelihood of seeing fearful faces. Additionally, a group by probability interaction was found ($F(2,82) = 8.46$, $p < 0.001$) which was followed up as described below. All other main effects and interactions were not significant (all $F < 2.1$).

Follow-up one-way ANOVAs revealed that, compared to LD controls, HD participants' likelihood ratings were significantly *lower* on trials with a 75% chance of showing a happy face ($F(1,41) = 7.59$, $p = 0.009$). By contrast, HD subjects' ratings were significantly *higher* than those of controls on trials with a 25% chance of showing a happy ($F(1,41) = 7.69$, $p = 0.008$) or fearful ($F(1,41) = 6.95$, $p = 0.012$) face. There were no group differences on trials with a 50% chance of showing a happy ($F(1,41) = 0.001$, $p = 0.976$) or fearful ($F(1,41) = 0.07$, $p = 0.794$) expression, nor on trials with a 75% chance of displaying a fearful face ($F(1,41) = 1.38$, $p = 0.248$).

7.1.2 Supplementary fMRI Results

7.1.2.1 Neural Prediction Value Encoding – One Sample T-Tests

Visual inspection of the parameter estimates extracted from the peak voxels of the group contrast suggested that LD participants encoded social reward predictions positively, while HD participants appeared to encode them negatively. To formally test this effect, one-sample t-tests against zero were performed separately for the two groups on the extracted parameter estimates. It was found that insula ($t(21) = 2.59$; $p = 0.017$) and parietal ($t(21) = 2.86$; $p = 0.009$) parameter estimates were significantly *above* zero in the LD group, while they were significantly *below* zero in the HD group ($t(20) = 3.06$; $p = 0.006$; $t(20) = 3.06$; $p = 0.006$, respectively). This suggests that BOLD responses of LD individuals tracked the prediction value for happy faces, while neural responses of HD subjects appeared to track the prediction value for neutral faces.

This suggestion was further supported by whole-brain one sample t-tests, which revealed that HD subjects demonstrated *inverse* social reward prediction encoding in a parietal lobe cluster (MNI coordinates: 22 -64 56; $Z = 3.69$; $p_{uncorrected} = 0.003$; although this result did not quite reach significance after family wise error correction on the cluster level; $p_{FWE\text{-}corrected} = 0.192$). By contrast, LD participants did not show any encoding of inverse social reward prediction values (even at an uncorrected cluster level threshold). However, as reported in the main paper, LD subjects did display *positive* reward prediction encoding in the temporal lobe and fusiform gyrus, while no such effects were seen in HD individuals.

7.1.2.2 Neural Prediction Value Encoding – ROI Analysis

A recent meta-analysis identified the subgenual anterior cingulate cortex (sgACC) as the only region which consistently encoded model-derived prediction values across studies (Chase et al., 2015). Thus, a region of interest analysis was performed on this area. For this purpose, MarsBar (Brett et al., 2002) was used to extract prediction-related parameter estimates from a 8mm sphere (as in Ham, Greenberg, Chase, & Phillips, 2016) around the sgACC coordinates indicated in the meta-analysis (ROI 1: 4 34 -6; ROI 2: -6 28 -20). A one-way ANOVAs performed on the extracted parameter estimates revealed no group differences for social reward prediction (ROI 1: $F(1,41) = 0.01$, $p = 0.932$; ROI 2: $F(1,41) = 0.37$, $p = 0.545$) or social aversion prediction (ROI 1: $F(1,41) = 2.56$, $p = 0.117$; ROI 2: $F(1,41) = 1.22$, $p = 0.276$) encoding.

7.1.2.3 Neural Prediction Value Encoding – Individual Parameters

When individual parameter values were used in the computational model to derive prediction values for the parametric modulation analysis, similar results were obtained as when average parameters were used (as in the main paper). Specifically, it was found that HD subjects showed reduced social reward prediction encoding in the precuneus, inferior parietal lobe and superior temporal lobe compared to LD controls (see Table S1). No significant group differences were observed for social aversion prediction encoding.

Table S1. *Parametric modulation results for social reward prediction encoding in individuals with low (LD) vs high (HD) depression scores using individual modelling parameters*

	MNI coordinates				
Brain Region	X	Y	Z	Z score	*p* value
LD > HD					
Precuneus	20	-50	46	3.18	0.005
Inferior Parietal Lobe	32	-58	48	3.12	
Superior Temporal Lobe	38	-56	18	3.26	0.001

Voxelwise thresholded at p<0.01; whole-brain cluster p values family-wise error corrected at p < .05

7.2 Supplement for Chapter 4

7.2.1 Supplementary fMRI Results

7.2.1.1 Neural Prediction Value Encoding – One Sample T-Tests

Visual inspection of the parameter estimates extracted from the peak voxels of the placebo vs 5-HT group contrast suggested that participants on placebo encoded social reward predictions positively, while 5-HT depleted subjects appeared to encode them negatively. To formally test this effect, one-sample t-tests against zero were performed separately for the two groups on the parameter estimates. It was found that, for participants on placebo, all extracted parameter estimates were significantly *above* zero, including in the premotor cortex ($t(21) = 2.44$; $p = 0.024$), the dorsal anterior cingulate cortex (ACC; $t(21) = 3.92$; $p = 0.001$), the superior ($t(21) = 1.88$; $p = 0.074$) and middle ($t(21) = 2.63$; $p = 0.016$) temporal lobe, the insula ($t(21) = 2.44$; $p = 0.024$), and the fusiform gyrus ($t(21) = 2.65$; $p = 0.015$). By contrast, for 5-HT depleted subjects, all extracted parameter estimates were significantly *below* zero, including in the premotor cortex ($t(23) = 5.28$; $p < 0.001$), the dorsal ACC ($t(23) = 2.60$; $p = 0.016$), the superior ($t(23) = 3.56$; $p = 0.002$) and middle ($t(23) = 4.04$; $p = 0.001$) temporal lobe, the insula ($t(23) = 3.42$; $p = 0.002$), and the fusiform gyrus ($t(23) = 2.87$; $p = 0.009$). This suggests that the BOLD response in individuals on placebo tracked the prediction of happy faces, while the neural response of 5-HT depleted subjects appeared to track the prediction of *neutral* faces.

This suggestion was furthers supported by whole brain one sample t-tests, which revealed that 5-HT depleted individuals demonstrated *inverse* social reward prediction encoding in a range of areas, including the bilateral temporal lobe and precuneus (see Table S1). By contrast, neither DA depleted participants nor subjects on placebo showed any encoding of inverse reward prediction values.

Table S1. *Regions encoding inverse social reward predictions in 5-HT depleted subjects*

	MNI coordinates				
Brain Region	X	Y	Z	*Z* score	*p* value
Left Superior Temporal Lobe	-44	-44	14	4.36	<0.001
Cerebellum (extending to the Fusiform Gyrus)	-8	-56	-12	4.31	<0.001
Right Middle Temporal Lobe	68	-46	8	3.86	0.001
Precuneus	6	-62	54	4.44	<0.001

Voxelwise thresholded at p<0.005; whole-brain cluster p values family-wise error corrected at p < .05

7.2.1.2 Neural Prediction Value Encoding – ROI Analysis

In a recent meta-analysis the subgenual anterior cingulate cortex (sgACC) was reported to be the only region which consistently encoded model-derived prediction values across studies (Chase et al., 2015). Thus, a region of interest analysis was performed on this area. For this purpose, MarsBar (Brett et al., 2002) was used to extract mean prediction-related parameter estimates from a 8mm sphere (as e.g. in Ham et al., 2016) around the sgACC coordinates indicated in the meta-analysis (ROI 1: 4 34 -6; ROI 2: -6 28 -20).

One-way ANOVAs performed on the extracted parameter estimates revealed no group differences for social reward (ROI 1: $F(2,67) = 1.95$, $p = 0.151$; ROI 2: $F(2,67) = 0.94$, $p = 0.398$) or social aversion (ROI 1: $F(2,67) = 1.87$, $p = 0.162$; ROI 2: $F(2,67) = 0.26$, $p = 0.774$) prediction encoding.

7.2.1.3 Neural Prediction Value Encoding – Individual Parameters

Using individual parameter values in the computational model to calculate prediction values for the parametric modulation fMRI analysis yielded similar results as using average parameters. Specifically, it was found that social reward prediction encoding was significantly reduced in 5-HT depleted subjects, compared to placebo controls, in the dorsal anterior cingulate cortex (ACC)/ dorsomedial prefrontal cortex (PFC), the premotor cortex/ dorsolateral PFC, the bilateral temporal lobe/ fusiform gyrus, and the precuneus (see Table S1).

Moreover, stronger social aversion prediction representations were observed in the 5-HT depletion compared to the DA depletion group in the precentral gyrus, motor gyrus/ mid cingulate cortex and dorsolateral PFC (see Table S2). All other group comparisons and main effects revealed no significant clusters.

Table S2. *Parametric modulation results for social prediction encoding using individual model parameters*

	MNI coordinates				
Brain Region	X	Y	Z	Z score	*p* value
Social Reward Prediction Encoding					
Placebo > 5-HT Depletion					
Premotor Cortex (BA 6) extending to the dlPFC (BA 8)	-26	8	46	4.08	0.005
Dorsal ACC	10	24	26	3.72	0.001
Dorsomedial PFC	-10	48	32	3.49	
Left Superior Temporal Lobe	-46	-42	16	4.13	0.037
Right Middle Temporal Lobe	54	-42	4	3.57	0.043
Right Lingual/ Fusiform Gyrus	22	-74	0	3.60	0.017
Cerebellum	-14	-68	-20	3.98	<0.001
Left Fusiform Gyrus	-32	-66	-12	3.33	
Precuneus	-16	-64	24	3.13	0.043
Social Aversion Prediction Encoding					
5-HT Depletion > DA Depletion					
Precentral Gyrus	-16	-8	54	4.21	<0.001
Motor cortex/ Medial Cingulate	14	-14	50	4.14	0.044
Dorsolateral PFC	34	18	44	4.03	0.013

Voxelwise thresholded at p<0.005; whole-brain cluster p values family-wise error corrected at p < .05; ACC, anterior cingulate cortex, dlPFC, dorsolateral prefrontal cortex; BA, Brodmann Area

7.3 Ethical Approval

7.3.1 Ethical Approval for Chapter 2

-------- Original message --------

From: Eugene McSorley <e.mcsorley@reading.ac.uk>
Date: 10/11/2016 12:48 (GMT+00:00)
To: Ciara McCabe <c.mccabe@reading.ac.uk>
Cc: PCLS Ethics <pclsethics@reading.ac.uk>
Subject: Re: new ethics application 2016-152-CM

Hi Ciara

I have reviewed the ethics associated with this project and I'm happy for it to proceed.

all the best

Eugene

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7.3.2 Ethical Approval for Chapter 3

University of Reading

Coordinator for Quality Assurance in Research
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Dr Ciara McCabe
School of Psychology and Clinical Language Sciences
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23 January 2017

Dear Ciara

UREC 16/08: Reward-based reinforcement learning in depression.
Amendment favourable opinion

Thank you for your application (email dated 12 December 2017 and including attachment refers) requesting and detailing amendments to the above project (*extension of study until December 2017; updating of study personnel; minor revision of inclusion/exclusion criteria; addition of second testing session and questionnaires; corresponding alteration to reimbursement level and participant information sheet*). I can confirm that the UREC Chair has reviewed that request and is happy for the project to continue.

Yours sincerely

Dr M J Proven
Coordinator for Quality Assurance in Research (UREC Secretary)

cc: Dr John Wright (Chair); Professor Laurie Butler, Head of School; Alex Antonesei (PhD student)

7.3.3 *Ethical Approval for Chapter 4*

University of Reading

Coordinator for Quality Assurance in Research
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Dr Ciara McCabe
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19 January 2016

Dear Ciara

UREC 15/61: Effect of Amino Acid Depletion on Reward and Aversion Processing. *Favourable opinion with condition*

Thank you for the application (emails dated 12 and 13 December 2015 and 4 January 2016, from Anna Frey and including attachments refer). On the basis of these documents I can confirm that the Chair is pleased to confirm a favourable ethical opinion subject to the following condition:

(i) Please ensure that information on the support available for volunteers suspected, at screening, of suffering from a psychiatric disorder (as described in Section 2.5, 4. Of the SREC form) is included in the study Participant Information Sheet.

I would be grateful for sight of the revised Information Sheet before the study commences.

Please note that the Committee will monitor the progress of projects to which it has given favourable ethical opinion approximately one year after such agreement, and then on a regular basis until its completion.

Please also find attached Safety Note 59: Incident Reporting in Human Interventional Studies at the University of Reading, to be followed should there be an incident arising from the conduct of this research.

The University Board for Research and Innovation has also asked that recipients of favourable ethical opinions from UREC be reminded of the provisions of the University Code of Good Practice in Research. A copy is attached and further information may be obtained here:

http://www.reading.ac.uk/internal/res/QualityAssuranceInResearch/reas-RSqar.aspx

Yours sincerely

Dr M J Proven
Coordinator for Quality Assurance in Research (UREC Secretary)
cc: Dr John Wright (Chair); Professor Laurie Butler (Head of School); Anna Frey (PhD student)