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"The role of amphetamine-induced dopamine hypersensitivity in reward-based learning processes"

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The point is ... that there is no point in driving yourself mad trying to stop yourself going mad. You might just as well give in and save your sanity for later.

The Hitchhiker's Guide to the Galaxy, Douglas Adams (1979)

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List of Abbreviations

AMPH	**Amph**etamine, here: D-amphetamine
BOLD	**B**lood-**O**xygen-**L**evel **D**ependent
BP	**B**lood **P**ressure
CrI	**Cr**edible **I**nterval
DAT	**D**op**a**mine **T**ransporter
DEQ	**D**rug **E**ffects **Q**uestionnaire
fMRI	**F**unctional **M**agnetic **R**esonance **I**maging
GLM	**G**eneral **L**inear **M**odel
HC	**H**ippo**C**ampus
HGF	**H**ierarchical **G**aussian **F**ilter
HR	**H**eart **R**ate
LOOIC	**L**eave-**O**ne-**O**ut Cross-Validation **I**nformation **C**riterion
M.I.N.I.	**M**ini-**I**nternational **N**europsychiatric **I**nterview
MLM	**M**ulti**l**evel **M**odel
MNI space	**M**ontreal **N**eurological **I**nstitute space
PE	**P**rediction **E**rror
PET	**P**ositron **E**mission **T**omography
PLAC	**Plac**ebo
ROI	**R**egion **o**f **I**nterest
SnPM	**S**tatistical **N**on**P**arametric **M**apping
SPM	**S**tatistical **P**arametric **M**apping
STR	**Str**iatum
VMAT2	**V**esicular **M**onoamine **T**ransporter **2**

1 Introduction

Fixed, false beliefs (delusions) and abnormal perception (hallucinations) are hallmarks of psychosis (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). While psychosis has been primarily associated with schizophrenia representing the positive symptoms of schizophrenia, psychosis is not unique to schizophrenia. Indeed, psychoses have been reported for other psychiatric conditions like bipolar disorder and severe depression, as well as for neurological conditions like temporal lobe epilepsy and Parkinson's Disease (Howes & Kapur, 2009; Winton-Brown, Fusar-Poli, Ungless, & Howes, 2014). Additionally, psychotic symptoms can occur on a sub-clinical level: about 8% of the general population report psychotic experiences of which only half ever reach a clinical stage (van Os et al., 2009). Because of its marked differences with respect to thought and perception, psychosis is an interesting phenomenon of investigation for cognitive science. Hence, research on psychosis may not only help affected individuals, but may also provide insights on and improve understanding of many topics central to cognitive science such as decision-making or motivation (for an overview of research on psychosis and cognition see Green & Harvey, 2014). Due to its complexity, psychosis begs for a multidisciplinary and multi-methodological research strategy making it even more interesting for cognitive scientists. Since research on psychosis and schizophrenia has often been mixed (Howes & Kapur, 2009), this thesis mostly relies on research on schizophrenia while the focus is more specifically on psychosis.

1.1. Dopamine, Schizophrenia & Psychosis

Dopamine is one of the brain's main neurotransmitters. The dopamine system is part of the diffuse modulatory systems, which means that it modulates activity in various brain regions despite a relatively small number of dopamine-synthesizing neurons (Wise, 2004). It does so through several pathways: dopamine-synthesizing neurons in the midbrain, mainly in the ventral tegmental area and the substantia nigra pars compacta, project to more distant brain regions like the prefrontal cortex, the ventral and dorsal striatum, and anterior temporal structures such as the amygdala and the hippocampus (Wise, 2004). As such, the dopamine system makes up a large part of the basal ganglia which together with the frontal cortex

are involved in various motoric, cognitive and limbic functions needed for goal-directed behaviour (Haber & Knutson, 2010; Wise, 2004).

Concerning dopamine's role in psychosis, dopamine has long been implicated in schizophrenia, and thereby psychosis. The dopamine hypothesis of schizophrenia is based on the observation that dopamine levels of various brain regions in schizophrenic individuals differ from those in non-schizophrenic individuals (Howes & Kapur, 2009). Elevated dopamine synthesis capacity is among the best replicated findings in schizophrenia (Howes et al., 2012). Accordingly, already earliest formulations of the dopamine hypothesis stated a dysregulated dopaminergic system as the neurochemical basis of schizophrenia. However, Howes and Kapur (2009) paint a more complex picture. Firstly, dopamine does not work in isolation but seems to be regulated by and interact with other neurotransmitter systems, especially the glutamatergic system. Secondly, dopamine abnormalities have also been identified outside of the striatum, namely the prefrontal cortex, where dopamine levels seem to be reduced. Lastly, Howes and Kapur (2009) have argued that the dopamine hypothesis actually applies only to psychosis-in-schizophrenia and not all of schizophrenia.

1.1.1. Dopamine dysregulation in psychosis (& schizophrenia)

Despite these discrepancies on the details of the dopamine hypothesis, what seems to hold true is that dopamine levels are elevated in the striatum of patients with schizophrenia (Howes et al., 2012). This most likely arises from aforementioned elevated dopamine synthesis and release capacity (Howes et al., 2012; Winton-Brown et al., 2014). Dopamine concentration depends on tonic and phasic activation of dopaminergic neurons. Tonic firing regulates baseline dopamine levels. Phasic firing regulates temporary spikes in dopamine levels (also called transients). Both seem dysregulated in psychosis (Maia & Frank, 2017). Importantly, several studies have reported these abnormalities also in the prodromal stage of schizophrenia, in individuals at high risk of developing psychosis (Howes & Kapur, 2009), and in patients with temporal lobe epilepsy who experience psychoses (Winton-Brown et al., 2014). Furthermore, dopamine release to stress also seems to be elevated in patients with psychosis and in patients at risk of developing psychoses (Howes, McCutcheon, Owen, & Murray, 2017). Together, these findings tie into the idea of endogeneous sensitisation and a neurodevelopmental model of schizophrenia (Howes et al., 2017; Weidenauer et al.,

2017). According to these ideas, genetic and environmental factors endogenously sensitise the dopaminergic system in early life stages. Hyperresponsiveness to stress and other stimuli that target the dopamine system ultimately results in the development of psychosis. Overall, while dopaminergic pathophysiology in the striatum is well established for psychotic variants of schizophrenia, attempts to link the neurochemical abnormalities to the phenomenological abnormalities of the positive symptoms of schizophrenia (i.e. psychosis) have been fairly recent.

1.1.2. Dopamine, reward processing & prediction errors

One way by which dopamine dysregulation has been implied in psychotic symptoms is through its role in reward processing (Haber & Knutson, 2010). The concept of reward originates in behaviourist theories of associative learning, namely conditioning. Conditioning describes the process by which organisms learn to perceive associations between events in their environment and to adapt their behaviour according to these learnt associations (Jozefowiez, 2012). In conditioning, associations are usually between two stimuli (Pavlovian conditioning) or between an action and its consequences in the environment (instrumental conditioning). Rewards in conditioning refer more to physical objects or events that motivate reward-seeking behaviour (Wise, 2004). Reward in reward processing more generally refers to the positive value that is assigned to objects, behaviours or internal states, and that motivates goal-directed behaviour (Winton-Brown et al., 2014).

Concerning the role of dopamine in reward processing, Schultz (1998) has shown in a series of animal studies, that used classic reward-based learning tasks, that dopaminergic neurons are sensitive to unexpected absence or presence of rewards. The author suggested that these dopamine responses to unpredicted stimuli encoded a reward prediction error, i.e. the difference between the predicted and the actual outcome (Schultz, 1998). This prediction error would serve as global learning signal which propagates to other reward-processing brain regions and thereby facilitates decision-making and learning. Since then, several studies with human subjects have confirmed behavioural, dopamine-related neural abnormalities in patients with schizophrenia at different levels of reward processing, including reward anticipation, reinforcement learning and reward-based decision-making (Strauss, Waltz, & Gold, 2014).

The idea that dopamine signals code reward prediction errors ties well into the predictive processing framework. This framework aims at providing a unified understanding of perception, cognition, and action (Clark, 2013). According to predictive processing, the brain is a "prediction machine" that uses top-down prior expectations to (1) predict expected sensory inputs and to (2) compare predicted inputs to actual sensory inputs (Clark, 2013). Differences between predicted and actual input (i.e. prediction errors) are theorised to propagate throughout the brain, adjusting expectations and behaviour so that future mismatches are less pronounced (Clark, 2013). Depending on how strict or lenient the framework is interpreted, predictive processing has been argued to simply conceptualize neurocognitive functions or to even provide a unified theory of action and perception, that potentially extends to adaptive behavior (Clark, 2013; Sims, 2017).

From a predictive processing perspective, delusions and hallucinations can be conceptualised as false or suboptimal inferences about the world that arise from a disrupted integration of input and predictions (Griffin & Fletcher, 2017). Aberrant dopamine signalling in the midbrain, which is hypothesised to represent aberrant reward prediction error signalling, seems particularly plausible to underlie such disrupted integration. Considering the hypothesis that dopamine functions as global learning signal, aberrant dopamine signalling could drive aberrant updating of expectations and, hence, learning of aberrant associations while also drawing attention to stimuli that wrongly deviate from predictions (Anticevic & Corlett, 2012). Accordingly, the role of dopamine in learning has been increasingly conceptualised in computational terms (see Maia & Frank, 2017 for an exemplary computational account of dopamine dysregulation in psychosis). But although the understanding that dopamine codes reward prediction errors fits well into a predictive processing framework and can neatly be described by computational models, dopamine appears to code more than reward-related aspects of stimuli.

1.1.3. Dopamine & salience processing

Indeed, striatal dopamine responses have been suggested to more generally code the incentive salience of stimuli (Berridge, 2012; Winton-Brown et al., 2014). According to this idea, dopamine surges after unpredicted stimuli reflect the mediating role of dopamine in the attribution of incentive salience. Salience attribution describes a selection process by which stimuli are prioritised according to their importance to an organism (Kapur, 2003;

Winton-Brown et al., 2014). The ability to distinguish between relevant and irrelevant stimuli is central to an organism's survival in a complex, stimulus-rich world. This is especially true for humans. Given our limited cognitive and motor resources, it is crucial to attend to and select the right stimuli to act upon (Winton-Brown et al., 2014). Prioritisation occurs by attributing salience to stimuli, which can be internal (thoughts) or external (events). Some stimuli like a sudden loud noise are highly relevant and naturally attract attention (i.e. are attributed salience). Usually, however, salience attribution to a stimulus is highly contextual, depending on internal states such as goals, beliefs or history (Winton-Brown et al., 2014). Dopamine surges are thought to help channel attention to those stimuli that are most relevant while less relevant stimuli are possibly suppressed (Winton-Brown et al., 2014). So, how does salience attribution relate to the phenomenology of psychosis?

According to the aberrant salience hypothesis, abnormal dopamine signalling in psychosis disrupts the regular stimulus-related dopamine release which is essential to dopamine's control in mediating salience attribution (Kapur, 2003). Excessive context-independent dopamine surges label internal and external stimuli as relevant, which normally would not have been labelled relevant. Dopamine's function thus turns from mediating salience to creating salience (Kapur, 2003). Concerning phenomenological abnormalities in psychosis, this framework conceptualises delusions as top-down attempts to make sense of emerging abnormally salient events and hallucinations as internal stimuli that have falsely been attributed with salience (Kapur, 2003). Together with other cognitive and interpersonal abnormalities, that often accompany prodromal phases of psychosis, these dopaminergic abnormalities give way to the development of full blown psychoses (Kapur, 2003).

Regarding dopamine's hypothesised role in aberrant prediction error signalling in psychosis, the aberrant salience attribution hypothesis is compatible with a predictive processing account of psychosis. Aberrant prediction error signalling can be conceptualised as driving salience attribution to irrelevant internal and external events (Anticevic & Corlett, 2012). The aberrant salience attribution hypothesis also does not preclude earlier findings on reward-based learning in psychosis. Dopamine-dependent attribution of incentive salience can still change reward-based learning as it motivates a reward's salience value. Yet, it does not do so primarily (Berridge, 2012). Admittedly, some researchers argue that such understanding is mostly based on dopamine signalling in the limbic striatum and that

dysregulated dopamine responses in psychosis should better be understood in terms of gating aberrant thoughts and percepts and not in terms of aberrant value assignment (Maia & Frank, 2017). However, research accumulates whereby various dopaminergic brain regions are involved in processing of multiple types of salience, including novelty salience, aversion salience, emotional salience and physical salience (Winton-Brown et al., 2014).

1.2. Overview of Methods & Findings on Salience Processing in Psychosis

Research on psychosis and more generally on schizophrenia has been difficult not only due to severity of the disorder, but also due to the diversity of subjects. Subject samples that have been used in psychosis research entail individuals at high-risk of developing psychosis, first-episode psychotic patients, and long-term psychotic patients, who can be medicated with typical or atypical antipsychotics, unmedicated, or drug-naïve. Especially the medication aspect makes interpretation across studies difficult because anti-psychotic drugs target the dopamine system directly (Howes & Kapur, 2009). This potentially confounds any findings on the role of dopamine in salience processing.

1.2.1. Salience processing tasks & imaging techniques

Depending on which type of salience processing is investigated, researchers have used different types of task paradigms (Winton-Brown et al., 2014). However, most studies employ variants of reward-based reinforcement learning tasks that look at reward-related salience processing. In these tasks, participants learn to associate a cue with a rewarding outcome. Importantly, cues are usually task-relevant or task-irrelevant. Task-relevant cues are expected to reinforce certain behaviours, for instance, speeding up reaction times, which is thought to reflect salience attribution (Winton-Brown et al., 2014). Besides reward-based learning paradigms, researchers have also developed reward-independent salience attribution paradigms. This thesis covers only the most interesting paradigms in more detail.

Among reward-based learning tasks, the monetary incentive delay task is one of the most frequently used ones (Knutson, Adams, Fong, & Hommer, 2001). Participants are shown different cues that predict the probability of a financial reward, punishment or no

monetary outcome. They have to correctly respond to a target cue that follows the outcome-predicting cue. Importantly, participants have to wait a varying amount of time between outcome-predicting and target cue. The task thus allows to investigate neural activation during anticipation of relevant outcome-predicting stimuli (rewarding or punishing outcome) and neutral outcome-predicting stimuli (neither rewarding nor punishing outcome; Knutson et al., 2001). Ventral dopamine responses to predictive cues during reward anticipation are thought to link affective salience to predictive cues which facilitates initiation of goal-directed behaviour (Strauss et al., 2014).

Different to the monetary incentive delay paradigm, the salience attribution test combines implicit and explicit measures of salience attribution (Roiser et al., 2009). Participants have to respond to cues that differ on one relevant (reward-predicting) dimension and one irrelevant (non-predicting) dimension, for example, shape and colour. Implicit measures of salience attribution are reaction times. Explicit measures of salience attribution are subjective ratings of how likely a specific cue is to predict a reward. Increases in subjective ratings of reward probabilities for relevant, reward-predicting cues represent explicit measures of adaptive salience attribution; speeded responses after salient, reward-predicting cues represent implicit measures of adaptive salience attribution (Roiser et al., 2009). By contrast, the absolute difference between subjective ratings of reward probabilities for the two levels of the irrelevant dimension serves as explicit measure of aberrant salience attribution, and the absolute difference in response time between the two levels of the irrelevant dimension serves as implicit measure of aberrant salience attribution (Roiser et al., 2009).

Concerning non-reward-related salience processing, a visual variant of the oddball task has been used to investigate novelty-related salience processing (Bunzeck & Düzel, 2006). In this variant, the presentation of the standard image with neutral emotional valence is randomly interspersed with the presentation of different types of oddball pictures, namely a neutral picture, a neutral picture requiring a button press, a picture with negative emotional valence, and a novel picture that is different for every novel oddball trial. What is interesting about this task is that it allows to determine neural responses to pure stimulus novelty and not only rareness by contrasting novel and neutral oddballs (Bunzeck & Düzel, 2006).

Reversal learning tasks are another variant of reward-based learning tasks that probe salience processing (Feeney, Groman, Taylor, & Corlett, 2017). They are particularly interesting when it comes to psychosis because they directly target affective, inferential, and

behavioural processes, all of which seem impaired in patients with schizophrenia (Schlagenhauf et al., 2014). During deterministic reversal learning tasks, participants have to repeatedly choose between two (or more) stimuli (Feeney et al., 2017). The correct choice is rewarded whereas the wrong choice is not rewarded or even punished. Participants have to learn which stimulus is the correct / better choice by trial and error. Furthermore, the correct choice reverses occasionally. These reversals represent relevant events in response to which participants have to change their behaviour (i.e. update their belief) to stay with the correct / better choice. During probabilistic variants of this task, the correct choice is more likely to be rewarded but can also be not rewarded or even punished (e.g. 75% rewarded versus 25% not rewarded or punished). Hence, different from deterministic variants of reversal learning tasks where it suffices to simply update one's behaviour after reversals in reward-associations, probabilistic variants add another level of uncertainty (Feeney et al., 2017). Participants have to differentiate between true reversals (i.e. relevant events that require a change in behaviour) and trials in which the correct choice was simply unrewarded (i.e. irrelevant events that do not require a change in behaviour). Ideally, outcomes that are unexpected due to changes in the environment (reversals) should have a greater impact than outcomes that are unexpected due to a generally volatile environment (Nassar, Wilson, Heasly, & Gold, 2010).

To find neural correlates to behavioural findings, salience processing tasks are usually combined with imaging methods that allow to measure dopamine-related neural activation such as Positron Emission Tomography (PET) imaging or functional magnetic resonance imaging (fMRI). Both PET and fMRI have advantages and disadvantages. Molecular imaging with PET allows to directly measure dopamine neurotransmission *in vivo*, but it also relies on injection of radioactive tracers to measure neurotransmission (Winton-Brown et al., 2014). By contrast, fMRI is non-invasive as neural activation is measured with the blood oxygenation level dependent (BOLD) contrast, but it relies on inference that activation in brain regions that are known to be dopamine-rich, such as the ventral striatum, reflect *true* dopaminergic effects (Winton-Brown et al., 2014). fMRI studies usually interpret altered responses to neutral stimuli in dopamine-rich regions as neural correlates of aberrant salience attribution to neutral stimuli (Winton-Brown et al., 2014). More recently, however, neuropharmacological models have been developed that use dopamine stimulants to target the

dopamine system more directly, namely the ketamine and the amphetamine model of psychosis in schizophrenia (Boileau et al., 2006; Corlett, Honey, & Fletcher, 2007). These models are thought to bridge the inferential gap by eliciting dopaminergic abnormalities in healthy volunteers similar to those observed in psychotic and pre-psychotic individuals.[1]

1.2.2. Findings on aberrant salience processing in psychosis

Studies on reward-related salience processing have repeatedly found behavioural and neural differences in individuals with psychosis or psychotic-like symptoms. Findings converge on diminished neural and behavioural responses to reward-predicting (relevant) stimuli and exaggerated responses to irrelevant stimuli (Deserno, Schlagenhauf, & Heinz, 2016). Blunted dopamine responses to reward-predicting (relevant) stimuli in the ventral striatum of patients with schizophrenia during monetary incentive delay tasks have further been associated with positive and negative symptoms of schizophrenia (Winton-Brown et al., 2014). Negative symptoms of schizophrenia are for example anhedonia (Green & Harvey, 2014) Importantly, this aberrant responsiveness does not seem to stem from an inability to distinguish between rewarding and neutral stimuli which seems intact in psychotic patients (Murray et al., 2008). Besides aberrant neural responses in the ventral striatum, the midbrain, hippocampus, amygdala, and prefrontal regions have also been implicated in aberrant salience processing (Murray et al., 2008; Romaniuk et al., 2010).

Studies that investigated salience attribution more explicitly corroborate these findings on aberrant salience attribution in reward-based learning tasks. Using the salience attribution test, one study has found reduced salience attribution to relevant stimuli in medicated schizophrenia patients compared to healthy controls (Roiser et al., 2009). Additionally, a subgroup of schizophrenia patients with delusions exhibited increased aberrant salience attribution compared to schizophrenia patients without delusions. Another study using the salience attribution test showed that unmedicated participants at ultra-high risk of developing psychosis more frequently assigned significance to irrelevant stimuli and exhibited abnormal activity in the ventral striatum to irrelevant stimuli (Roiser, Howes, Chaddock, Joyce, & McGuire, 2013). Both measures correlated with the severity of pre-delusional symptoms. Furthermore, dopamine synthesis capacity in the striatum correlated inversely

[1] This thesis focuses on the amphetamine sensitisation model, for more details see section 1.3.

with hippocampal responses to irrelevant stimuli in the high-risk group but not in controls (Roiser et al., 2013).

Psychosis also seems to affect salience processing under uncertainty. Patients with psychosis have been found to display increased switching behaviour during both deterministic and probabilistic reversal learning (Feeney et al., 2017). Switching behaviour in reversal learning tasks describes how participants change or do not change their choice of the "correct stimulus" after each trial, in other words, whether participants do or do not update their belief of which is the "correct choice". Increased switching behaviour (or belief updating) has been interpreted as reflecting aberrant salience attribution to neutral (irrelevant) events due to an underlying chaotic dopamine signalling in psychosis (Feeney et al., 2017; Kapur, 2003). Psychotic patients also achieve less reversals when they depended on patients' performance, but are quicker at adapting their response after reversals because of increased switching behaviour (Feeney et al., 2017). Importantly, increased switching behaviour seems to correlate with the severity of psychotic symptoms in clinical populations as well as with the intensity of psychosis-like experiences and beliefs in sub-clinical populations (Feeney et al., 2017). A study that investigated reversal learning in unmedicated, primarily first-episode psychotic patients confirmed these findings (Schlagenhauf et al., 2014). Even when controlling for task-solving strategies, psychotic patients showed excessive switching behaviour and reduced sensitivity to rewards. Behavioural findings were accompanied by reduced activation to reversals in the ventral striatum. The authors hypothesised that this striatal hypoactivation is connected to the hyperdopaminergic levels characteristic for patients with psychosis since neural activation to reward prediction errors has been shown to inversely correlate with the dopamine synthesis capacity in the ventral striatum (Schlagenhauf et al., 2014, 2013). Accordingly, the authors suggest that more noisy neural prediction error signals result from either elevated tonic dopamine levels or increased phasic dopamine release (Schlagenhauf et al., 2014).

Another study that combined Bayesian modelling and fMRI found that increased switching behaviour during reversal learning in medicated schizophrenia patients was due to a heightened belief that the environment was volatile (Deserno et al., 2020). This was reflected by increased neural activation in the dorsolateral prefrontal cortex. Importantly, the computational model that yielded these results could replicate behavioural findings of unmedicated patients with schizophrenia. This indicates that increased perceived environmental

volatility is also present in unmedicated states. The authors suggested that abnormally increased beliefs about a volatile environment could make subjects overly sensitive to new inputs resulting in overly flexible updating to irrelevant input because subjects would not properly detect regularities in the environment (Deserno et al., 2020).

Studies that used reward-independent salience processing tasks have reported behavioural and neural findings in patients with psychosis similar to aberrant, reward-based salience processing. For instance, one study found abnormal learning of neutral stimuli in medicated patients with schizophrenia (Jensen et al., 2008). The study used an aversive learning task, which is a reinforcement task in which the outcome is unpleasant and induces avoidance behaviour. Patients could not distinguish between aversion-predicting and neutral stimuli. They also displayed a stronger activation of the ventral striatum in response to neutral stimuli. Another study found increased subjective emotional arousal in response to neutral stimuli in psychotic patients (Haralanova, Haralanov, Beraldi, Möller, & Hennig-Fast, 2012). An earlier PET study already found reduced phasic neural responses to emotionally salient images in the right ventral striatum, and elevated tonic activity in the amygdala and the right ventral striatum while overall performance measures did not differ from controls (Taylor, Phan, Britton, & Liberzon, 2005). Using an affective classification task in which participants had to rate words as pleasant, unpleasant or neutral, one study found that delusional patients were more likely to rate words as unpleasant and were slower in classifying neutral words compared to controls (Holt et al., 2006). In a functional connectivity study, patients with schizophrenia showed increased neural activity in striatum, hippocampus and prefrontal brain regions as well as increased connectivity between these regions for neutral stimuli. This was the opposite to the decreased activity in and connectivity between these regions that was found in controls (Diaconescu et al., 2011).

Concerning novelty-related salience processing, a recent study found differences in individuals at ultra-high risk of developing psychosis (Modinos et al., 2020). Using the visual oddball paradigm as described before, the study found that high-risk individuals did not differ in their behavioural response to controls, but that their hippocampal activation to novel (i.e. relevant) events was significantly reduced in comparison to hippocampal activation in controls (Modinos et al., 2020). Using Dynamic Causal Modelling, the study further found dysfunctional connectivity to relevant events between hippocampus, striatum and midbrain. Individuals at high risk exhibited increased neural connectivity in response to

relevant events from hippocampus to striatum and from midbrain to hippocampus, but reduced connectivity in response to relevant events from midbrain to striatum. This reduced connectivity from midbrain to striatum was even more marked in a small subgroup of high-risk individuals who later developed psychosis compared to high-risk individuals who did not develop psychosis (Modinos et al., 2020).

By contrast, a recent study did not find any difference in salience processing related to novelty or aversion in individuals at ultra-high risk of developing psychosis (Winton-Brown et al., 2017). The study used an extended version of the monetary incentive delay task that not only allows to investigate reward-related but also aversion- and novelty-related salience processing (Winton-Brown et al., 2017). In this task variant, all three dimensions (reward prediction, aversion, and novelty) are inherent in the cue (here, a picture) that precedes the outcome, and are manipulated independently from one another. The authors have argued that the lack of differences in novelty- and aversion-related salience processing might have been because the task design potentially placed different demands on different types of salience processing. Hence, it did not allow proper comparison of these types in the task (Winton-Brown et al., 2017).

Combining computational modelling with a variant of reversal learning, fMRI and PET, another study found that misattribution of salience was linked to the propensity of paranoid ideation in healthy volunteers (Nour et al., 2018). More precisely, the strength of subclinical paranoia correlated inversely with behavioural responsiveness to relevant stimuli: the stronger the paranoid ideation, the less sensitive participants were to relevant events and the more participants updated their beliefs after irrelevant events. Neural activity in the midbrain and ventral striatum correlated with how strongly a belief was updated. This was further reflected in negative correlations between dopamine receptor availability in the midbrain and midbrain activation, and between striatal dopamine release capacity and striatal activation (Nour et al., 2018).

Overall, research suggests that salience processing is disrupted in individuals with psychosis as well as in individuals with subclinical psychotic symptoms. Behavioural evidence for aberrant salience attribution is accompanied by abnormal neural activation in various brain regions that are involved in dopamine signalling, most prominently the striatum,

hippocampus and midbrain, as well as prefrontal regions. Co-occurence of aberrant behavioural and neural responses to relevant and irrelevant events thus supports the interpretation that chaotic dopamine signalling underlies aberrant salience attribution. The fact that both behavioural and neural responses have been shown to be abnormal in pre-psychotic stages further supports aforementioned neurodevelopmental models of psychosis (Howes et al., 2017; Kapur, 2003).

1.3. Bridging the Inferential Gap: The Amphetamine Sensitisation Model

Although researchers repeatedly report evidence for dopamine's role in salience processing, it is difficult to disentangle the role of dopamine in salience processing from other factors. Firstly, psychotic patients often take or have taken medication that potentially alters or has altered dopamine neurotransmission (Howes & Kapur, 2009). Secondly, fMRI studies lack the molecular-level clarity on the role of dopamine in aberrant salience processing. They only represent functional activation in brain regions that involve dopamine signalling and not directly the working of dopamine on brain processes (Winton-Brown et al., 2014).

One method that promises a more direct investigation of the role of dopamine neurotransmission in psychosis is the amphetamine sensitisation model (Weidenauer et al., 2017). In pharmacology, sensitisation describes the phenomenon that repeated exposure to a substance can increase sensitivity to this substance with respect to behavioural and neurochemical responses (Weidenauer et al., 2017). Sensitisation effects have been shown for various substances, including amphetamines. Repeated stimulation of dopamine receptors through repeated amphetamine administration is thought to trigger molecular and biological changes that promote increased dopamine release, thereby approximating the dopamine dysregulation characteristic to psychosis (Boileau et al., 2006). Importantly, already low doses of amphetamine have been shown to increase dopamine release and psychomotor responses in healthy male volunteers for up to one year (Boileau et al., 2006). Hence, amphetamine sensitisation has been proposed as a safe pharmacological model to investigate the role of dopamine signalling in psychosis in healthy volunteers in a controlled way. So how exactly does amphetamine work?

Amphetamines are a group of synthetic psychostimulants derived from phenethylamine

that target the dopaminergic, noradrenergic, and serotonergic brain system (Weidenauer et al., 2017). While the overall mechanism through which amphetamines act on these systems is the same, different amphetamines have different affinities to these systems (Weidenauer et al., 2017). For the amphetamine sensitisation model, D-amphetamine (hereafter, amphetamine) is particularly interesting because it primarily targets dopamine transporters in presynaptic neurons.[2] It does so by interacting with the transmembrane dopamine transporter (DAT) and the vesicular monoamine transporter 2 (VMAT2) which both are crucial for regulating extracellular dopamine concentration (Weidenauer et al., 2017). Amphetamine enters presynaptic dopamine neurons through DAT, located in the membrane of presynaptic dopamine neurons, and interacts with the cytosolic site of DAT. It thereby reverses the dopamine transport direction of DAT from taking up dopamine from the synpatic cleft to releasing dopamine into the synaptic cleft. Once inside presynaptic neurons, amphetamine also binds to VMAT2, located at dopamine-storing vesicles, where it stimulates the release of vesicular dopamine into the cytosol. Amphetamine thereby increases the amount of cytosolic dopamine. Consequently, significantly more dopamine is available for release and is released into the synapse resulting in prolonged elevation of extracellular dopamine levels (Weidenauer et al., 2017).

The amphetamine sensitisation model has already been applied with success in healthy volunteers. A recent PET study showed that amphetamine sensitisation based on Boileau et al. (2006)'s dosing scheme increases dopamine release in stimulant-naïve healthy volunteers to levels that are indistinguishable from first-episode psychotic patients (Weidenauer et al., 2020). Furthermore, Boileau's amphetamine sensitisation regimen has also been used successfully in fMRI studies on the role of dopamine in working memory (O'Daly, Joyce, Tracy, Stephan, et al., 2014) and reward processing (O'Daly, Joyce, Tracy, Azim, et al., 2014). Both studies found changes in neural activation of dopaminoceptive brain regions matching neural response profiles in psychosis. During memory encoding, sensitised participants displayed increased neural activation in the medial temporal lobe (hippocampus) and the right dopaminergic midbrain (ventral tegmental area and substantia nigra; O'Daly, Joyce, Tracy, Stephan, et al., 2014). During reward processing, sensitised participants showed decreased activation in the dorsal striatum during decision-making, but increased activation of the

[2]Note that D-amphetamine also targets the noradrenergic system which is not of interest for this thesis though.

same region during reward anticipation (O'Daly, Joyce, Tracy, Azim, et al., 2014). Furthermore, participants showed blunted activation to reward outcomes in the amygdala. Both studies further found sensitisation effects on subjective responsiveness to amphetamine, but no effects on physiological or behavioural measures (O'Daly, Joyce, Tracy, Azim, et al., 2014; O'Daly, Joyce, Tracy, Stephan, et al., 2014). These findings support the idea that the amphetamine sensitisation model represents a promising way to explore dopamine-dependent salience processing in healthy volunteers without the confounds of neither psychosis medication nor the inferential gap between the BOLD signal in fMRI and actual dopamine signalling.

1.4. Thesis Rationale: Research Questions & Interdisciplinarity

Until now, evidence for the link between dopamine dysregulation and aberrant salience processing in humans has been mostly correlational, relying on the inherent dopamine dysregulation of patients with psychosis (Winton-Brown et al., 2014). By actively manipulating dopamine levels of healthy volunteers with amphetamine, we investigated the following research questions:

- Does amphetamine-induced dopamine hypersensitivity affect reward-based salience processing under uncertainty in healthy individuals on behavioural and neural levels?
- If yes, how does it affect it?

Thereby, we hope to expand the knowledge about the hypothesised causal link between dopamine dysregulation and aberrant salience processing. Importantly, salience processing is investigated in the context of reward-based learning. To do so, this thesis combines theories and methods from neuroscience, psychology, computational modelling, and pharmacology. Neural activity was captured with fMRI, salience processing was captured with a reward-based reversal learning variant, and dopamine levels of healthy volunteers were manipulated with an amphetamine sensitisation regime and an acute amphetamine challenge. Furthermore, the thesis builds on a predictive processing account of cognition. Such interdisciplinary approach allows to investigate the role of dopamine-mediated perception of random (irrelevant) and relevant stimuli in an uncertain environment more thoroughly. Importantly, and different from regular reversal learning tasks, the reward-based predictive

inference task used in this thesis better mimics real life dynamic environments by (1) including different sources of uncertainty and by (2) including decision-making not in terms of choosing between different options but in terms of predicting outcomes (Nassar et al., 2010). It thereby juxtaposes the need to tolerate inaccuracy of predictions (the need to not respond to events despite fluctuations in environmental stimuli that appear relevant but are actually random or irrelevant events), and the need to respond to changes in the environment responding to events that need behavioural adjustment (i.e. relevant events; Griffin & Fletcher, 2017).

Based on previous neural and behavioural findings, we expected to see the following:

- Increased belief updating in sensitised participants (i.e. we expected sensitised participants to be more responsive to changes in the environment that are due to random and, thus, irrelevant events).
- Better and faster detection of relevant events due to chance hits (i.e. we expected participants to detect more reversals and to detect them faster when sensitised but not because they properly adapt their predictions to reversals but because they update their predictions more excessively)[3].
- Increased neural responses to irrelevant (random) events in salience-processing regions, namely striatum, hippocampus, and dopaminergic midbrain.
- Reduced neural responses to relevant events (reversals) in salience-processing brain regions, namely the striatum, hippocampus, and dopaminergic midbrain.

The following two chapters go into detail on the methods and measures used in this thesis. *Chapter 2* covers general methods such as the amphetamine sensitisation and amphetamine challenge scheme, the task, and the overall procedure. *Chapter 3* deals more specifically with how we measured salience-processing and how we analysed our data. It also provides hypotheses on how we expected dopamine hypersensitivity to affect salience processing that are more specific to our behavioural and neural measures of salience processing. After reporting our findings in *chapter 4*, we discuss these in the context of existing literature in *chapter 5*. We also point out several limitations and introduce potential follow-up analyses.

[3]See section 3.3.2.(iii) for why this does not contradict previous findings of worse performance-dependent reversal detection (Feeney et al., 2017).

2 Methods

2.1. Subjects

This thesis was part of a larger study. A smaller sample size was planned, but could not be achieved due to the COVID-19 situation. Ultimately, a total of 9 healthy male volunteers participated in the study (aged 21-30 years old, median 27 years). They were recruited from an existing participant pool. To qualify for participation, volunteers had to be German native speakers and right-handed as confirmed with Flinders Handedness survey (Nicholls, Thomas, Loetscher, & Grimshaw, 2013). Participants also underwent a general physical examination as well as neuropsychological assessments. Exclusion criteria were (1) any psychiatric and neurological disorders assessed by Mini-International Neuropsychiatric Interviews (M.I.N.I. German Version 5.0.0; Sheehan et al., 1998) and medical history, (2) physiological, biochemical, or haematological abnormalities assessed by thyroid function test, blood cell count, serum electrolytes, liver and kidney function, and urinalysis, (3) clinically relevant cardio-vascular abnormalities assessed by ECG, vital signs recordings and medical history (e.g. myocardial infection, angina pectoris, arterial hypertension, arteriosclerosis), (4) regular substance use (exceeding a total of five exposures to psychoactive substances) or alcohol abuse in past or presence based on declared history and urine tests (excluding nicotine), and (5) MR scanner incompatibility. Participants gave informed consent after admission to the study. They were reimbursed with a flat fee of €340 and could gain up to about €110 from completing all tasks of the overall study.

2.2. Experimental Design

A double-blind, placebo-controlled study design was adopted combining an amphetamine sensitisation and an amphetamine challenge paradigm. Participants were randomly assigned to amphetamine (n = 8) or placebo group (n = 1) and underwent a (sham) sensitisation scheme. After sensitisation, participants of both groups received amphetamine. The study was conducted at the Psychiatric Clinic of the Medical University of Vienna and at the

Dental Clinic of the Dental Medical University of Vienna. As this thesis was part of a larger study, participants completed more tasks than will be reported here.

2.2.1. Amphetamine sensitisation & amphetamine challenge

Following Boileau's (2006) dosing scheme, participants in the sensitisation group received D-amphetamine at 0.4 mg/kg body weight on 3 consecutive days with a minimum of 48 hours between administration. D-amphetamine was administered orally in form of Attentin® 5 mg capsules. This kept doses as uniform as possible over subjects with varying body weights (see table 2.1). Participants in the placebo group received Mannitol instead. On the last day of the study (A4), about 14 to 21 days after the third drug administration day, participants in both groups underwent an amphetamine challenge. For this, amphetamine was administered orally based on the same dosing scheme as used for sensitisation (see table 2.2 for an overview of the different study days). Both placebo and amphetamine tablets were administered in pharmacological capsules. Drugs were administered at the Psychiatric Clinic of the Medical University of Vienna.

Table 2.1: Amphetamine sensitisation and amphetamine challenge dosing scheme.

Body weight [*kg*]	**Number of Attentin® tablets**	**D-amphetamine total dose [*mg*]**	**Resulting D-amphetamine [*mg/kg* body weight]**
56 - 68	5	25	0.37 - 0.45
69 - 81	6	30	0.37 - 0.44
82 - 94	7	35	0.37 - 0.43

Note. Based on Boileau et al. (2006).

2.2.2. Procedure

Participants came for a total of 8 study days (table 2.2). The first and and fifth study day (B1 & B2) were pure behavioural days on which participants completed several tasks, including the predictive inference task analysed in this study. The second study day (A1) was the first sensitisation day on which participants received their first dose of amphetamine / placebo. They completed the same tasks as on behavioural days. This day comprised an additional scanning session during which participants completed the predictive inference task in the

MR scanner. The third and fourth study day (A2 & A3) were pure (sham) sensitisation days during which participants received their second and third dose of amphetamine / placebo. The sixth study day (M1) was also a scanning session during which participants completed the predictive inference and other tasks in the MR scanner. The seventh study day (A4) was identical to the second study day. This time, however, both groups received amphetamine. For the fMRI analysis, this thesis focuses on scans of the first and last day of amphetamine administration during which participants completed the reward-based predictive inference task in the MR-Scanner (session A1 & A4). The behavioural analysis includes data from all study days on which participants completed the predictive inference task (B1, A1, B2, M1 & A4).

All study days except M1, started between 9 and 11 AM at the psychiatric clinic. This kept hormonal levels comparable between participants. Scanning day M1 and scanning sessions on day A1 and A4 were completed at the dental clinic.

On sensitisation day A2 and A3, participants received the respective dose of D-amphetamine or placebo about 15 minutes after arrival. Baseline heart rate, blood pressure and saliva samples were obtained about 10 minutes before amphetamine/placebo administration. Starting with drug administration, these measures were obtained at 30 minutes intervals (at about 0, 30, 60, 90 minutes after drug administration). Participants additionally filled out the Drugs Effects Questionnaire (DEQ) at the same intervals. All physiological measures were collected seated with an electronic sphygmomanometer. If participants did not show any abnormal signs, they were dismissed about 90 minutes after drug administration.

On testing day A1 and A4, participants were asked to come on an empty stomach. Upon arrival, participants underwent a urine drug test. Participants who were tested positive for drugs were excluded from further participation. Furthermore, participants were asked to report any alcohol consumption within the last 24 hours and rescheduled if they had consumed any alcohol. Baseline and post-administration physiological and self-report measures were obtained at the same intervals as on sensitisation days. About 100 minutes after drug administration during which participants completed several other tasks, a research assistant walked participants to the dental clinic for scanning. Here, additional physiological and DEQ measurements were obtained before and after scanning about 120, 215,

and 250 minutes after drug administration. MR scanning started about 150 minutes after drug administration during which participants completed the reward-based predictive-inference task. This ensured that participants completed the task when subjective effects of amphetamine administration were peaking (Weidenauer et al., 2020). Participants were dismissed about 250 minutes after drug administration.

There were no specific regulations for behavioural days B1 and B2 and scanning day M1. No physiological or self-report measures were obtained on these days. Before every scanning session, participants had to fill out an MR-compatibility questionnaire.

Table 2.2: Testing Schedule.

	Sensitisation period			**Washout period**	**Post-sensitisation period**	
0 D	1 D	3 D	5 D	$\sim$ 14 D	19 D	20 D
B1	A1	A2	A3		B2+M1	A4
	AMPH/ PLAC	AMPH/ PLAC	AMPH/ PLAC			AMPH/ AMPH
	fMRI				fMRI	fMRI
task	task				task+task	task

Note. This table shows which data was obtained on which day of the study. Physiological data for sensitisation assessment was collected on day A1-A4, behavioural data was analysed for B1, A1, B2, M1, and A4. fMRI data was collected on day A1 and A4. Note that indicated times are approximate. There was a minimum of 48 hours between each AMPH / PLAC administration during the sensitisation period and a minimum of two weeks latency between the last day of sensitisation and the first testing day post-sensitisation. D = day(s); AMPH / PLAC = participants received amphetamine or placebo for (sham) sensitisation outside of the scanner; AMPH / AMPH = participants of both groups received amphetamine; fMRI = participants completed the predictive-inference task inside the scanner; task = participants completed the reward-based predictive inference task.

2.3. Reward-based predictive-inference task

The task used in this thesis was adapted from the predictive-inference task by Nassar et al. (2010) which mimics changes in a dynamic environment. In our task, participants repeatedly predicted a number on a number bar that ranged from 0 to 100, representing the potential amount of money to be earned. They then saw the actual output and could update their prediction based on previous trials.

The output number was drawn from a normal distribution. Mean and variance of the output-determining distribution changed several times throughout a block. Changes in distribution were based on a noisy process that manipulated both the volatility of the environment (in terms of changes in mean) and the reliability of the outcome (in terms of high or low variance). The probability of a change in mean (experimental reversal) was set to 0.1 after the first three trials. A new mean was drawn from a uniform distribution within an interval between 0 to 90 after a reversal. The variance of the distribution could be high ($SD =$ 15) or low (SD = 5) and changed with a probability of 0.4 once a reversal occurred.

Participants completed one practice run and five regular runs on different study days. During scanning sessions (A1, M1 & A4), participants completed 2 blocks of 120 trials while lying in the scanner. The task was presented on an MR-compatible screen. Scanning was stopped between blocks allowing participants to rest if necessary. Participants used a response box for their responses. During non-scanning sessions (B1 & B2), participants completed 240 trials in a single run seated at a regular desktop computer and used the keyboard for their responses.

Each block started with an initial resting phase of 3 seconds during which a white fixation dot was shown against black background at the centre of the screen. A trial comprised a prediction and an outcome phase. During the prediction phase, participants predicted the next number on a horizontal bar that was shown on the screen. For this, they moved along the bar and confirmed their choice with the respective buttons on the response box / keyboard. Their position on the bar was visualised by the bar filling up green. Trials were restricted to 20 seconds. A red line at the top of the screen showed the remaining time. If participants exceeded time limits, “Too slow” popped up on the screen and the next trial started.

Besides predicting numbers, participants had to indicate how confident they were of their current prediction. To do so, participants held down the confirmation button when they confirmed their prediction. The longer they pressed it, the more confident they were. Confidence ratings were visualised by a vertical line that appeared at the right end of the green bar. The longer participant pressed the confirmation button, the more the vertical line filled up and eventually turned red. If participants reported two unrealistic / inadequate confidence ratings twice in a row, "Confidence rating!!!" was flashed on the screen during the prediction phase of the next trial. Unrealistic confidence ratings were low confidence ratings

despite a small difference between predicted and actual return as well as high confidence ratings despite a large difference between predicted and actual return. Confidence ratings were limited to 1.4 seconds. Confidence ratings were not used in this thesis.

After participants confirmed their prediction, their prediction was shown for 0.3 seconds before the outcome phase started. The inter-stimulus interval between prediction and outcome phase was jittered between 1.5 and 2.5 seconds during which a white fixation dot appeared on black background at the screen centre. Once the outcome phase started, the same horizontal bar was shown as during prediction. This time, the bar was filled yellow, indicating the actual outcome for this trial. A vertical, black line on the bar indicated the participant's predicted number. This way, participants could see their prediction error, i.e. how much their predicted number differed from the actual number. The outcome screen was shown for 1 second after which the next trial started. The inter-trial interval was fixed at 0.1 seconds during which a white fixation dot was shown against black background at screen centre.

2.3.1. Task instructions

Task instructions were in German. Full instructions were provided once before the practice run and in a shortened version before regular runs. Instructions were embedded in a story to increase participant engagement. Participants were told that they would visit a different planet where they would find an alien that went mining for gold in different mines of that planet. For this, prediction and outcome screen additionally showed an alien at the screen's centre and a mine above it. The horizontal bar represented the amount of gold returned from a mine. A trial represented one day. Participants were told that the alien would ask them each day to estimate how much gold it would bring back before going mining. If their estimation was close to the actual return, the alien would share its return with them.

Like in the original task (Nassar et al., 2010), participants were told that mines differed in the daily average of how much gold the alien brought back and how difficult it was for the alien to find gold in the mine. Hence, returns between trials would fluctuate more for some and less for other mines. Additionally, participants were instructed that the alien changed mines automatically after some trials without informing the participant. We included this information to reduce the level of uncertainty related to the task structure. The idea was that the instructions would allow participants to intuit about both the noise (i.e. the variance of

the underlying distribution from which the number for the actual return was drawn) and the occasional experimental reversal (Nassar et al., 2010). To keep participants motivated, each trial was associated with a monetary reward. The amount of money that participants gained in one trial was a function of (1) how close their prediction was to the actual outcome and (2) the amount of the actual outcome (i.e. with how much gold the alien returned). Accordingly, participants were advised to aim for the average return of a mine when making their predictions.

2.4. fMRI data acquisition

Functional neuroimaging data were acquired with a 3 Tesla Magnetom Skyra MRI system (Siemens Medical, Erlangen, Germany) equipped with a 32-channel head coil and a high-performance gradient system for fast, high-resolution whole-brain multiband echoplanar imaging at the Neuroimaging Center of the University of Vienna at the Dental Clinic of Vienna Medical University. fMRI parameters were: echo time (TE)/repetition time (TR) = 34/704 ms, flip angle = 50°, interleaved acquisition, 32 axial slices coplanar the connecting line between anterior and posterior commissure, field of view = 210 mm, matrix size = 96x96, voxel size = 2.2x2.2x3.5 mm. Furthermore, structural images were acquired using magnetisation-prepared rapid gradient-echo sequence (TE/TR = 2.29/2300 ms, 176 sagittal slices, voxel size = 0.9 x 0.9 x 0.9 m, flip angle = 8°, field of view = 240 mm).

3 Analysis

This chapter describes the methods as well as a more detailed rationale for our data analysis. After a general overview on Bayesian Multilevel Modelling, which we used to analyse subjective and physiological measures of amphetamine sensitisation as well as behavioural measures of salience processing, we cover analyses for the respective types of data more specifically. Behavioural data were prepared in MATLAB[1] and analysed in R[2]. Subjective and physiological measures were analysed in R only. fMRI data were analysed in MATLAB only.

3.1. Bayesian Multilevel Modelling

As the number of participants was smaller than expected with unequal sample sizes for amphetamine and placebo group, we focused on Bayesian statistical modelling for the analysis of subjective, physiological and behavioural data. Bayesian statistical modelling is especially useful when analysing repeated measurements and unequal sample sizes (Nalborczyk, Batailler, Loevenbruck, Vilain, & Bürkner, 2017). For this, we built linear Bayesian Multilevel Models (MLMs), which are hierarchical regression analyses implemented by the `brms` package in R (Bürkner, 2017). `brms` uses the probabilistic programming language `Stan` to fit models. `Stan` uses Markov Chain Monte Carlo (MCMC) algorithms and the No-U-Turn Sampler (NUTS) extension to draw samples from the posterior distribution over model parameters (Bürkner, 2017). Once sampled, model parameters (the effects of the respective predictor) are summarized by the mean and standard deviation of their posterior distribution and the two-sided 95% credible interval (CrI) of the mean. Different from confidence intervals in frequentist statistics, Bayesian statistics allows for probability statements based on CrIs (Nalborczyk et al., 2017). For instance, a 95% CrI means that there is a 0.95 probability that the interval entails the population value of the specific estimate, given the data, the model, and its priors. At the same time, CrIs express how certain the model is about its estimate.

[1] Version 9.0.0.341360 (R2016a), The MathWorks Inc., Natick, Massachusetts, US
[2] Version 2019, R Core Team, Vienna, Austria, `https://www.R-project.org`

We also included an effect size approximation to Cohen's d for multilevel models, δ_t. It is the estimated difference between group means of the constant effect of interest, divided by the square root of the sum of all variance components (Nalborczyk et al., 2017). δ_t is also reported in terms of the mean of the posterior distribution and its two-sided 95% CrI. To see the probability of effects being positive or negative, we also looked at the percentage of the posterior distribution of each estimate above (positive) and below 0 (negative). More details on model definition, model fitting and model comparison procedures are reported in the respective sections.

3.2. Assessment of Sensitisation

To see whether amphetamine sensitisation worked, we examined the effect of sensitisation and amphetamine on self-reported drug effects and physiological measures obtained on sensitisation and testing days (A1, A2, A3, & A4). Subjective drug effects were measured with the drug effects questionnaire (DEQ). Physiological measures entailed heart rate and diastolic blood pressure. Like behavioural data, all measures were analysed with Bayesian MLMs using the same model: *response variable* $\sim$ *session + sensitised + amphetamine + (session | ID)*. Sensitisation and amphetamine were dummy-coded (1 = sensitised, 0 = not sensitised; 1 = amphetamine, 0 = no amphetamine / placebo). Sessions were coded as categorical predictor with 4 levels (1 = A1, 2 = A2, 3 = A3, 4 = A4). We included the amphetamine administration predictor to control for the effect of acute amphetamine administration as the only day after sensitisation on which we obtained subjective and physiological measures coincided with the amphetamine challenge for participants in both groups. Different to behavioural and fMRI data analyses, we did not do extensive model fitting and comparison for physiological data as these only served as cross-checks that sensitisation worked (for details on model definition see figure C.1).

3.2.1. Subjective response: drug effects questionnaire

The drug effects questionnaire (DEQ) is a common questionnaire to capture the subjective experience of the effect of an administered drug (Morean et al., 2013). It examines the subjective experience along four subjective states, namely "feeling the effect of the drug", "feeling high", "liking the effect of the drug" and "wanting more of the drug" (hereafter, *feel*, *high*,

like and *more*). DEQ uses visual analogue scales. Participants indicate how much they agree to the statements on a line ranging from "not at all" to "extremely". The score is determined by the distance between the left anchor point and the participant's mark on the line (not at all = 1, extremely = 10). To test for sensitisation effects, we calculated the difference of the peak reported effect to baseline for each DEQ-item and each session and investigated whether there was an effect of sensitisation and amphetamine, using Bayesian multilevel modelling. We expected to see positive effects of acute amphetamine administration and sensitisation, i.e. we expected participants to show increased self-report drug effects when sensitised and / or amphetamine-challenged.

3.2.2. Physiological response: heart rate & blood pressure

Concerning physiological responses, we calculated the difference between baseline heart rate and blood pressure and the measure that was maximally distanced from baseline separately for all subjects and sessions. Importantly, this peak difference could take on a positive or negative sign. We then analysed effects of amphetamine administration and sensitisation with Bayesian MLMs as described above. We expected some effects of acute amphetamine administration and sensitisation on heart rate and blood pressure in terms of elevated heart rate and blood pressure in amphetamine-challenged and / or sensitised participants. However, given previous study findings (Boileau et al., 2006; O'Daly, Joyce, Stephan, Murray, & Shergill, 2011), we did not expect large effects.

3.3. Behavioural Analysis

For the analysis of behavioural data, we were interested in how sensitisation affected the perception of and response to relevant and random (irrelevant) events in an uncertain environment. To recall, the task environment (i.e. the planet on which the alien went mining) was programmed to be volatile. Volatility was expressed on several levels, which were all reflected in the amount of gold returned from mining (i.e. the actual return). Firstly, the actual return varied from trial to trial according to the underlying distribution from which it was drawn. This distribution changed randomly and the time points of changes were determined by a probabilistic process. Secondly, underlying distributions had different levels of noise as they could be assigned high (SD = 15) or low variance (SD = 5).

In this context, relevant events were trials in which the change in the actual return occurred due to changes in the mean of the underlying distribution from which values for the actual return were drawn (experimental reversal). Such trials required participants to adjust their predictions to achieve good task performance (i.e. to make predictions close to the underlying average return of a mine). Successful reversals described participants' adjustments of predictions to the changed underlying mean after an experimental reversal. A successful reversal was the first trial after an experimental reversal in which participants' prediction was within a narrow interval around the new underlying mean (within $SD/2$). Trials in which the change in actual return did not occur due to changes in the underlying distribution were regarded as random (irrelevant) events. These did not require behavioural adjustment for a good task performance. How much meaning participants attributed to noise (i.e. random / irrelevant events) was seen as a behavioural measure of aberrant salience attribution. To investigate sensitisation effects on salience attribution, we looked at the overall behaviour in low and high noise trials and at responses to experimental reversals. As high noise trials fluctuated more strongly than low noise trials, analyses focused particularly on the interplay of sensitisation and noise.

We divided our behavioural data analysis according to the following questions:

1. Did sensitisation affect participants' overall behaviour in an uncertain environment?

   (i) Did sensitisation influence how well participants performed in the task?

   (ii) Did sensitisation make participants more likely to update their beliefs?

2. Did sensitisation affect participants' responses to actual reversals in an uncertain environment?

   (iii) Did sensitisation influence how well participants detected experimental reversals in an uncertain environment?

   (iv) Did sensitisation influence how long participants needed to successfully adapt their predictions after experimental reversals?

   (v) Did participants' successful adaptations of predictions represent chance hits?

3.3.1. Did sensitisation affect participants' overall behaviour in an uncertain environment?

For sensitisation effects on general behaviour, we looked at participants' (i) overall task performance, and (ii) their overall updating behaviour.

(i) Did sensitisation influence how well participants performed in the task?

We defined task performance in terms of how well participants could predict the average return of a mine (to recall, participants were advised to predict the average return of a mine during instructions). A good performance was a trial in which a participant's predicted return was within $SD/2$ of the mean of the distribution from which actual return of the trial was drawn (i.e. prediction $< \mu \pm SD/2$). As we were interested in the interplay of a volatile environment and sensitisation, the number of $SD/2$-trials were calculated separately for low and high noise trials relative to the total number of low and high noise trials.

We expected sensitised participants to perceive the task environment as more volatile, making them more likely to attribute salience to random events and update their predictions more frequently (i.e. to switch). Instead of settling around an average return as advised, we predicted that sensitised participants perceived simple fluctuations in returns as experimental reversals (as changes in mines in instructional terms) and would try to adapt their predictions accordingly. With respect to task performance, we expected sensitisation to lower the relative number of trials within the $SD/2$-interval. Independent from sensitisation, we expected acute amphetamine administration to elevate responsiveness to perceived changes in the environment equally decreasing the number of trials within the $SD/2$-interval. We expected these effects to be elevated in trials with high noise ($SD = 15$) as changes there were more frequent and potentially more pronounced than in low noise trials.

(ii) Did sensitisation make participants more likely to update their beliefs?

To see whether sensitisation increased belief updating, we examined participants' updating behaviour. Updating behaviour was defined in terms of the absolute difference between the predicted return of a given trial and that of the previous trial relative to the prediction error of the previous trial ($update = |prediction_{i+1} - prediction_i| / prediction\ error_i$). We calculated average updates for low and high noise trials separately to account for the effect of volatility.

The rationale behind updating behaviour was the same as for task performance. We interpreted increased responsiveness to feedback (i.e. the difference between predicted and actual return shown during the outcome phase) as induced by sensitisation to reflect increased aberrant salience attribution to random events. Different from task performance, however, updating as we defined it represented a less conservative measure. It accounted for the dependency of behaviour across trials, namely the dependency of participants' prediction on what they previously predicted as well as on the fluctuation in outcome as reflected in the prediction error of the previous trial. Participants who might not have performed well at approximating the average might have still settled on an average outside the $SD/2$-interval. At the same time, increased updating behaviour would automatically preclude good task performance. We expected both acute amphetamine administration and sensitisation to increase updating behaviour as reflected in increased average updates. Similarly, we expected high noise to boost this effect.

3.3.2. Did sensitisation affect participants' responses to actual reversals in an uncertain environment?

For sensitisation effects on behaviour to actual reversals (i.e. relevant events), we first examined participants' (iii) reversal detection scores, followed by (iv) how long participants needed to adjust their predictions after an experimental reversal, (v) how consistent they behaved after successfully adapting their predictions. This way, we wanted to see whether successful reversals only happened by chance or whether successful reversals reflected participants' actual adaptation of predictions to changes in the environment.

(iii) Did sensitisation influence how well participants detected experimental reversals in an uncertain environment?

To see whether sensitisation affected how well participants detected experimental reversals (relevant events), we calculated reversal detection scores. These were the number of successful reversals divided by the total number of experimental reversals. We defined a successful reversal as the first trial after an experimental reversal in which the predicted return was within $SD/2$ of the underlying mean. The reversal detection score represented a crude measure to see how well participants learnt and adapted their predictions after experimental

reversals. Importantly, we did not distinguish between low and high noise trials for this measure.

We expected participants to perform better at responding to experimental reversals when sensitised than when not sensitised, i.e. to detect more reversals. This seems to contradict previous findings according to which psychotic patients achieve less reversals (Feeney et al., 2017). However, here reversals were performance-dependent whereby achieving a reversal referred to participants continuously choosing the "correct" stimulus after a reversal for a specified number of times (Waltz & Gold, 2007). This automatically excluded chance hits to count as successful reversals. The way we measured reversal detection was performance-independent so that chance hits could potentially be counted as successful reversals. Accordingly, while we expected sensitised participants to detect more reversals, we expected this to be by chance, i.e. to be because of increased updating behaviour due to increased responsiveness to any kind of event (even noise). This is why we also examined how participants continued to respond after they reversed successfully (see section (v)).

(iv) Did sensitisation influence how long participants needed to successfully adapt their predictions after experimental reversals?

Another way to see whether sensitisation affected detection of relevant events is to see how how long participants needed to adapt their predictions to an experimental reversal. For this, we assessed the average number of trials after an experimental reversal until participants successfully adapted their predictions (i.e. the first trial that was within $SD/2$ to the mean of the underlying distribution). We expected participants to be faster in successfully changing their predictions when sensitised. A similar effect was expected for amphetamine administration.

(v) Did participants' successful adaptations of predictions represent chance hits?

Chances to make a prediction which is within $SD/2$ to the underlying mean might be higher for participants who change predictions more excessively. Our definition of successful reversals allowed for such chance hits to be identified as successful reversals. To account for this possibility, we examined how long participants' predictions remained in the $SD/2$-interval to the underlying mean after successful reversals (pointing to a *true* adaptation of predictions to the experimental change), and how strongly participants updated predictions after

successful reversals. We defined closeness to the average as the average number of consecutive $SD/2$-trials after successful reversals. Updating behaviour was computed as the average updating behaviour after successful reversal until the next experimental reversal. We expected sensitisation to decrease the number of consecutive trials in which participants' predictions were close to the underlying mean. We expected increased updating behaviour post successful reversals to accompany this effect. This would reflect blunted reversal learning behaviour as has been observed in patients with schizophrenia (Maia & Frank, 2017).

3.3.3. Hierarchical regression analysis

Analysis of all variables of interest with Bayesian MLMs followed the 3-step procedure outlined in Nalborczyk et al. (2017). It included (i) defining a probability model, (ii) computing the posterior distributions of each parameter that is defined by the model, and (iii) evaluating the fit and predictive performance of the model. Models were fed with data from testing days B1, A1, B2, M1 and A4.

Model definition

We fit different models to the data to predict the variable of interest, e.g. overall updating behaviour. Models included both constant and varying effects. Here, constant effects, also called population-level effects, represented effects that were shared across participants. Varying effects were specified at the individual level, modelling subject-specific variability. All models but the null model included the constant effect of session. The remaining predictors, sensitisation and amphetamine, were then added step-wise to the model starting with sensitisation. For analyses of overall task performance and updating behaviour as well as task performance and updating behaviour after successful reversal, we defined two more models: one that included a noise level predictor and one which further included interaction effects between sensitisation and noise and between amphetamine and noise. To allow for this, we separated data for these variables into averages of high and low noise trials, respectively. Amphetamine, sensitisation and noise predictors were dummy-coded (*amphetamine*: 1 = amphetamine administered, *sensitisation*: 1 = sensitised, *noise*: 1 = noisy). Session was modelled as categorical predictor with 5 levels (1 = B1, 2 = A1, 3 = B2, 4 = M1, 5 = A4).

Models were built successively (see table 3.1). We started with a simple intercept model, the null model (M0), to which increasingly complex models were compared to. The first

Table 3.1: Model Formulas.

Model	Model formula
M0	$response\ variable \sim 1 + (1\|ID)$
M1	$response\ variable \sim 1 + session + (1\|ID)$
M2	$response\ variable \sim 1 + session + amphetamine + (1\|ID)$
M3	$response\ variable \sim 1 + session + amphetamine + sensitised + (1\|ID)$
M4	$response\ variable \sim 1 + session + amphetamine + sensitised + (session\|ID)$
M5*	$response\ variable \sim 1 + session + amphetamine + sensitised + noise + (session\|ID)$
M6*	$response\ variable \sim 1 + session + amphetamine + sensitised + noise + amphetamine : noise + sensitised : noise + (session\|ID)$

Note. Response variable = e.g. updating behaviour, ID = subject ID, session = testing day, categorical predictor with 5 levels (1 = B1, 2 = A1, 3 = B2, 4 = M1, 5 = A4), amphetamine = amphetamine administration (1 = amphetamine, 0 = no amphetamine / placebo), sensitised = sensitisation status (1 = sensitised, 0 = not sensitised)
* Model 5 & 6 were only fitted for analyses of overall and post successful reversal task performance and updating behaviour.

proper model (M1) included session as constant effect. It accounted for a global effect of session and for random variation in this effect across subjects. The second model (M2) included constant effects of session and sensitisation. The third model (M3) included constant effects of session, sensitisation and amphetamine administration. The fourth model (M4) included an additional varying effect of session. For analyses of updating behaviour and task performance, a fifth model (M5) included the constant effect of noise, and a sixth model (M6) included additional interaction effects between noise and amphetamine as well as noise and sensitisation.

Constant and varying intercept in all models accounted for individual differences in overall changes in the variable of interest, for instance, updating behaviour. The varying slope for session in model 4, 5 and 6 modelled the variability of the respective variable of interest across subjects. Including varying effects allowed for better estimation of constant effects of interest because of the partial pooling of information about variance across different levels (Nalborczyk et al., 2017).

Sensitisation and amphetamine represented important predictors for investigating the effect of sensitisation. The noise predictor was important for investigating the effect of volatility on the variables of interest. Interaction effects between noise and amphetamine,

and between noise and sensitisation allowed to investigate more closely how noise affected sensitisation and amphetamine effects. As interaction effects in multilevel models are difficult to interpret (McElreath, 2020), we calculated γ. It is the sum of the respective constant effect and its interaction effect with noise ($\gamma = \beta + \beta_{interaction}$; for details on the interaction model, see figure C.6).

Model fitting

For model fitting, we ran four Markov Chain Monte Carlo (MCMC) algorithm simulations (chains) to approximate the posterior distribution of each model. The number of iterations per chain was set to 1,000 of which 200 were used for warm-up, leaving 3,200 post-warm-up samples as posterior plausibilities of model parameters. All models started with weakly informative priors and a Normal (Gaussian) response distribution. If chains did not converge, we adjusted the number of iterations and warm-ups and `adapt_delta` based on recommendations provided by the `brms` package (for details on the exact models, see figure C.2 for model 3, figure C.3 for model 4, and figure C.5 for model 5). We evaluated convergence using the $\hat{R}$ index ($\hat{R} < 1.01$ for chain convergence), the effective sample size of the posterior distribution of each parameter and visual inspection of the trace plots (Nalborczyk et al., 2017).

Model comparison

We compared models with respect to how well they simulated the generative process of interest, i.e. how well they predicted unobserved data, and how well they fit the observed data. The models' out-of-sample predictive performance was approximated with the leave-one-out cross-validation procedure as built into the `brms` package. The procedure's index (LOOIC) serves as estimate of how well a model predicts unobserved data (Nalborczyk et al., 2017). Model fits to observed data were evaluated with the Bayesian R^2. The combination of both evaluation methods allowed to rule out that models performed well at explaining the observed data while performing worse than simpler models at predicting new data (overfitting). This thesis only reports results from the model that best predicted unobserved data (lowest LOOIC). If several models showed similar predictive performance (difference < 10; Turi et al., 2018), that model was chosen as "winning" model which had the highest Bayesian R^2 index, i.e. the model that best explained the observed data.

3.4. fMRI Analysis

fMRI data from both testing days (A1 & A4) were pre-processed and analysed in MATLAB using the SPM12 software package[3].

3.4.1. Pre-processing

Before pre-processing, MRI data was converted to NiFTi format. Following the SPM12 manual[4], within-subject pre-processing steps included slice-time correction, realignment, unwarping, co-registration and unified segmentation. To enable between-subject comparison, images were spatially normalised to Montreal Neurological Institute (MNI) space and smoothed with a 3D Gaussian kernel of 4 mm full-width at half-maximum (FWHM).

Slice-time correction was needed to correct for differences in image acquisition time between sampled slices as images were acquired at interleaved mode. The slice acquired at the middle of the sequence (i.e. at TR/2) served as reference slice. Both realignment and unwarping correct for subjects' movements. These can introduce great movement artefacts in functional images, causing loss of sensitivity (not detecting true activation) and loss of specificity (detecting false positives). For realignment, the first scan of each session of a participant was realigned long 6 parameters (3 for translations (mm) and 3 for rotations (degrees)) to the first scan of the first session. Then, all images of a session were realigned to the first image of that session. Unwarping corrects for susceptibility-by-movement interactions whereby subjects' movements result in severe geometrical distortions, especially where air and tissue interface. During co-registration, the anatomical information of functional images is linked with a structural image as structural images yield superior anatomical localisation. Unified segmentation includes segmentation, bias correction and spatial normalisation of structural images. Segmentation separates different types of tissue (e.g. grey matter and white matter) based on tissue probability maps. Bias correction accounts for inherent intensity inhomogeneity of MRI, facilitating the subsequent normalisation process. Normalisation helps to establish a voxel-to-voxel correspondence between brains of different subjects allowing comparisons of neural activation between subjects. For this, T1-weighted, anatomical images were normalised and transformed to MNI template of unified segmentation. Normalisation parameters were then applied to all functional images. During

[3] Wellcome Trust Centre for Neuroimaging, London, UK, `http://www.fil.ion.ucl.ac.uk/spm`
[4] `https://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf`

smoothing, residual anatomical differences and registration errors are blurred over, which increases signal-to-noise ratio (by suppressing noise and effects that are due to residual differences in functional and gyral anatomy). It further results in superior spatial overlap, makes data more normally distributed and increases sensitivity to effects of similar scale to kernel (for details on each processing step see appendix B, or the SPM12 manual).

3.4.2. First-level analysis

We used the general linear model (GLM) approach to calculate statistical parametric maps of BOLD activation. First-level models were built for each subject and scan day. As we were interested in how participants processed relevant and irrelevant, random events under uncertainty, GLMs included four regressors of interest: experimental reversal trials and non-reversal trials separately for high and low noise trials. Regressors were modelled at the onset of the outcome phase for the whole length of the outcome phase (i.e. 1 second). We used parametric design, so that trial-wise behavioural absolute prediction errors (PE; the absolute difference between participants' predictions and the actual outcome as shown to them during the outcome phase) modulated the amplitude of the trial-related outcome regressor (Schlagenhauf et al., 2014). Parametric modulators model the variation around task-related neural activities. The GLM also included six realignment parameters from pre-processing as regressors of no interest to account for movement-induced variance. Regressors were convolved with a canonical haemodynamic response function, high-pass filtered (128 seconds cutoff), and corrected for serial correlations using a first-order autoregressive model. Contrast images were generated for each parametric modulator for each participant, leaving the following contrast images for group-level analyses:

- Regressor 1: reversal high noise (PE modulated)
- Regressor 2: no reversal high noise (PE modulated)
- Regressor 3: reversal low noise (PE modulated)
- Regressor 4: no reversal low noise (PE modulated).

We expected amphetamine-sensitisation to disrupt dopamine signalling in brain regions processing salience. More precisely, we expected aberrant salience attribution as reflected in aberrant brain activity to irrelevant and relevant events. Irrelevant, random events were

defined as trials in which no experimental reversal occurred. Relevant events were all other trials. We also expected noise to have an effect on salience processing. Accordingly, we separated regressors for non-reversal and experimental reversal trials by level of noise. Overall, we expected to see increased BOLD responses to non-reversal trials (irrelevant events) and decreased BOLD responses to experimental reversals (relevant events) after sensitisation. We expected high noise trials to impair salience processing in both groups but we expected disruptions to be greater in sensitised participants.

3.4.3. Group-level analysis

As we wanted to examine sensitisation effects on salience processing, we focused on changes in neural activation in brain regions that have shown salience-related responses in previous imaging studies and that involve dopamine-signalling. These were bilateral hippocampus, striatum and right dopaminergic midbrain (Modinos et al., 2020; see table 3.2 for details on the ROIs). Following Modinos et al. (2020), ROI images were created with the WFU_PickAtlas toolbox[5] using predefined anatomical masks of the striatum (caudate, pallidum, putamen) and the hippocampus from the Automated Anatomical Labelling atlas (AAL). We used a 6 mm sphere at [MNI *xyz*: 8 -20 -18] for the right-sided, dopaminergic midbrain including the ventral tegmental area and the substantia nigra. These ROIs were then used as masks for group-level analyses.

Table 3.2: Regions of interest used in fMRI analysis.

Region of Interest	**Hemisphere**	**Subregions**	**Atlas**
Hippocampus	bilateral		AAL
Striatum	bilateral	Pallidum Caudate Putamen	AAL
Dopaminergic midbrain	right	Substantia nigra Ventral tegmental area	6mm sphere at [MNI *xyz*: 8 -20 -18]

Note. Based on Modinos et al. (2020). AAL = Automated Anatomical Labelling atlas, TD Lobe = Talairach Daemon Lobar atlas, MNI = Montreal Neurological Institute Space.

Due to our small sample size, we used non-parametric alternatives to regular *t*-tests

[5] https://www.nitrc.org/projects/wfu_pickatlas

provided by the Statistical nonParametric Mapping (SnPM) toolbox[6]. SnPM provides permutation tests using the GLM and pseudo *t*-statistics for independent observations (Nichols & Holmes, 2002). We compared differences within groups with one-sample *t*-tests and differences between groups with two-sample *t*-tests for both scan days. We further compared differences in neural activation before and after (sham) sensitisation with paired *t*-tests. Due to corrupted data, we did not conduct all tests for all participants. As participants were not evenly distributed across group, we conducted one-sample and paired *t*-tests only for the amphetamine group (see table 3.3 for an overview of which test included which dataset).

We tested all regressors of interest with masks of the different ROIs. This corresponds to small volume correction[7]. The maximal number of permutations was set to 5,000. We usually tested for positive effects except for paired *t*-tests examining neural activation in response to non-reversal trials (paired *t*-tests for regressors 2 and 4), as we hypothesised increased responses to random events after sensitisation. Here, testing negative effects correspond to testing the contrast of A4>A1. We did not smooth variance so that *t*-statistics reported here are not pseudo *t*-statistics (Nichols & Holmes, 2002). Activation inside our ROIs is reported at peak-level at family-wise error (FWE)-corrected $p < 0.05$. We did not look at whole-brain activation.

Table 3.3: Overview of statistical tests and datasets used in fMRI analysis.

		One-sample *t*-test		**Two-sample *t*-test**		**Paired *t*-test**
Group	**Participant**	**A1**	**A4**	**A1**	**A4**	
AMPH	1	x		x		
	2	x	x	x	x	x
	3	x	x	x	x	x
	4		x		x	
	5	x	x	x	x	x
	6	x	x	x	x	x
	7	x	x	x	x	x
	8	x	x	x	x	x
PLAC	9			x	x	

Note. AMPH = amphetamine sensitised group, PLAC = placebo (sham) sensitised group.

[6] Version SnPM 13.1.08, `http://www.nisox.org/Software/SnPM13/`

[7] `https://groups.google.com/forum/#!topic/snpm-support/khUyM3H20TQ`

4 Results

In this chapter, we first present our findings on sensitisation effects on subjective experience of drug effects and on physiological measures, followed by our findings from behavioural and fMRI analysis. Generally, both subjective and physiological measures of sensitisation hint at some, yet uncertain effect of sensitisation. Likewise, our behavioural and fMRI results remain tentative as to the role of sensitisation in salience processing.

4.1. Subjective & Physiological Data

4.1.1. Sensitisation effects on subjective drug effects

We found weakly positive, but imprecise effects of sensitisation on DEQ components. These provide inconclusive evidence that sensitisation subjectively increased perceived effects of the drug after sensitisation (*feel*: β = 0.45, 95% CrI = [-2.20, 3.00], δ_t = 0.17, 95% CrI = [-1.02, 1.34]), increased the feeling of being high (*high*: β = 0.82, 95% CrI = [-2.25, 3.84], δ_t = 0.22, 95% CrI = [-0.73, 1.21]), increased the liking of the effect (*like*: β = 0.47, 95% CrI = [-2.13, 3.04], δ_t = 0.18, 95% CrI = [-0.97, 1.35]), and increased the wanting for more of the drug (*more*: β = 0.18, 95% CrI = [-1.96, 2.26], δ_t = 0.09, 95% CrI = [-0.96, 1.15]), given our data and model at hand. Effects were not precise as reflected in CrIs which included the plausibility of both strongly negative and strongly positive effects of sensitisation and highly uncertain effect sizes. Looking at the percentage of the posterior distribution of the sensitisation effect above 0 points to a slight trend towards a positive effect (*feel*: 61% > 0; *high*: 67% > 0; *like*: 62% > 0; *more*: 56% > 0).

Effects of amphetamine administration showed a similar pattern (*feel*: β = 1.15, 95% CrI = [-1.15, 3.41], δ_t = 0.44, 95% CrI = [-0.59, 1.47]; *high*: β = 1.09, 95% CrI = [-2.10, 4.22], δ_t = 0.29, 95% CrI = [-0.65, 1.33]; *like*: β = 1.17, 95% CrI = [-1.16, 3.41], δ_t = 0.44, 95% CI = [-0.57, 1.50]; *more*: β = 0.60, 95% CrI = [-1.38, 2.47], δ_t = 0.26, 95% CrI = [-0.74, 1.24]). While amphetamine effects tended to be stronger with narrower CrIs than sensitisation effects, effect estimation was still associated with large uncertainty, where CrIs included the possibility for positive and negative effects. Looking at the percentage of the estimate distribution above 0 suggests

a clearer trend towards a positive effect of amphetamine administration on all four DEQ-items (*feel*: 81% > 0, *high*: 72% > 0, *like*: 80% > 0, *more*: 71% > 0).

Including amphetamine as predictor in the model controlled for the acute effect of amphetamine administration. Hence, the fact that there was still a trend towards a positive effect of sensitisation on subjective responses to drug effects suggests that amphetamine sensitisation was successful with respect to the subjective drug effects, given our data and model. Importantly, large uncertainty in effect size estimation call for cautious interpretation of any of these effects though (see D.1 for details on models).

4.1.2. Sensitisation effects on heart rate & blood pressure

Concerning the effect of sensitisation and amphetamine administration on participants' heart rate, our model estimated that both sensitisation and amphetamine administration seemed to increase participants' heart rate. The means of the posterior distribution of the regression coefficients for sensitisation and amphetamine were both positive but associated with large uncertainties (*sensitisation*: β = 0.66, 95% CI = [-4.15, 5.37], δ_t = 0.04, 95% CI = [-0.29, 0.36]; *amphetamine*: β = 0.44, 95% CI = [-4.45, 5.15], δ_t = 0.03, 95% CI = [-0.32, 0.33]). Credible intervals for both variables included both strongly positive and strongly negative effects. Accordingly, it was almost equally likely for sensitisation to increase or decrease heart rate (59% > 0) or for amphetamine to increase or decrease heart rate (57% > 0). Together with effect sizes that approached 0, the observed positive effect of sensitisation on heart rate remains preliminary, given our data and model.

Concerning diastolic blood pressure, we found a positive effect of both sensitisation (β = 1.37, 95% CI = [-2.86, 5.48], δ_t = 0.15, 95% CI = [-0.39, 0.69]) and amphetamine (β = 1.91, 95% CI = [-2.95, 6.71], δ_t = 0.22, 95% CI = [-0.40, 0.88]). The 0.71 probability of the β distribution to be above 0 further supports that sensitisation seemed to increase diastolic blood pressure, however with large uncertainty. Similarly, the 0.74 probability of the effect of amphetamine to be above 0 supports a positive effect of amphetamine administration on blood pressure. As effects were associated with large uncertainties and small effect sizes, they should be regarded with caution. On average, our results point to a positive effect of sensitisation on blood pressure, but do not exclude negative effects. Consequently, evidence for sensitisation effects on blood pressure remain inconclusive.

Given our data and model, sensitisation seemed to affect physiological measures, tending to increase both heart rate and blood pressure. Effects were, however, associated with large uncertainty. Our results on subjective drug effects provide a slightly more convincing argument for successful sensitisation, increasing reported drug effects for all four aspects of the DEQ while also considering negative effects of sensitisation. Hence, it seems reasonable to infer that sensitisation did work to some extent, albeit with reservations, as results were still associated with uncertainty (see table D.1 for details on the models).

4.2. Behavioural results

4.2.1. Sensitisation effects on overall task performance & updating behaviour

(i) Sensitisation effects on how well participants performed in the task

Results concerning task performance are reported for model 6 (see table D.9 for results of model comparison and table D.15 for all population-level effects of model 6). According to this model, sensitisation tended to worsen task performance (remember that good task performance was defined as trials in which participants' predictions were within $SD/2$-interval around the mean of the underlying distribution; see figure 4.1, A). Yet, this effect was associated with uncertainty about its direction: the CrI considered both positive and negative effect estimates as plausible (β = -0.02, 95% CrI = [-0.13, 0.08], δ_t = -0.16, 95% CrI = [-1.04, 0.66]). Overall, the fact that 65% of the posterior distribution of the sensitisation effect is smaller than 0 hints at a trend towards a negative effect of sensitisation on task performance. According to our model, a noisy environment seemed to contribute to this negative effect of sensitisation while the effect was still associated with uncertainty, as reflected in a CrI that still considered positive and negative estimates (γ = -0.06, 95% CrI = [-0.18, 0.07], δ = -0.41, 95% CrI = [-1.32, 0.42]).

Concerning amphetamine, our model found a weakly negative, but uncertain effect of amphetamine on task performance (β = -0.05, 95% CrI = [-0.10, 0.01], δ_t = -0.32, 95% CrI = [-1.55, 1.03]). A 0.71 probability of the effect of amphetamine to be negative points to a trend that participants performed worse when administered amphetamine. Yet, the model also

considered positive effects of amphetamine on task performance. Similar to sensitisation effects, a noisy environment increased the overall negative effect of amphetamine but also increased uncertainty about the estimate (γ = -0.10, 95% CrI = [-0.28, 0.10], δ = -0.69, 95% CrI = [-2.01, 0.56]; see figure 4.1, B & C for task performance by noise level). Amphetamine effects were associated with slightly stronger, but still moderate effect sizes. Interestingly, the pure effect of noise on task performance was actually positive (β = 0.15, 95% CrI = [0.12, 0.19], δ_t = 1.07, 95% CrI = [0.55, 1.66]; 100% > 0). This was likely due to good task performance being defined as predictions within $SD/2$ of the underlying mean and $SD/2$-intervals becoming large enough during noisy trials for participants' predictions to be within this interval.

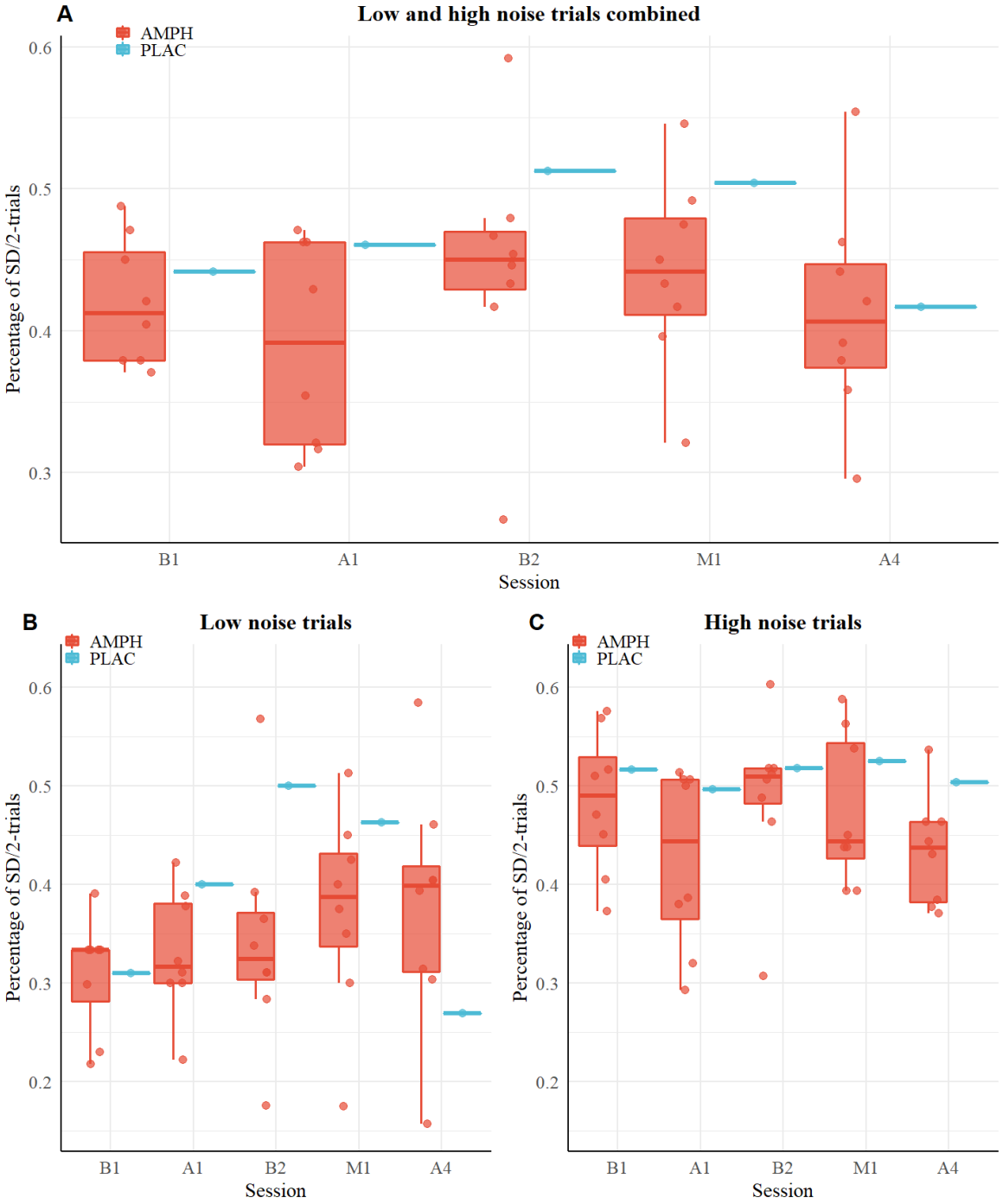
Overall, participants tended to perform worse in noisy and less noisy environments when amphetamine-challenged and / or sensitised while they tended to perform better in noisy environments when neither amphetamine-challenged nor sensitised. Given the small effect sizes for the effect of sensitisation in noisy and less noisy environments which were associated with large uncertainties, the trend to a negative effect of sensitisation on how good participants were at predicting the average return remains inconclusive.

(ii) Sensitisation effects on participants' susceptibility to attribute salience to random events

Results reported here are for model 6 (see table D.10 for results of model comparison and table D.16 for all population-level effects of model 6). Controlling for effects of noise and amphetamine, sensitisation tended to decrease how much participants updated their predictions between trials (see figure 4.2, A). This effect on updating behaviour was associated with uncertainty, as reflected in a relatively large CrI (β = -0.32, 95% CrI = [-0.69, 0.07], δ_t = -0.58, 90% CrI = [-1.35, 0.27]). A 92% probability for a negative sensitisation effect backs the trend towards decreased updating behaviour in sensitised participants although we cannot exclude that sensitisation could also increase how much participants updated their predictions between trials. Interestingly, there seemed to be little effect of noise on this effect (γ = -0.29, 95% CrI = [-0.74, 0.16], δ_t = -0.52, 95% CrI = [-1.33, 0.29]).

For amphetamine administration, our model estimated a mostly negative trend of the effect of amphetamine on participants' updating behaviour. However, it did not fully exclude also positive effects of amphetamine on updating behaviour (95% CrI = [-0.52, 0.04], δ_t = -0.43, 95% CrI = [-1.12, 0.16], 92% < 0). A noisy environment did not change this trend

Figure 4.1: Effects of sensitisation on overall task performance.



Note. The figure shows the percentage of trials in which predictions were within $SD/2$ of the underlying mean for all trials (A), for low noise (B), and for high noise trials (C). Boxplots include the median, 25th and 75th percentile, and 1.5 x inter-quartile range. Session B1 & A1 are pre-sensitisation, session B2, M1 & A2 are post-sensitisation. Amphetamine was administered on session A1 & A4 for AMPH-group, and on session A4 for PLAC-group. AMPH = amphetamine group; PLAC = placebo group.

much (γ = -0.26, 95% CrI = [-0.59, 0.08], δ_t = -0.48, 95% CrI = [-1.11, 0.14]; see figure 4.2, B & C for updating behaviour by noise level). Meanwhile, participants generally updated their predictions less in noisy environments when they did not receive amphetamine and were not sensitised (β = -0.17, 95% CrI = [-0.26, -0.08], δ_t = -0.30, 95% CrI = [-0.55, -0.10], 100% < 0).

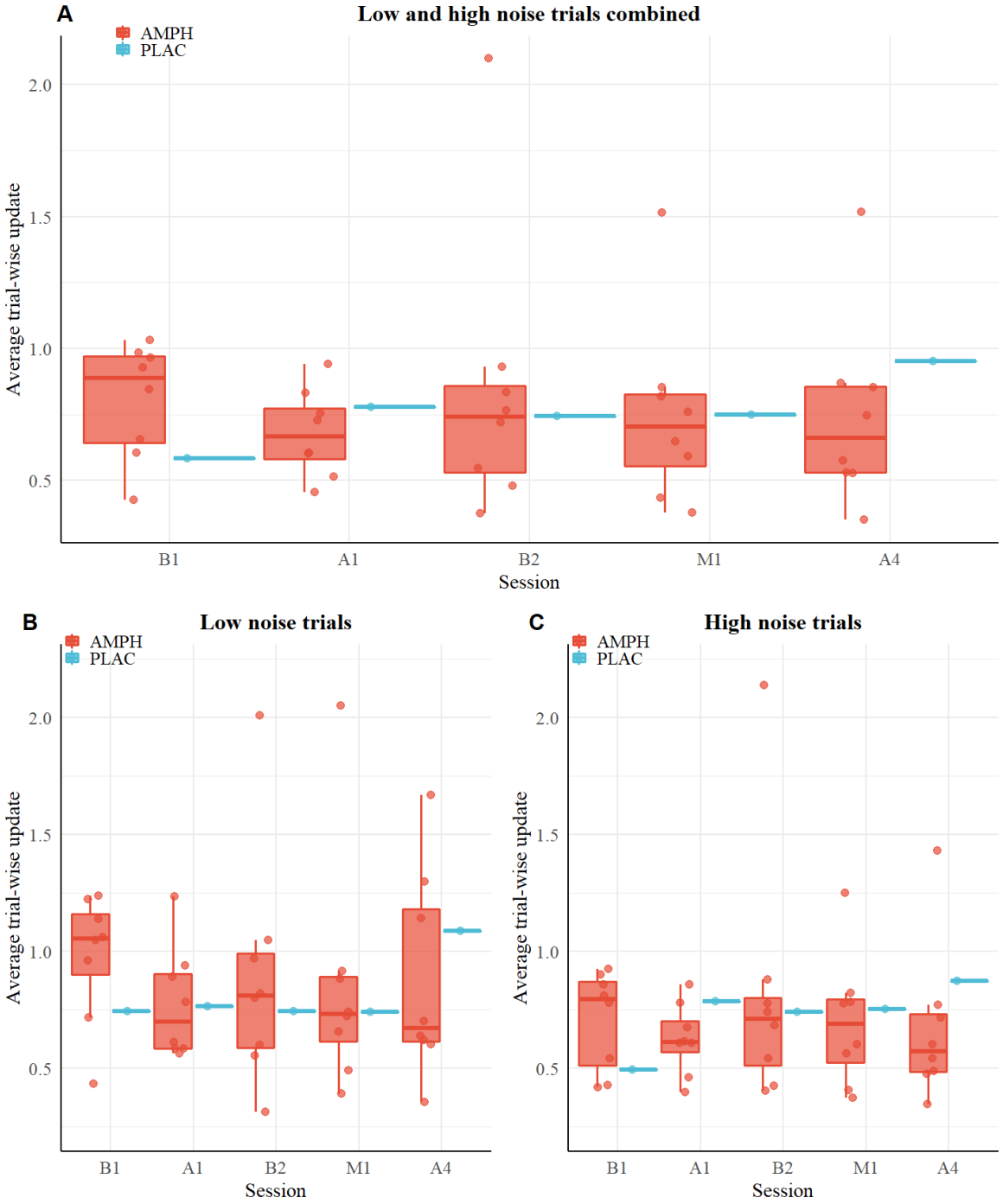
In sum, evidence for a negative effect of sensitisation on participants' updating behaviour is more convincing than for example for a negative sensitisation effect on task performance. However, given that effect sizes remain moderate and effects are still associated with uncertainty about the direction of the effect, reported sensitisation effects on participants' updating behaviour are still preliminary.

4.2.2. Sensitisation effects on responses to reversals

(iii) Sensitisation effects on how well participants detected experimental reversals

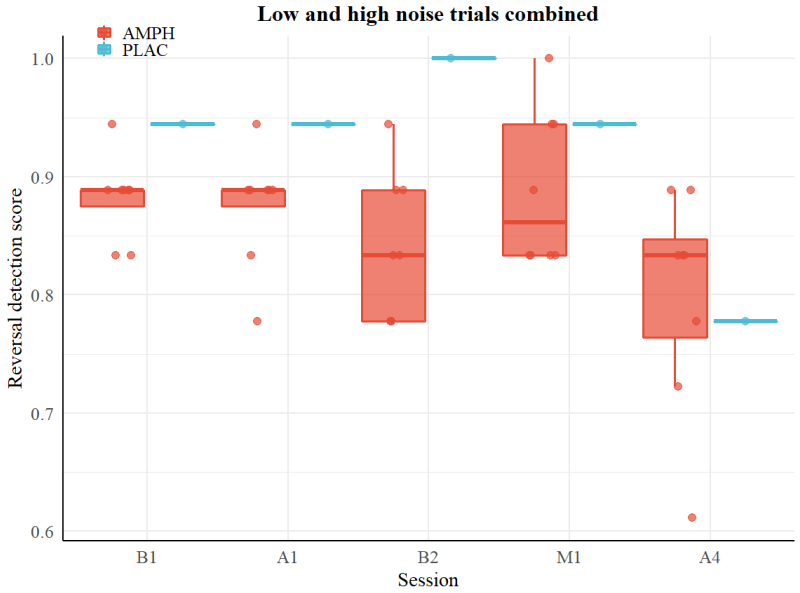
The varying slope model for reversal detection score did not converge even after adjusting the model inputs according to recommendations. Accordingly, we only report results for model 3, which only had a varying intercept (see table D.11 for results of model comparison and table D.17 for all population-level effects of model 3). Overall, results concerning the effect of sensitisation on how well participants detected relevant events (i.e. experimental reversals) are inconclusive. Based on model 3, sensitisation seemed to decrease how well participants detected relevant events (i.e. experimental reversals; see figure 4.3). This effect trended toward 0 (β = -0.06, 95% CrI = [-0.14, 0.02], δ_t = 0.01, 95% CrI = [0.00, 0.02]). There was a 90% probability for participants to detect experimental reversals less after sensitisation but the model also considered the possibility that participants detected more experimental reversals when sensitised. Likewise, amphetamine tended to decrease detection scores (β = -0.06, 95% CrI = [-0.19, 0.06], δ_t = 0.01, 95% CrI = [0.00, 0.04], 81% < 0). Both effects were associated with large uncertainty and effect sizes of 0. In general, the models chosen for analysis of reversal detection score did not explain our data well (see low Bayes R^2 in table D.11). Consequently, while our model points to no effect of sensitisation on the ability to detect experimental reversals, this finding remains inconclusive.

Figure 4.2: Effects of sensitisation on overall updating behaviour.



Note. The figure shows the average trial-by-trial update for all trials (A), for low noise (B), and high noise trials (C). Boxplots include the median, 25th and 75th percentile, and 1.5 x inter-quartile range. Session B1 & A1 are pre-sensitisation, session B2, M1 & A2 are post-sensitisation. Amphetamine was administered on session A1 & A4 for amphetamine-group, and on session A4 for placebo-group. AMPH = amphetamine group; PLAC = placebo group.

Figure 4.3: Effects of sensitisation on participants' ability to detect experimental reversals.

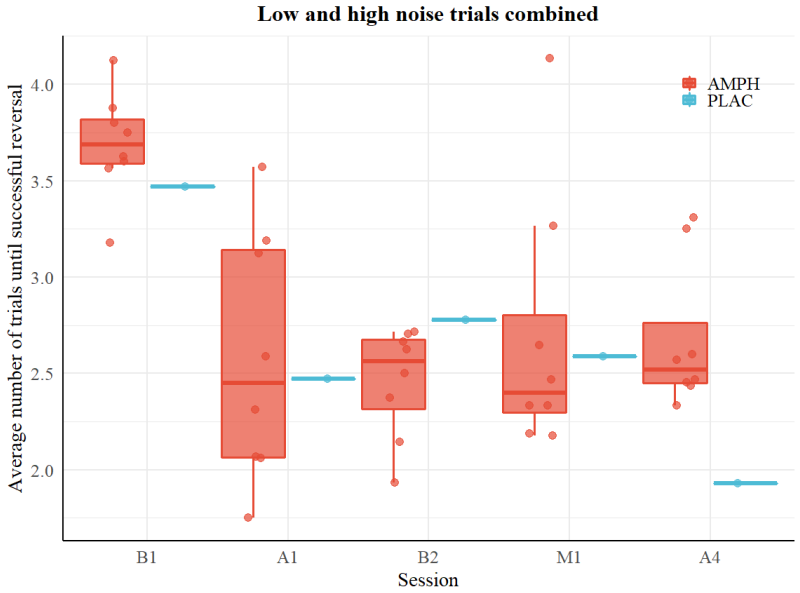


Note. The figure shows the percentage of successfully detected reversals. Boxplots include the median, 25th and 75th percentile, and 1.5 x inter-quartile range. Session B1 & A1 are pre-sensitisation, session B2, M1 & A2 are post-sensitisation. Amphetamine was administered on session A1 & A4 for AMPH-group, and on session A4 for PLAC-group. AMPH = amphetamine group; PLAC = placebo group.

(iv) Sensitisation effects on how long participants needed to successfully adapt their predictions

Results reported here are for model 4 (see table D.12 for results of model comparison and table D.18 for all population-level effects of model 4). According to our model and data, sensitisation seemed to have no effect on how long participants needed to successfully adapt their predictions after an experimental reversal (see figure 4.4). This was associated with a relatively large CrI where both positive and negative effects of sensitisation were plausible and an effect size of 0 (β = 0.00, 95% CrI = [-0.60, 0.57], δ_t = 0.00, 95% CrI = [-0.64, 0.68], 50% > 0). Meanwhile, amphetamine seemed to reduce the time how long participants needed to successfully adapt their predictions after an experimental reversal (β = -0.41, 95% CrI = [-1.53, 0.66], δ_t = -0.36, 95% CrI = [-1.46, 0.87]). Similar to the effect of sensitisation, the effect of amphetamine was also associated with large uncertainty but generally trended towards a negative effect (73% < 0). As before, our results do not allow a definite statement on the effect of sensitisation on how long participants needed to respond to experimental reversals.

Figure 4.4: Effects of sensitisation on how long participants needed to adapt their predictions after experimental reversals.



Note. The figure shows the average number of trials from experimental to successful reversal. Boxplots include the median, 25th and 75th percentile, and 1.5 x inter-quartile range. Session B1 & A1 are pre-sensitisation, session B2, M1 & A2 are post-sensitisation. Amphetamine was administered on session A1 & A4 for AMPH-group, and on session A4 for PLAC-group. AMPH = amphetamine group; PLAC = placebo group.

(v) Assessment of whether successful reversals were chance hits or proper behavioural adjustments

Results concerning task performance after successful reversals are reported for model 6 (see table D.13 for results of model comparison and table D.20 for all population-level effects of model 6). According to our model, sensitisation seemed to increase how long participant's predictions were within $SD/2$ to the mean of the underlying distribution once they successfully adapted their behaviour after experimental reversals (see figure 4.5, A). However, the effect was associated with large uncertainty where a negative effect was also plausible, but it generally trended towards being positive (β = 0.40, 95% CrI = [-0.26, 1.05], δ_t = 0.40, 95% CrI = [-0.41, 1.18], 85% > 0). This effect was even stronger when looking at noisy trials and associated with a larger effect size (γ = 0.99, 95% CrI = [0.16, 1.73], δ_t = 0.97, 95% CrI = [0.16, 1.88]). While our model was uncertain about the magnitude of this effect, as reflected in a broad CrI that considered smaller and larger values alike, our model only considered positive effects of sensitisation on how long participants exhibited good task performance in a noisy environment.

Similarly, amphetamine tended to increase the number of continuous $SD/2$-trials after successful reversals in both less noisy and even more in noisy environments (*not noisy*: β = 0.33, 95% CrI = [-0.47, 1.13], δ_t = 0.33, 95% CrI = [-0.61, 1.30], 77% > 0; *noisy*: γ = 0.56, 95% CrI = [-0.41, 1.54] , δ_t = 0.54, 95% CrI = [-0.40, 1.53]). However, our model reported large uncertainty about the effect of amphetamine, also considering negative estimates. Hence, it remains inconclusive as to how amphetamine affected how consistent participants were in predicting the average return after successful reversals.

In general, noise had a positive effect on task performance after successful reversals (β = 0.37, 95% CrI = [0.14, 0.62], δ_t = 0.37, 95% CrI = [0.07, 0.71], 99% > 0). Once participants successfully reversed their predictions after experimental reversals, participants' predictions seemed to stay longer within the $SD/2$-interval to the underlying mean in a noisy environment when participants were neither sensitised nor amphetamine-challenged (see figure 4.5, B & C for task performance post successful reversals by noise level). While our model was certain about a positive effect of noise on task performance after successful reversals, this effect was likely due to how we defined good task performance and due to $SD/2$-intervals becoming large enough for participants' predictions to be within these intervals.

Results concerning updating behaviour after successful reversals are reported for model 6 (see table D.14 for results of model comparison and table D.20 for all population-level effects of model 6). Based on this model, sensitisation tended to reduce how much participants updated their predictions between trials (see figure 4.6, A). Our model estimated a clear negative effect of sensitisation (β = -0.51, 95% CrI = [-0.96, -0.07], δ_t = -0.71, 95% CrI = [-1.54, 0.02], 97% < 0). It was however uncertain about how strong this negative effect was as reflected in the large CrI. While still negative, a noisy environment seemed to attenuate the effect and increased the CrI to also include potentially positive effects (γ = -0.37, 95% CrI = [-1.01, 0.19] , δ_t = -0.51, 95% CrI = [-1.31, 0.19]). Hence, while our model provided clear evidence for participants updating their predictions less when sensitised and when in a less noisy environment, evidence was less clear about whether sensitised participants updated their predictions more or less in a more noisy environment.

The effect of amphetamine on updating behaviour after successful reversals was also clearly negative but uncertain concerning the strength of the effect (β = -0.55, 95% CrI = [-1.02, -0.05], δ_t = -0.76, 95% CrI = [-1.71, 0.08], 96% < 0). The effect was slightly attenuated and became more uncertain when looking at updating behaviour after successful reversals

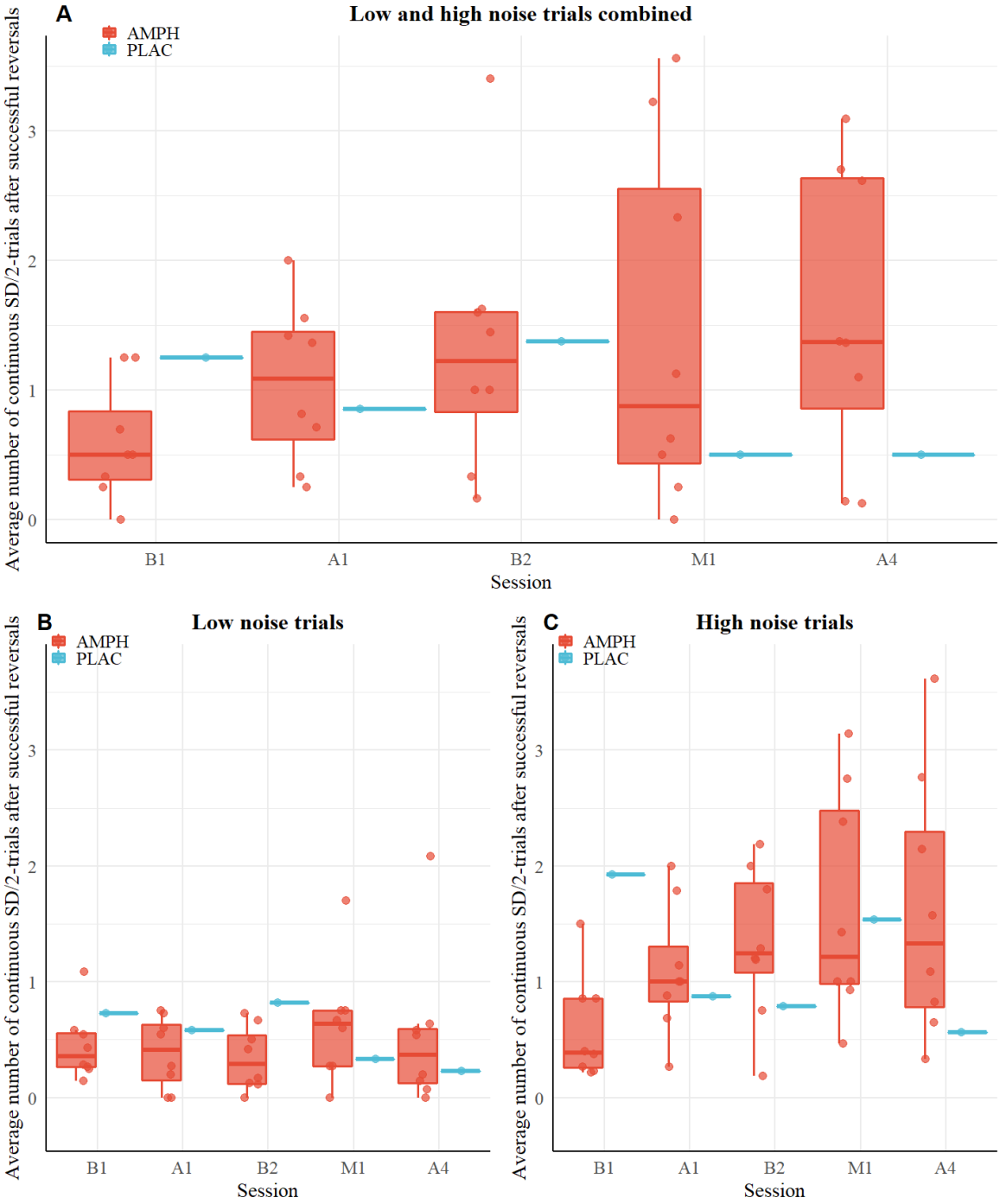
in high noise trials, including also positive values in the CrI (γ = -0.42, 95% CrI = [-0.89, 0.17], δ_t = -0.58, 95% CrI = [-1.53, 0.21]; see figure 4.6, B & C for updating behaviour post successful reversal by noise level). Interestingly, different from the pull toward slightly weaker negative effects of amphetamine and sensitisation on updating behaviour when participants experienced a noisy environment (where positive effects were also plausible), participants generally updated their predictions less in noisy environments when not sensitised and / or amphetamine-challenged (β = -0.30, 95% CrI = [-0.45, -0.16], δ_t = -0.42, 95% CrI = [-0.74, -0.14], 100% < 0).

Overall, sensitisation tended to increase how long participants' predictions remained within a close interval to the underlying mean after they successfully adapted their predictions in response to experimental reversals (i.e. relevant events). Sensitisation tended to decrease how much participants updated their predictions after successful reversals. Both effects point to participants' adjustments in predictions to not reflect chance hits but proper reversals (i.e. responses which where interpreted to reflect "correct" salience attribution to relevant events). However, sensitisation effects became more uncertain when looking at task performance and updating behaviour in noisy trials and where generally unclear about how strongly sensitisation affected behaviour after successful reversals. Hence, our findings need more scrutiny as to the actual effects of sensitisation on participants' behaviour after successful reversals in an uncertain environment.

4.3. fMRI results

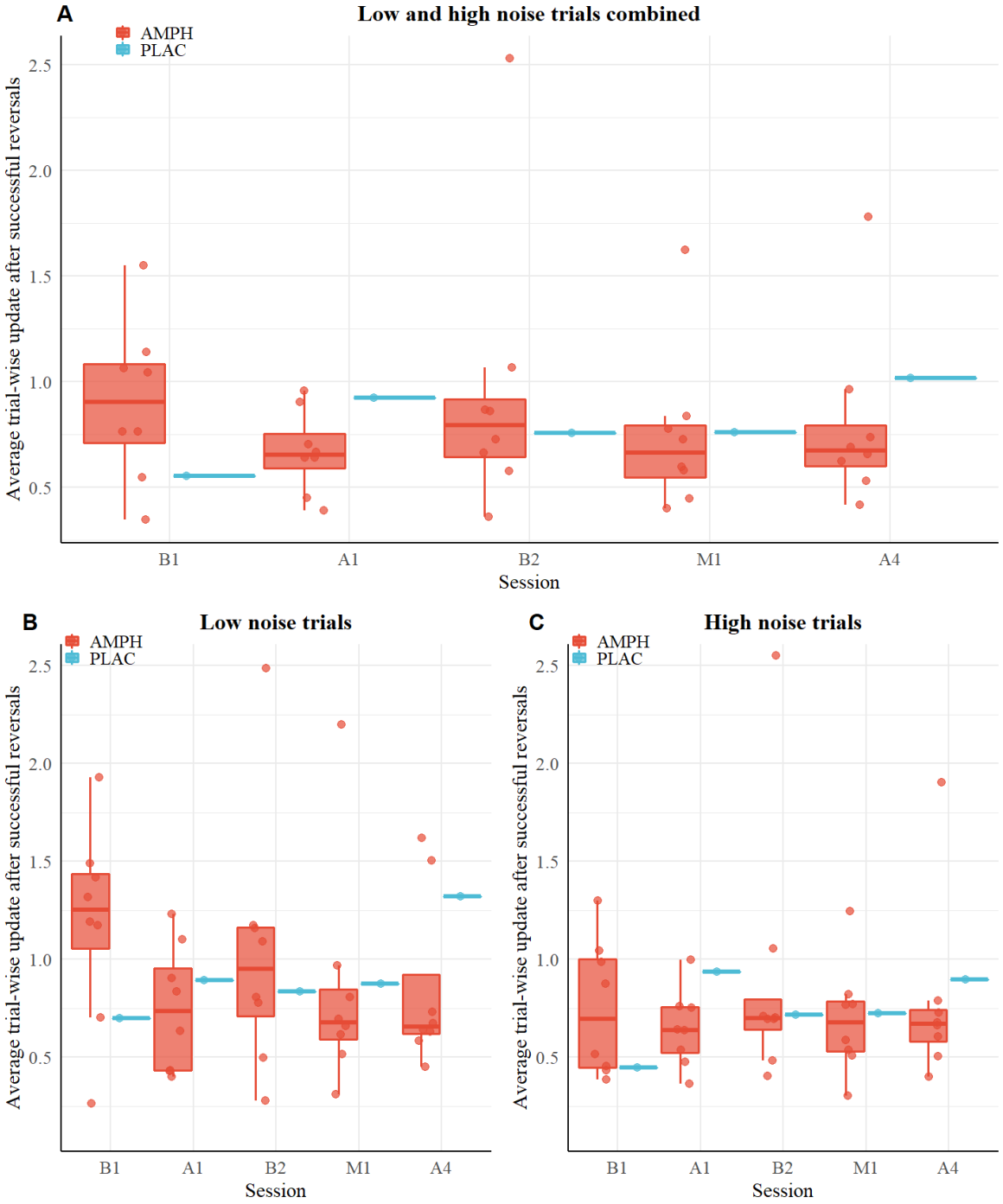
We did not find any significant differences in neural activation in response to experimental reversals (i.e. relevant events) and in response to non-reversal trials (i.e. irrelevant events) for both noisy and less noisy trials before and after sensitisation in hippocampus, striatum or dopaminergic midbrain of participants in the amphetamine group (all $p_{\text{FWE}} > 0.05$; see table 4.1). Furthermore, neural responses to experimental and non-reversal trials did not differ on any of the scan days and for any ROI within the amphetamine group and between the amphetamine and placebo group (all $p_{\text{FWE}} > 0.05$; see table 4.2 for within- and between-group differences in neural responses to experimental reversals, and table 4.3 for within- and between-group differences in neural responses to non-reversal trials). To conclude, amphetamine-sensitisation did not seem to affect neural activation in our ROIs.

Figure 4.5: Effects of sensitisation on task performance after successful reversals.



Note. The figure shows the average number of continuous trials in which prediction were within $SD/2$ of the underlying mean for all trials (A), for low noise (B), and for high noise trials (C). Boxplots include the median, 25th and 75th percentile, and 1.5 x inter-quartile range. Session B1 & A1 are pre-sensitisation, session B2, M1 & A2 are post-sensitisation. Amphetamine was administered on session A1 & A4 for AMPH-group, and on session A4 for PLAC-group. AMPH = amphetamine group; PLAC = placebo group.

Figure 4.6: Effects of sensitisation on updating behaviour after successful reversals.



Notes. The figure shows the average trial-by-trial update after successful reversals for all trials (A), and for low noise (B) and high noise trials (C). Session B1 & A1 are pre-sensitisation, session B2, M1 & A2 are post-sensitisation. Amphetamine was administered on session A1 & A4 for AMPH-group, and on session A4 for PLAC-group. Boxplots include the median, 25th and 75th percentile, and 1.5 x inter-quartile range. AMPH = amphetamine group; PLAC = placebo group.

Table 4.1: Results of permutation tests examining sensitisation effects on neural responses to reversal and non-reversal trials by noise level (AMPH-group).

Regressor	**ROI**	**Peak voxel coordinates**	**T**	$p_{\mathbf{FWE}}$
Within-subject differences for reversal trials pre- & post-sensitisation				
High noise reversals	HC	-	9.38	> 0.05
	STR	-	10.99	> 0.05
	MB	-	-	-
Low noise reversals	HC	-	9.73	> 0.05
	STR	-	9.35	> 0.05
	MB	-	-	-
Within-subject differences for non-reversal trials pre- & post-sensitisation				
High noise non-reversals	HC	-	8.78	> 0.05
	STR	-	10.16	> 0.05
	MB	-	-	-
Low noise non-reversals	HC	-	8.96	> 0.05
	STR	-	12.71	> 0.05
	MB	-	-	-

Note. The table shows within-subject differences in neural responses to reversal (top) and non-reversal trials (bottom) pre- and post-sensitisation for the AMPH group. We tested positive effects for reversal trials (A1>A4) and negative effects for non-reversal trials (A4>A1; all n = 6). No voxels survived the critical threshold T in HC and STR. There were no active voxels in the MB. ROI = region of interest used as mask; HC = hippocampus; STR = striatum; MB = right dopaminergic midbrain; T = voxel-level critical threshold.

Table 4.2: Results of permutation tests examining within- and between-group differences in neural responses to reversal trials pre- and post-sensitisation by noise level.

Regressor	ROI	Peak voxel coordinates	T	p_{FWE}
Within-group differences for reversal trials pre-sensitisation (AMPH-group)				
High noise reversals	HC	-	7.50	> 0.05
	STR	-	8.65	> 0.05
	MB	-	-	-
Low noise reversals	HC	-	7.04	> 0.05
	STR	-	7.31	> 0.05
	MB	-	-	-
Within-group differences for reversal trials post-sensitisation (AMPH-group)				
High noise reversals	HC	-	8.32	> 0.05
	STR	-	8.15	> 0.05
	MB	-	-	-
Low noise reversals	HC	-	7.54	> 0.05
	STR	-	9.76	> 0.05
	MB	-	-	-
Between-group differences for reversal trials pre-sensitisation				
High noise reversals	HC	-	11.94	> 0.05
	STR	-	10.01	> 0.05
	MB	-	-	-
Low noise reversals	HC	-	30.41	> 0.05
	STR	-	48.15	> 0.05
	MB	-	-	-
Between-group differences for reversal trials post-sensitisation				
High noise reversals	HC	-	16.15	> 0.05
	STR	-	11.73	> 0.05
	MB	-	-	-
Low noise reversals	HC	-	12.12	> 0.05
	STR	-	12.64	> 0.05
	MB	-	-	-

Note. The table shows within-group (top) and between-group (bottom) differences in neural responses to reversal trials pre- and post sensitisation. Within-group differences are only reported for the amphetamine group Within-group: $n = 7$. Between-group: $n = 8$. No voxels survived the critical threshold T in HC and STR. There were no active voxels in the MB. ROI = region of interest used as mask; HC = hippocampus; STR = striatum; MB = right dopaminergic midbrain; T = voxel-level critical threshold.

Table 4.3: Results of permutation tests examining within- and between-group differences in neural responses to non-reversal trials pre- and post-sensitisation by noise level.

Regressor	ROI	Peak voxel coordinates	T	p_{FWE}
Within-group differences for non-reversal trials pre-sensitisation (AMPH-group)				
High noise non-reversals	HC	-	8.58	> 0.05
	STR	-	8.93	> 0.05
	MB	-	-	-
Low noise non-reversals	HC	-	7.42	> 0.05
	STR	-	9.15	> 0.05
	MB	-	-	-
Within-group differences for non-reversal trials post-sensitisation (AMPH-group)				
High noise non-reversals	HC	-	8.09	> 0.05
	STR	-	6.72	> 0.05
	MB	-	-	-
Low noise non-reversals	HC	-	8.95	> 0.05
	STR	-	8.64	> 0.05
	MB	-	-	-
Between-group differences for non-reversal trials pre-sensitisation				
High noise non-reversals	HC	-	15.63	> 0.05
	STR	-	7.12	> 0.05
	MB	-	-	-
Low noise non-reversals	HC	-	5.87	> 0.05
	STR	-	9.70	> 0.05
	MB	-	-	-
Between-group differences for non-reversal trials post-sensitisation				
High noise non-reversals	HC	-	12.35	> 0.05
	STR	-	8.98	> 0.05
	MB	-	-	-
Low noise non-reversals	HC	-	10.26	> 0.05
	STR	-	11.49	> 0.05
	MB	-	-	-

Note. The table shows within-group (top) and between-group (bottom) differences in neural responses to non-reversal trials pre- and post sensitisation. Within-group differences are only reported for the amphetamine group Within-group: n = 7. Between-group: n = 8. No voxels survived the critical threshold T in HC and STR. There were no active voxels in the MB. ROI = region of interest used as mask; HC = hippocampus; STR = striatum; MB = right dopaminergic midbrain; T = voxel-level critical threshold.

5 Discussion & Conclusion

In line with previous studies, sensitisation did not seem to have a strong effect on physiological measures (heart rate & diastolic blood pressure), but tended to increase subjective experience of drug effects (O'Daly, Joyce, Tracy, Azim, et al., 2014; O'Daly, Joyce, Tracy, Stephan, et al., 2014). Effects were generally associated with large uncertainty. Keeping this in mind, we can still assume that amphetamine sensitisation was successful to some extent and that findings on behavioural and neural measures of salience processing do reflect sensitisation effects.

Evidence for the effect of sensitisation on participants' ability to predict the average return (task performance) and on how much participants updated their predictions after every trial (updating behaviour) was preliminary. Nevertheless, we will try to put our results into perspective. According to our model and data, participants seemed to be worse at estimating the average return when sensitised. While participants tended to perform worse in noisy environments when sensitised, they tended to perform better in noisy environments when not sensitised. This points to an increased belief updating behaviour which could implicate that sensitised participants had problems to filter noisy stimuli. However, the seemingly negative effect of sensitisation on updating behaviour sheds a different light on belief updating behaviour. When looking at this more lenient measure of belief updating that considered trial-wise dependencies between feedback and predictions, participants tended to update their predictions less between trials when sensitised than when not sensitised. Interestingly, this effect appeared slightly weaker when participants experienced a noisy environment despite being decisively negative. Overall, if the negative effect of sensitisation on updating behaviour proved true, it would differ from previous findings of increased belief updating or switching behaviour in psychotic and high-risk individuals (Schlagenhauf et al., 2014).

Unfortunately, we cannot make any statement about sensitisation effect on how well participants detected experimental reversals (i.e. how responsive participants were to relevant events). The tendency of sensitisation to impair how well participants detected reversals that our model estimated is uncertain. However, if it proved true, it would match previous

findings according to which psychotic patients have been shown to achieve fewer (although performance-dependent) reversals (see Waltz & Gold, 2007, or Feeney et al., 2017, for a review). Furthermore, the effect of sensitisation on how many trials our participant needed to detect reversals was equally likely to decrease and increase the time needed to adapt to experimental reversals (relevant events). This differs from previous studies which reported that psychotic patients are quicker in adapting their responses to reversals in reward contingencies (Feeney et al., 2017). As our findings were associated with large uncertainty, it remains inconclusive if and how sensitisation affected how participants processed relevant events that would ideally be attributed with salience.

By contrast, our models found comparably clear effects of sensitisation on how long participants' predictions remained close to the underlying mean and how much they changed their predictions once they adapted predictions after experimental reversals. Sensitisation increased how long participants performed well and decreased how much participants updated their predictions after successful reversals. Accordingly, changes in behaviour after experimental reversals did not seem to be simply by chance. Rather, sensitised participants were more stable in their behaviour once they reversed. Importantly, these effects were only certain when participants did not experience highly noisy environments. Overall, these findings speak against sensitised participants being less responsive to events that require behavioural responses (i.e. events that are at best attributed with some salience). This contradicts previous findings that patients with psychosis display decreased sensitivity to rewards during reversal learning (see particularly Schlagenhauf et al., 2014). Yet, given that we cannot say much about the influence of sensitisation on how good participants were at achieving reversals, any definite conclusions remain open for discussion.

While decreased updating behaviour in sensitised participants differs from over-switching behaviour as observed in patients with psychosis and at risk of developing psychosis (Feeney et al., 2017), it is in line with findings on reduced uncertainty-driven exploration in patients with schizophrenia (Strauss et al., 2014). Exploration describes behaviours where alternative actions are tried out to see whether they yield better outcomes than previous, already rewarding actions. By contrast, exploitation describes behaviours where previously rewarding actions (i.e. actions that yielded a positive outcome) are repeated (Strauss et al., 2014). The trade-off between exploration and exploitation is particularly strong in uncertain environments. Strauss et al. (2014) have argued that reduced exploration behaviour in

schizophrenia patients reflects an attempt to reduce uncertainty when the environment is unknown. With respect to our findings, it might be that sensitised participants settled on exploitative behaviour in order to reduce uncertainty. The fact that the negative sensitisation effect on updating behaviour was not strengthened when looking explicitly at noisy trials could reflect that a less noisy environment was already uncertain enough to trigger exploitative behaviour over exploratory behaviour. The fact that sensitisation generally tended to decrease updating behaviour, independent of whether participants reversed successfully or not, supports such interpretation. In the context of predictive processing, this reflects generally attenuated PE signalling whereby every sensory input is essentially perceived as noise, impairing any distinction between relevant and irrelevant events, i.e. between events that require behavioural responses and events that do not necessarily require behavioural responses (see Anticevic & Corlett, 2012).

However, it might also be that our measures of belief updating (predictions within $SD/2$ of the underlying mean and trial-wise prediction updating) might not properly capture updating behaviour. While we tried to capture underlying dependencies between prediction errors and predictions on each trial, we averaged these to obtain session-wise values. Hence, trial-wise nuances of such dependencies might actually have gotten lost. Since participants completed the task in a highly dynamic environment, it seems more adequate to analyse data in a trial-wise fashion. Another reason why we did not find any sensitisation effects on salience processing could be that the way we measured behavioural analogues to salience attribution was from an experimenter's perspective. Relevant events to which participants ideally attribute salience were trials in which the experimental conditions changed. However, only because we regarded these events as relevant does not mean that participants perceive them as relevant. This is especially true given that our task did not require a binary decision in trials and that the environment was generally noisy. Consequently, and different from regular reversal learning tasks, our participants did not receive straight forward feedback on the "correct" choice and did not have a clear point of reference for their predictions. In this context, it seems likely that the events that we defined as experimental reversals, and which usually are relevant events in classical reversal learning, might not have represented relevant events for our participants.

Possibilities for trial-wise behavioural analyses that aim at modelling relevant events from an individual's perspective are computational models that investigate belief updating

and perception under uncertainty. The approximated Bayesian Delta-Rule model (Nassar et al., 2010), the Rescorla-Wagner model (Schlagenhauf et al., 2014) or the Hierarchical Gaussian Filter (Mathys et al., 2014) are examples of such methods. Different from the measures adopted in this study, these methods focus less on external measures of reversal learning and relevant events but try to model participant's subjectively perceived relevance of events.

Especially the Hierarchical Gaussian Filter (HGF) seems promising to capture individual differences in belief updating in an uncertain environment (Cole et al., 2020; Mathys et al., 2014). The HGF builds on the idea that the brain constantly infers hidden states of the world by minimising the difference between its predictions and the actual sensory input (thereby matching predictive processing accounts of cognition). However, it expands this understanding by accounting for the inherent uncertainty of predictions (Cole et al., 2020). Accordingly, the HGF allows to look prediction errors at different levels from mere perceptual prediction errors to more complex prediction errors signifying beliefs about the uncertainty of the environment. Importantly, both bottom-up sensory input and top-down priors modulate how prediction errors are weighted with respect to their uncertainty and, hence, how they drive belief updating (Cole et al., 2020; Mathys et al., 2014). In this framework, aberrant precision-weighting of prediction errors at lower and higher levels could culminate into the development and persistence of psychotic symptoms. The HGF has already been used in model-based fMRI analysis of aberrant reward-based learning and inference processing under uncertainty in psychotic (Deserno et al., 2020) and in high-risk individuals (Cole et al., 2020).

Concerning sensitisation effects on neural activity in salience-processing regions, we did not find any significant difference in neural responses to relevant and random events in any of the regions of interest. Our results thus differ from earlier findings on sensitisation effects on reward processing (Schlagenhauf et al., 2014). Potential reasons for these findings tie into what we already discussed for behavioural findings. On the one hand, the lack of differentiated neural responses to relevant reversals and random noise in non-reversal trials might reflect participants' early settling on exploitative behaviour because they could not differentiate between experimental reversals and general noise. This could translate into a generally attenuated dopamine signalling which translates into an attenuated prediction error signalling in predictive processing terms. On the other hand, what we defined as relevant events (the changes in the underlying distribution from which actual returns were

drawn) might not have been perceived as relevant from a participant's perspective. Hence, events that were relevant from our point of view may not have triggered neural responses in salience-processing regions.

Including more subjective measures of relevant events and uncertainty might be a useful next step for analysis. Apart from computational models, an alternative to incorporate more subjective perceptions of relevant events into the analysis could be to include the confidence ratings from the task as predictors in the behavioural models and as parametric modulators in the fMRI analysis. These reflect subjective evaluation of how certain participants were about their predictions and might touch on how convincing (i.e. how relevant and hence potentially salient) observed changes in the environment have been. Another step for fMRI analysis could be to explore whole-brain activation in response to experimental reversals and non-reversal trials as well as activation in other regions implicated in aberrant reversal learning, particularly the prefrontal cortex (Anticevic & Corlett, 2012; Feeney et al., 2017). A closer look into the latter region could also help to investigate whether the reduced updating behaviour observed in sensitised participants reflects reduced exploration behaviour as a mechanism to reduce uncertainty. Frontal and medial areas in the prefrontal cortex are thought to govern exploration-exploitation behaviours (Strauss et al., 2014). Furthermore, future fMRI analyses could incorporate the behavioural measures of salience processing more for example through correlation analyses.

5.1. Limitations & Future Perspectives

Besides aforementioned shortcomings of potentially defining behavioural variables too generally (analysing session-wise averages instead of examining trial-wise behaviour) or of defining relevance from an experimenter's point of view, this thesis has several limitations. The most important limitation is the small sample size and the uneven assignment of participants to amphetamine and placebo group. Any comparison of groups where one group consists of a single participant necessarily lacks informative value. Accordingly, it is not surprising that many results from our behavioural analysis were associated with rather wide credible intervals and small effect sizes. Very likely, our models' uncertainties about their effect estimates stems from the small sample size. The problem of a small sample size is even stronger for our fMRI analysis. We only had data from two scan session both of which

entailed amphetamine administration for participants in the amphetamine group. Hence, the fact that we did not observe differences in neural responses to hypothetically relevant and irrelevant events might reflect some effect of amphetamine. This brings me to the next limitation of this thesis.

Amphetamine seemed to play a significant role for some of the behavioural variables analysed in this thesis. Thus, sensitisation effects reported for behavioural variables might mask an interaction between amphetamine and sensitisation status. One way to expand the current behavioural analysis is to add an interaction effect between amphetamine and sensitisation status in the models. This allows to better disentangle the separate effects of both predictors. Concerning measures of how well participants were at detecting experimental reversals and how long participants needed to successfully adapt predictions after experimental reversals, it would be good to examine these measures again but separately for low and high noise trials.

Another shortcoming is that the study only accepted male volunteers. Schizophrenia seems to manifest differently in men and women (Sun, Walker, Dean, van den Buuse, & Gogos, 2016). Research on sex differences in schizophrenia has mostly focused on the role of oestrogen in schizophrenia (Sun et al., 2016). However, progesterone has been suggested to have a protective role in the development and severity of schizophrenia (Sun et al., 2016). Both oestrogen and progesterone have been shown to interact with the dopaminergic system, which was a reason to exempt female participants from this study. However, future studies should include female participants. Generalisation from findings of all-male studies to the general, also female, population are questionable (Rich-Edwards, Kaiser, Chen, Manson, & Goldstein, 2018).

Lastly, the current analysis did not account for differences in working memory capacity. Already simple reinforcement learning tasks seem to draw on working memory (Deserno et al., 2016). Given that our task was rather complex, it is plausible that processes observed during the task also reflected influences of higher-order systems. Future analyses should account for participants' different working memory capacities, especially since cognitive deficits are a frequent symptom in schizophrenia (Green & Harvey, 2014) and amphetamine sensitisation has been shown to affect neural responses during memory encoding (O'Daly, Joyce, Tracy, Stephan, et al., 2014).

5.2. Conclusion

This thesis represents a first attempt to investigate the role of dopamine hypersensitivity in behavioural and neural salience processing more directly. For this, it combined pharmacological manipulation of dopamine levels in healthy volunteers with fMRI and a reversal learning task that included more realistic types of environmental uncertainty. Unfortunately, our results on the effect of amphetamine-induced dopamine hypersensitivity on behavioural and neural salience processing in healthy volunteers remain preliminary. Sensitisation tended to decrease updating behaviour which, if proven correct, would contradict excessive salience attribution to noisy events as reported for psychotic individuals. Simultaneously, sensitisation tended to diminish participants' ability to determine the underlying task structure (namely the average return) which hints at some form of aberrant salience attribution to noisy events. Given our definition of relevant and irrelevant events and our choice of analysis, we did not find any effects of sensitisation on neural responses in hippocampus, striatum and right dopaminergic midbrain to relevant and irrelevant events. For more definite statements, both behavioural and fMRI data need further analyses to better capture the effect of sensitisation on salience processing. And even then, results should still be interpreted with caution given the small sample size and uneven distribution of amphetamine- and placebo-sensitised participants, and should be validated by future studies with more participants. Nonetheless, the multi-methodological, interdisciplinary approach of this study is a promising way to investigate the hypothesised role of dopamine in salience processing in healthy volunteers on both behavioural and neural levels.

A Appendix: Abstracts

A.1. Abstract

Dopamine is thought to code prediction errors (PEs) between predicted and actual sensory inputs that propagate throughout the brain, thereby facilitating decision-making and learning. As dopamine dysregulation and abnormal reward-based learning are characteristic for psychotic disorders, it has been suggested that disrupted PE signalling underlies psychotic disorders. More recently, impaired PE signalling has been suggested to mediate aberrant salience attribution in psychosis whereby relevant events are not attributed salience while irrelevant events are misattributed salience. Several studies support a link between disrupted dopamine-mediated PE signalling and abnormal salience processing in psychosis. Yet, evidence is mostly correlational, relying on the inherent dopamine dysregulation of participants with psychosis. By directly targeting the dopamine system of healthy volunteers, this thesis investigates whether and how amphetamine-induced dopamine hypersensitivity affects behavioural and neural salience processing under uncertainty. Following a double-blind amphetamine sensitisation protocol, healthy, male volunteers were randomly assigned to amphetamine or placebo group. The amphetamine group (n = 8) repeatedly received low doses of D-amphetamine inducing a slight amphetamine sensitisation that is thought to approximate the dopamine hypersensitivity observed in psychosis. The placebo group (n = 1) received Mannitol. Participants completed a reward-based predictive-inference task before and after sensitisation. They had to predict outcomes based on stimulus-outcome contingencies which changed dynamically throughout the task. Neural responses were recorded with fMRI. We found some preliminary effects of sensitisation on different behavioural measures of salience processing, e.g. a trend to reduce belief updating. Sensitisation did not seem to affect neural responses to relevant and irrelevant events in the hippocampus, striatum and the right dopaminergic midbrain. Overall, our results do not allow for any definite statements on sensitisation effects on behavioural and neural salience processing and need further scrutiny. Hence, this thesis includes recommendations for future analyses.

A.2. Zusammenfassung

Dopamin soll Vorhersagefehler zwischen erwarteten und tatsächlichen Sinneseindrücken kodieren, die sich im Gehirn verbreiten und dadurch Entscheidungsfindung und Lernen unterstützen sollen. Es wird angenommen, dass das Signalisieren von Vorhersagefehler in psychotischen Erkrankungen beeinträchtigt ist, da ein dysreguliertes Dopaminsystem und abnormales belohnungsbasiertes Lernen charakteristisch für diese sind. Seit einiger Zeit wird ein beeinträchtigtes Signalisieren von Vorhersagefehlern bei Psychosen mit der fälschlichen Zuschreibung von Salienz zusammengebracht. Demnach werden irrelevante Stimuli fälschlich mit Salienz und relevante Stimuli nicht mit Salienz assoziiert. Mehrere Studien stützen einen Zusammenhang zwischen Dopamin-gestützter Salienzzuschreibung und Psychosen. Die Ergebnisse sind zumeist jedoch korrelativ, da sie auf der inhärenten Dopamindysregulierung psychotischer Proband*innen beruhen. In dieser Arbeit wurde der Dopaminhaushalt von gesunden Probanden direkt manipuliert, um zu untersuchen, ob und wie Amphetamin-induzierte Dopaminhypersensibilisierung behaviorale und neuronale Salienzverarbeitung unter Ungewissheit beeinflusst. Hierfür wurden gesunde, männliche Probanden einem doppel-blinden Amphetaminsensibilierungsprotokoll folgend randomisiert der Amphetamin- oder der Placebogruppe zugeteilt. Die Amphetamingruppe (n = 8) erhielt wiederholt geringe Dosen an D-Amphetamin, wodurch eine leichte Amphetaminsensibilisierung hervorgerufen wird, die der Dopaminhypersensibilisierung in Psychosen ähneln soll. Die Placebogruppe (n = 1) erhielt Mannitol. Probanden absolvierten eine belohnungsbasierte Lernaufgabe vor und nach der Sensibilisierungsphase. Hierbei mussten Probanden zukünftige Ergebnisse anhand von Kontingenzen zwischen Stimuli und Ergebnissen voraussagen, die sich jedoch konstant änderten. Salienzbezogene Hirnaktivität wurde mit fMRT aufgezeichnet. Sensibilisierung schien eine, jedoch nicht eindeutige, Wirkung auf behaviorale Salienzverarbeitung zu haben. So tendierten Probanden beispielsweise dazu, ihre Meinung seltener zu aktualisieren, wenn sie sensibilisiert waren. Sensibilisierung schien die Hirnaktivität auf irrelevanten und relevanten Ereignisse im Hippocampus, Striatum und rechten dopaminergen Mittelhirn nicht zu beeinflussen. Unsere Ergebnisse lassen keine endgültige Aussage über die Wirkung von Dopaminhypersensibilisierung auf behaviorale und neuronale Salienzverarbeitung zu und bedürfen weiterer Untersuchungen. Es werden Verbesserungsvorschläge vorgestellt.

B Appendix: Preprocessing Steps

Pre-processing steps included slice-time correction, realignment, unwarping, co-registration, unified segmentation, spatial normalisation and smoothing. The following detailed explanation of the preprocessing steps is based on the SPM12 manual (`https://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf`).

Slice-time correction is a common pre-processing step for echo-planar scanning. In echo-planar scanning, images of slices are sampled sequentially or interleaved. Both modes result in temporal differences between the first and last sampled slice. However, precise timing with respect to activation-evoking stimuli is essential for time course analyses of the BOLD signal in fMRI. Slice-time correction accounts for these temporal differences in sampling. During slice-time correction, the image acquisition time between slices is corrected by shifting the signal phase by a given amount such that the data on each slice corresponds to the same point in time. The amount of shift is determined with respect to a reference slice which was the slice acquired in the middle of the sequence (i.e. at TR/2).

Both realignment and unwarping are motion correction measures. Functional images are acquired as time series so that a subject's movement can introduce great movement artefacts in functional images. These movement artefacts can lead to loss of sensitivity (missing out on true activation) and loss of specificity of neural activity (detecting false positives) in an fMRI experiment.

Realignment is the first step to remove movement artefacts in fMRI time series. For this, the first scan of each session of a participant was realigned to the first scan of the first session. Next, all images of a session were realigned to the first image of that session. Images are realigned along 6 parameters, 3 for translations (mm) and 3 for rotations (degrees). However, realignment cannot fully remove all movement-induced variance in fMRI time series. This is due to the susceptibility-by-movement interaction whereby an image collected for a given subject position will not be identical to that collected at another position. Subject's movements result in severe geometrical distortions, especially in regions where air and tissue interface, which are corrected during unwarping.

Co-registration links the anatomical information of functional images with a structural

image. This is done because structural images yield superior anatomical localisation. Moreover, co-registration allows for more precise spatial normalisation.

Unified segmentation includes segmentation, bias correction and spatial normalisation of structural images. MRI entails several artefacts from noise, intensity inhomogeneities and bias field differences in sequences and partial volumes which make normalisation difficult. During segmentation, different types of tissue such as grey matter and white matter are separated based on tissue probability maps. Unified segmentation further includes bias correction which accounts for inherent intensity inhomogeneity of MRI facilitating the subsequent normalisation process.

Normalisation is needed to establish a voxel-to-voxel correspondence between brains of different subjects which allows comparisons of neural activation between subjects. For this, images are normalised to a standard brain template (standard space). It increases statistical power, allows for group analyses, and enables generalisation and comparison across different studies. During normalisation, functional images are matched to the Montreal Neurological Institute (MNI) space which is the standard space used in SPM. To accomplish this, T1-weighted, anatomical images were normalised and transformed to match the MNI template unified segmentation. Normalisation parameters were then applied to all functional images. To fit to MNI space, images are translated across and rotated around the three axes as well as scaled and sheared.

Functional images were smoothed with a 3D Gaussian kernel of 4 mm full-width at half-maximum (FWHM). Smoothing is the weighted averaging of neighbouring voxels. This way, residual anatomical differences and registration errors are blurred over which increases signal-to-noise ratio (by suppressing noise and effects that are due to residual differences in functional and gyral anatomy). Smoothing further results in superior spatial overlap, makes data more normally distributed and increases sensitivity to effects of similar scale to kernel.

C Appendix: Model Definition

C.1. Model for Subjective & Physiological Data Analysis

Figure C.1: Varying intercept and slope model used for subjective and physiological data analysis.

$$
\begin{aligned}
RV &\sim (\mu_i, \sigma_e) \\
\mu_i &= \alpha + \alpha_{ID[i]} + (\beta + \beta_{ID[i]}) \times session_i + \beta \times sensitised_i + \beta \times amph_i \\
\begin{bmatrix} \alpha_{ID} \\ \beta_{ID} \end{bmatrix} &\sim MVN\left(\begin{bmatrix} \alpha \\ \beta \end{bmatrix}, S\right) \\
S &= \begin{pmatrix} \sigma_\alpha & 0 \\ 0 & {}_\beta \end{pmatrix} R \begin{pmatrix} \sigma_\alpha & 0 \\ 0 & \sigma_\beta \end{pmatrix} \\
\alpha &\sim Normal(0, \sigma) \\
\alpha_{ID} &\sim Normal(0, \sigma_{ID}) \\
\beta &\sim Normal(0, 3) \\
\beta_{ID} &\sim Normal(0, 3) \\
\sigma_e &\sim HalfCauchy(0, 2) \\
\sigma &\sim HalfCauchy(0, 2) \\
\sigma_{ID} &\sim HalfCauchy(0, 2) \\
\sigma_\alpha &\sim HalfCauchy(0, 2) \\
\sigma_\beta &\sim HalfCauchy(0, 2) \\
R &\sim LKJcorr(2)
\end{aligned}
$$

Note. RV = response variable; session = testing day (1 = A1, 2 = A2, 3 = A3, 4 = A4); sensitised = sensitisation status (1 = sensitised); amph = amphetamine administration (1 = amphetamine administered).

C.2. Models for Behavioural Data Analysis

M3: Varying Intercept Model for Behavioural Data Analysis

Figure C.2: Varying intercept model (M3) for behavioural data analysis.

$$
\begin{aligned}
RV &\sim (\mu_i, \sigma_e) \\
\mu_i &= \alpha + \alpha_{ID[i]} + \beta \times session_i + \beta \times sensitised_i + \beta \times amph_i \\
\alpha &\sim Normal(0, \sigma) \\
\alpha_{ID} &\sim Normal(0, \sigma_{ID}) \\
\beta &\sim Normal(0, 3) \\
\sigma_e &\sim HalfCauchy(0, 2) \\
\sigma_{ID} &\sim HalfCauchy(0, 2)
\end{aligned}
$$

Note. RV = response variable; session = testing day (1 = A1, 2 = A2, 3 = A3, 4 = A4); sensitised = sensitisation status (1 = sensitised); amph = amphetamine administration (1 = amphetamine administered).

M4: Varying Intercept & Slope Model with Noise Predictor for Behavioural Analysis

Figure C.3: Varying intercept and slope model (M4) for behavioural data analysis.

$$
\begin{aligned}
RV &\sim (\mu_i, \sigma_e) \\
\mu_i &= \alpha + \alpha_{ID[i]} + (\beta + \beta_{ID[i]}) \times session_i + \beta \times sensitised_i + \beta \times amph_i \\
\begin{bmatrix} \alpha_{ID} \\ \beta_{ID} \end{bmatrix} &\sim MVN\left(\begin{bmatrix} \alpha \\ \beta \end{bmatrix}, S \right) \\
S &= \begin{pmatrix} \sigma_\alpha & 0 \\ 0 & {}_\beta \end{pmatrix} R \begin{pmatrix} \sigma_\alpha & 0 \\ 0 & \sigma_\beta \end{pmatrix} \\
\alpha &\sim Normal(0, \sigma) \\
\alpha_{ID} &\sim Normal(0, \sigma_{ID}) \\
\beta &\sim Normal(0, 3) \\
\beta_{ID} &\sim Normal(0, 3) \\
\sigma_e &\sim HalfCauchy(0, 2) \\
\sigma &\sim HalfCauchy(0, 2) \\
\sigma_{ID} &\sim HalfCauchy(0, 2) \\
\sigma_\alpha &\sim HalfCauchy(0, 2) \\
\sigma_\beta &\sim HalfCauchy(0, 2) \\
R &\sim LKJcorr(2)
\end{aligned}
$$

Note. RV = response variable; session = testing day (1 = A1, 2 = A2, 3 = A3, 4 = A4); sensitised = sensitisation status (1 = sensitised); amph = amphetamine administration (1 = amphetamine administered); S = covariance matrix; R = correlation matrix.

Correlation Matrix of Models with Varying Slope

Figure C.4: Correlation matrix of varying slope models.

$$R = \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$$

M5: Varying Intercept & Slope Model with Noise Predictor for Behavioural Data Analysis

Figure C.5: Varying intercept and slope model with noise predictor (M5) for behavioural data analysis.

$$\begin{aligned}
RV &\sim (\mu_i, \sigma_e) \\
\mu_i &= \alpha + \alpha_{ID[i]} + (\beta + \beta_{ID[i]}) \times session_i + \beta \times sensitised_i + \beta \times amph_i + \beta \times noise_i \\
\begin{bmatrix} \alpha_{ID} \\ \beta_{ID} \end{bmatrix} &\sim MVN\left(\begin{bmatrix} \alpha \\ \beta \end{bmatrix}, S \right) \\
S &= \begin{pmatrix} \sigma_\alpha & 0 \\ 0 & {}_\beta \end{pmatrix} R \begin{pmatrix} \sigma_\alpha & 0 \\ 0 & \sigma_\beta \end{pmatrix} \\
\alpha &\sim Normal(0, \sigma) \\
\alpha_{ID} &\sim Normal(0, \sigma_{ID}) \\
\beta &\sim Normal(0, 3) \\
\beta_{ID} &\sim Normal(0, 3) \\
\sigma_e &\sim HalfCauchy(0, 2) \\
\sigma &\sim HalfCauchy(0, 2) \\
\sigma_{ID} &\sim HalfCauchy(0, 2) \\
\sigma_\alpha &\sim HalfCauchy(0, 2) \\
\sigma_\beta &\sim HalfCauchy(0, 2) \\
R &\sim LKJcorr(2)
\end{aligned}$$

Note. RV = response variable; session = testing day (1 = B1, 2 = A1, 3 = B2, 4 = M1, 5 = A4); sensitised = sensitisation status (1 = sensitised); amph = amphetamine administration (1 = amphetamine administered); noise = noise level (1 = high noise/variance); S = covariance matrix; R = correlation matrix.

M6: Interaction Model for Behavioural Data Analysis

Figure C.6: Noise interaction model (M6) with varying intercept and slope for behavioural data analysis.

$$
\begin{aligned}
RV &\sim (\mu_i, \sigma_e) \\
\mu_i &= \alpha + \alpha_{ID[i]} + (\beta + \beta_{ID[i]}) \times session_i + \beta \times sensitised_i + \beta \times amph_i \\
&\quad + \beta \times noise_i + \beta \times sensitised_i \times noise_i + \beta \times amphetamine_i \times noise_i \\
\begin{bmatrix} \alpha_{ID} \\ \beta_{ID} \end{bmatrix} &\sim MVN\left(\begin{bmatrix} \alpha \\ \beta \end{bmatrix}, S \right) \\
S &= \begin{pmatrix} \sigma_\alpha & 0 \\ 0 & {}_\beta \end{pmatrix} R \begin{pmatrix} \sigma_\alpha & 0 \\ 0 & \sigma_\beta \end{pmatrix} \\
\alpha &\sim Normal(0, \sigma) \\
\alpha_{ID} &\sim Normal(0, \sigma_{ID}) \\
\beta &\sim Normal(0, 3) \\
\beta_{ID} &\sim Normal(0, 3) \\
\sigma_e &\sim HalfCauchy(0, 2) \\
\sigma &\sim HalfCauchy(0, 2) \\
\sigma_{ID} &\sim HalfCauchy(0, 2) \\
\sigma_\alpha &\sim HalfCauchy(0, 2) \\
\sigma_\beta &\sim HalfCauchy(0, 2) \\
R &\sim LKJcorr(2)
\end{aligned}
$$

Note. RV = response variable; session = testing day (1 = B1, 2 = A1, 3 = B2, 4 = M1, 5 = A4); sensitised = sensitisation status (1 = sensitised); amph = amphetamine administration (1 = amphetamine administered); noise = noise level (1 = high noise/variance); S = covariance matrix; R = correlation matrix.

D Appendix: Model Comparison & Results

D.1. Subjective & Physiological Measures

D.1.1. LOOICs & Bayes R^2

Note that we did not do extensive model comparison for subjective and physiological measures.

DEQ-items

Table D.1: LOOIC & Bayes R^2 of models for DEQ-items.

DEQ-item	LOOIC (SE)	Bayes R^2 (SE)
feel	158.68 (11.97)	0.40 (0.13)
high	166.60 (6.90)	0.63 (0.13)
like	158.30 (11.86)	0.72 (0.09)
more	142.75 (12.45)	0.39 (0.12)

Note. LOOIC = leave-one-out information criterion as calculated through LOO cross-validation procedure; SE = standard error

Heart rate & diastolic blood pressure

Table D.2: LOOIC & Bayes R^2 of models for heart rate and diastolic blood pressure.

DEQ-item	LOOIC (SE)	Bayes R^2 (SE)
HR	155.88 (6.98)	0.26 (0.25)
BP	135.17 (9.61)	0.19 (0.15)

Note. HR = heart rate; BP = diastolic blood pressure, LOOIC = leave-one-out information criterion as calculated through LOO cross-validation procedure; SE = standard error

D.1.2. Model Results

We only report population-level (constant effects that are shared across subjects). All chains converged ($\hat{R}$ = 1.00).

DEQ-item *feel*

Table D.3: Population-level effects of model for *feel* DEQ-item.

Model Formula			
feel ∼ *session + sensitised + amphetamine + (session | ID)*			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	0.71	[-1.61, 3.09]	1.00
sessionA2	-0.06	[-1.51, 1.38]	1.00
sessionA3	-0.60	[-1.96, 0.78]	1.00
sessionA4	-0.97	[-3.49, 1.69]	1.00
sensitised	0.45	[-2.20, 3.00]	1.00
amph_admin	1.15	[-1.15, 3.41]	1.00

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect; amph_admin = AMPH effect.

DEQ-item *high*

Table D.4: Population-level effects of model for *high* DEQ-item.

Model Formula			
high ∼ *session + sensitised + amphetamine + (session | ID)*			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	1.43	[-1.63, 3.07]	1.00
sessionA2	0.89	[-1.51, 1.43]	1.00
sessionA3	0.84	[-1.95, 0.80]	1.00
sessionA4	1.56	[-3.54, 1.61]	1.00
sensitised	1.58	[-2.13, 3.04]	1.00
amph_admin	1.40	[-1.16, 3.41]	1.00

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect; amph_admin = AMPH effect.

DEQ-item *like*

Table D.5: Population-level effects of model for *like* DEQ-item.

Model Formula			
like ∼ session + sensitised + amphetamine + (session | ID)			
β	**Estimate**	**95%**	$\hat{R}$
Intercept	1.43	[-1.63, 3.07]	1.00
sessionA2	0.89	[-1.51, 1.43]	1.00
sessionA3	0.84	[-1.95, 0.80]	1.00
sessionA4	1.56	[-3.54, 1.61]	1.00
sensitised	1.58	[-2.13, 3.04]	1.00
amph_admin	1.40	[-1.16, 3.41]	1.00

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect; amph_admin = AMPH effect.

DEQ-item *more*

Table D.6: Population-level effects of model for *more* DEQ-item.

Model Formula			
more ∼ session + sensitised + amphetamine + (session | ID)			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	1.73	[-0.23, 3.77]	1.00
sessionA2	-1.53	[-2.47, -0.54]	1.00
sessionA3	-1.64	[-2.58, -0.63]	1.00
sessionA4	-0.86	[-2.91, 1.20]	1.00
sensitised	0.18	[-1.96, 2.26]	1.00
amph_admin	0.60	[-1.38, 2.47]	1.00

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect; amph_admin = AMPH effect.

Heart rate

Table D.7: Population-level effects of model for heart rate.

Model Formula			
HR ∼ session + sensitised + amphetamine + (session | ID)			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	25.87	[17.08, 34.69]	1.00
sessionA4	-0.56	[-5.12, 4.08]	1.00
sensitised	0.66	[-4.15, 5.37]	1.00
amph_admin	0.44	[-4.45, 5.15]	1.00

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect; amph_admin = AMPH effect.

Diastolic blood pressure

Table D.8: Population-level effects of model for blood pressure.

Model Formula			
BP ∼ session + sensitised + amphetamine + (session | ID)			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	-5.22	[-11.17, 0.94]	1.00
sessionA4	0.81	[-3.46, 5.05]	1.00
sensitised	1.37	[-2.86, 5.48]	1.00
amph_admin	1.91	[-2.95, 6.71]	1.00

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect; amph_admin = AMPH effect.

D.2. Behavioural Data

D.2.1. Model Comparison Results

Results were reported for the "winning" model, which was the model with the best predictive performance (the lowest LOOIC). If several models had similar LOOICs (i.e. ΔLOOIC < 10 to the best performing model), results were reported for the model with the best explanatory performance (the highest Bayesian R^2).

Overall task performance

Table D.9: Model comparison with LOOIC & Bayes R^2, overall task performance.

Model	LOOIC (SE)	ΔLOOIC (SE)	Bayes R^2 (SE)
M5	-202.65 (10.67)	0 (0)	0.63 (0.05)
M6*	-201.37 (11.21)	1.28 (5.47)	0.65 (0.05)
M4	-200.44 (12.07)	2.21 (4.93)	0.55 (0.05)
M0	-160.50 (10.70)	42.15 (10.38)	0.17 (0.07)
M1	-153.80 (11.40)	48.85 (10.56)	0.22 (0.07)
M2	-152.55 (11.51)	50.10 (10.55)	0.23 (0.07)
M3	-151.53 (11.42)	51.12 (10.57)	0.24 (0.07)

Note. LOOIC = leave-one-out information criterion as calculated through LOO cross-validation procedure; ΔLOOIC = difference of model LOOICs to model with best LOOIC; SE = standard error.
* winning model

Overall updating behaviour

Table D.10: Model comparison with LOOIC & Bayes R^2, overall updating behaviour.

Model	LOOIC (SE)	ΔLOOIC (SE)	Bayes R^2 (SE)
M5	-43.77 (21.94)	0 (0)	0.84 (0.03)
M6*	-38.77 (22.99)	5.00 (2.07)	0.84 (0.03)
M4	-11.45 (22.57)	32.32 (21.25)	0.69 (0.04)
M0	-4.56 (21.73)	39.21 (19.77)	0.61 (0.05)
M1	-0.37 (20.39)	43.40 (17.90)	0.62 (0.04)
M3	1.24 (20.62)	45.01 (17.94)	0.63 (0.04)
M2	1.42 (20.61)	45.19 (17.80)	0.62 (0.04)

Note. LOOIC = leave-one-out information criterion as calculated through LOO cross-validation procedure; ΔLOOIC = difference of model LOOICs to model with best LOOIC; SE = standard error.
* winning model

Reversal detection score

Table D.11: Model comparison with LOOIC & Bayes R^2, reversal detection score.

Model	LOOIC (SE)	ΔLOOIC (SE)	Bayes R^2 (SE)
M1	-108.58 (10.20)	0 (0)	0.34 (0.09)
M2	-106.67 (9.83)	1.90 (2.50)	0.35 (0.09)
M0	-101.70 (13.94)	6.88 (7.27)	0.08 (0.07)
M3*	-100.52 (11.08)	8.06 (6.37)	0.37 (0.08)

Note. LOOIC = leave-one-out information criterion as calculated through LOO cross-validation procedure; ΔLOOIC = difference of model LOOICs to model with best LOOIC; SE = standard error.
* winning model

Number of trials to successful reversal

Table D.12: Model comparison with LOOIC & Bayes R^2, number of trials to successful reversal.

Model	LOOIC (SE)	ΔLOOIC (SE)	Bayes R^2 (SE)
M1	65.46 (12.51)	0 (0)	0.57 (0.08)
M4*	67.70 (11.44)	2.24 (5.82)	0.82 (0.08)
M2	67.84 (12.20)	2.38 (1.08)	0.57 (0.08)
M3	70.22 (11.81)	4.77 (3.35)	0.58 (0.08)
M0	90.26 (7.56)	24.80 (11.31)	0.07 (0.07)

Note. LOOIC = leave-one-out information criterion as calculated through LOO cross-validation procedure; ΔLOOIC = difference of model LOOICs to model with best LOOIC; SE = standard error.
* winning model

Number of consecutive *SD*/2-trials after successful reversal

Table D.13: Model comparison with LOOIC & Bayes R^2, number of consecutive $SD/2$-trials after successful reversal.

Model	LOOIC (SE)	ΔLOOIC (SE)	Bayes R^2 (SE)
M6*	135.54 (15.59)	0 (0)	0.74 (0.04)
M5	143.12 (16.73)	7.57 (7.41)	0.69 (0.04)
M4	145.29 (17.09)	9.75 (11.92)	0.61 (0.05)
M3	191.78 (16.54)	56.23 (11.69)	0.34 (0.07)
M2	192.18 (16.72)	56.63 (11.73)	0.33 (0.07)
M0	192.26 (18.36)	56.71 (13.28)	0.24 (0.08)
M1	193.99 (17.46)	58.44 (12.05)	0.31 (0.07)

Note. LOOIC = leave-one-out information criterion as calculated through LOO cross-validation procedure; ΔLOOIC = difference of model LOOICs to model with best LOOIC; SE = standard error.
* winning model

Updating behaviour after successful reversal

Table D.14: Model comparison with LOOIC & Bayes R^2, updating behaviour after successful reversal.

Model	LOOIC (SE)	ΔLOOIC (SE)	Bayes R^2 (SE)
M5	41.87 (15.72)	0 (0.00)	0.72 (0.04)
M6*	44.36 (15.96)	2.48 (5.26)	0.73 (0.04)
M4	56.08 (17.85)	14.21 (14.69)	0.59 (0.05)
M3	62.50 (17.48)	20.62 (13.29)	0.56 (0.05)
M0	62.56 (19.58)	20.69 (16.28)	0.50 (0.06)
M1	63.89 (17.53)	22.01 (13.29)	0.54 (0.05)
M2	65.74 (17.75)	23.87 (13.54)	0.54 (0.05)

Note. LOOIC = leave-one-out information criterion as calculated through LOO cross-validation procedure; ΔLOOIC = difference of model LOOICs to model with best LOOIC; SE = standard error.
* winning model

D.2.2. Results of "Winning" Models

Note that we only report population-level effects.

Model 6: overall task performance

Table D.15: Population-level effects of model 6, overall task performance.

Model Formula			
mean number of SD/2 trials ∼ session + sensitised + amphetamine + noise + noise:sensitised + noise:amphetamine + (session | ID)			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	0.32	[0.28, 0.36]	1.00
sessionA1	0.05	[-0.09, 0.20]	1.00
sessionB2	0.07	[-0.04, 0.17]	1.00
sessionM1	0.07	[-0.03, 0.17]	1.00
sessionA4	0.12	[-0.08, 0.31]	1.00
sensitised	-0.02	[-0.13, 0.08]	1.00
amph_admin	-0.05	[-0.20, 0.10]	1.00
noise	0.15	[0.12, 0.19]	1.00
sensitised:noise	-0.04	[-0.08, 0.01]	1.00
amph_admin:noise	-0.05	[-0.10, -0.01]	1.00
γ	**Estimate**	**95% CrI**	$\hat{R}$
sensitised+noise	-0.06	[-0.18, 0.07]	-
amph+noise	-0.10	[-0.28, 0.10]	-

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect when low noise; amph_admin = AMPH effect when low noise; sensitised:noise = interaction effect between sensitisation and noise; amph_admin:noise = interaction effect between sensitisation and noise; amph+noise = amphetamine effect when noisy; sensitised+noise = sensitisation effect when high noise.

Model 6: overall updating behaviour

Table D.16: Population-level effects of model 6, overall updating behaviour.

Model Formula			
mean update $\sim$ *session + sensitised + amphetamine + noise + noise:sensitised + noise:amphetamine + (session | ID)*			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	0.90	[0.75, 1.06]	1.00
sessionA1	0.11	[-0.15, 0.37]	1.00
sessionB2	0.29	[-0.09, 0.68]	1.00
sessionM1	0.22	[-0.14, 0.59]	1.00
sessionA4	0.50	[-0.01, 1.00]	1.00
sensitised	-0.32	[-0.69, 0.07]	1.00
amph_admin	-0.24	[-0.52, 0.04]	1.00
noise	-0.17	[-0.26, -0.08]	1.00
sensitised:noise	0.03	[-0.07, 0.14]	1.00
amph_admin:noise	-0.03	[-0.14, 0.08]	1.00
γ	**Estimate**	**95% CrI**	$\hat{R}$
sensitised+noise	-0.29	[-0.74, 0.16]	-
amph+noise	-0.26	[-0.59, 0.08]	-

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect when low noise; amph_admin = amphetamine effect when low noise; sensitised:noise = interaction effect between sensitisation and noise; amph_admin:noise = interaction effect between sensitisation and noise; amph+noise = amphetamine effect when noisy; sensitised+noise = sensitisation effect when high noise.

Model 4: reversal detection score

Table D.17: Population-level effects of model 4, reversal detection score.

Model Formula			
percentage of reversals detected ∼ session + sensitised + amphetamine + (session | ID)			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	0.89	[0.85, 0.93]	1.00
sessionA1	0.05	[-0.07, 0.17]	1.00
sessionB2	0.02	[-0.06, 0.11]	1.00
sessionM1	0.06	[-0.03, 0.15]	1.00
sessionA4	0.02	[-0.14, 0.19]	1.00
sensitised	-0.06	[-0.14, 0.02]	1.00
amph_admin	-0.06	[-0.19, 0.06]	1.00

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect; amph_admin = amphetamine effect.

Model 4: number of trials to successful reversal

Table D.18: Population-level effects of model 4, number of trials to successful reversal.

Model Formula			
mean number of trials to successful reversal ∼ session + sensitised + amphetamine + (session | ID)			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	3.66	[3.46, 3.84]	1.00
sessionA1	-0.72	[-1.71, 0.36]	1.00
sessionB2	-1.16	[-1.75, -0.56]	1.00
sessionM1	-0.95	[-1.59, -0.27]	1.00
sessionA4	-0.64	[-1.87, 0.65]	1.00
sensitised	0.00	[-0.60, 0.57]	1.00
amph_admin	-0.41	[-1.53, 0.66]	1.00

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect; amph_admin = amphetamine effect.

Model 6: number of consecutive *SD*/2-trials after successful reversal

Table D.19: Population-level effects of model 6, number of consecutive $SD/2$-trials after successful reversal.

Model Formula			
mean consecutive SD/2-trials after successful reversal ∼ session + sensitised + amphetamine + noise + noise:sensitised + noise:amphetamine + (session | ID)			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	0.41	[0.08, 0.75]	1.00
sessionA1	-0.27	[-1.02, 0.48]	1.00
sessionB2	-0.40	[-1.02, 0.24]	1.00
sessionM1	-0.11	[-0.75, 0.54]	1.00
sessionA4	-0.66	[-1.86, 0.54]	1.00
sensitised	0.40	[-0.26, 1.05]	1.00
amph_admin	0.33	[-0.47, 1.13]	1.00
noise	0.37	[0.14, 0.62]	1.00
sensitised:noise	0.58	[0.29, 0.88]	1.00
amph_admin:noise	0.22	[-0.06, 0.51]	1.00
γ	**Estimate**	**95% CrI**	$\hat{R}$
sensitised+noise	0.99	[0.16, 1.73]	-
amph+noise	0.56	[-0.41, 1.54]	-

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect when low noise; amph_admin = amphetamine effect when low noise; sensitised:noise = interaction effect between sensitisation and noise; amph_admin:noise = interaction effect between sensitisation and noise; amph+noise = amphetamine effect when noisy; sensitised+noise = sensitisation effect when high noise.

Model 6: updating behaviour after successful reversal

Table D.20: Population-level effects of model 6, updating behaviour after successful reversal.

Model Formula			
mean update after successful reversal ∼ session + sensitised + amphetamine + noise + noise:sensitised + noise:amphetamine + (session | ID)			
β	**Estimate**	**95% CrI**	$\hat{R}$
Intercept	1.07	[0.83, 1.32]	1.00
sessionA1	0.22	[-0.25, 0.68]	1.00
sessionB2	0.41	[-0.10, 0.92]	1.00
sessionM1	0.24	[-0.19, 0.67]	1.00
sessionA4	0.80	[0.04, 1.54]	1.00
sensitised	-0.51	[-0.96, -0.07]	1.00
amph_admin	-0.55	[-1.02, -0.05]	1.00
noise	-0.30	[-0.45, -0.16]	1.00
sensitised:noise	0.14	[-0.03, 0.31]	1.00
amph_admin:noise	0.13	[-0.05, 0.31]	1.00
γ	**Estimate**	**95% CrI**	$\hat{R}$
sensitised+noise	-0.37	[-0.89, 0.17]	-
amph+noise	-0.42	[-1.01, 0.19]	-

Note. CrI = credible interval of estimated mean from posterior distribution of parameter; $\hat{R}$ = potential scale reduction factor on split chains ($\hat{R}$ = 1 at convergence); sensitised = sensitisation effect when low noise; amph_admin = amphetamine effect when low noise; sensitised:noise = interaction effect between sensitisation and noise; amph_admin:noise = interaction effect between sensitisation and noise; amph+noise = amphetamine effect when noisy; sensitised+noise = sensitisation effect when high noise.

Bibliography

Anticevic, A., & Corlett, P. R. (2012). Cognition-emotion dysinteraction in schizophrenia. *Frontiers in psychology*, *3*, 392. doi: 10.3389/fpsyg.2012.00392

Berridge, K. C. (2012). From prediction error to incentive salience: mesolimbic computation of reward motivation. *The European journal of neuroscience*, *35*(7), 1124–1143. doi: 10.1111/j.1460-9568.2012.07990.x

Boileau, I., Dagher, A., Leyton, M., Gunn, R. N., Baker, G. B., Diksic, M., & Benkelfat, C. (2006). Modeling sensitization to stimulants in humans: an 11craclopride/pet study in healthy men. *Archives of general psychiatry*, *63*(12), 1386–1395. doi: 10.1001/archpsyc.63.12.1386

Bunzeck, N., & Düzel, E. (2006). Absolute coding of stimulus novelty in the human substantia nigra/vta. *Neuron*, *51*(3), 369–379. doi: 10.1016/j.neuron.2006.06.021

Bürkner, P.-C. (2017). brms : An r package for bayesian multilevel models using stan. *Journal of Statistical Software*, *80*(1). doi: 10.18637/jss.v080.i01

Clark, A. (2013). Whatever next? predictive brains, situated agents, and the future of cognitive science. *The Behavioral and brain sciences*, *36*(3), 181–204. doi: 10.1017/S0140525X12000477

Cole, D. M., Diaconescu, A. O., Pfeiffer, U. J., Brodersen, K. H., Mathys, C. D., Julkowski, D., … Stephan, K. E. (2020). Atypical processing of uncertainty in individuals at risk for psychosis. *NeuroImage. Clinical*, *26*, 102239. doi: 10.1016/j.nicl.2020.102239

Corlett, P. R., Honey, G. D., & Fletcher, P. C. (2007). From prediction error to psychosis: ketamine as a pharmacological model of delusions. *Journal of psychopharmacology (Oxford, England)*, *21*(3), 238–252. doi: 10.1177/0269881107077716

Deserno, L., Boehme, R., Mathys, C., Katthagen, T., Kaminski, J., Stephan, K. E., … Schlagenhauf, F. (2020). Volatility estimates increase choice switching and relate to prefrontal activity in schizophrenia. *Biological psychiatry. Cognitive neuroscience and neuroimaging*, *5*(2), 173–183. doi: 10.1016/j.bpsc.2019.10.007

Deserno, L., Schlagenhauf, F., & Heinz, A. (2016). Striatal dopamine, reward, and decision making in schizophrenia. *Dialogues in clinical neuroscience*, *18*(1), 77–89.

Diaconescu, A. O., Jensen, J., Wang, H., Willeit, M., Menon, M., Kapur, S., & McIntosh, A. R. (2011). Aberrant effective connectivity in schizophrenia patients during appetitive conditioning. *Frontiers in human neuroscience*, *4*, 239. doi: 10.3389/fnhum.2010.00239

Feeney, E. J., Groman, S. M., Taylor, J. R., & Corlett, P. R. (2017). Explaining delusions: Reducing uncertainty through basic and computational neuroscience. *Schizophrenia bulletin*, *43*(2), 263–272. doi: 10.1093/schbul/sbw194

Green, M. F., & Harvey, P. D. (2014). Cognition in schizophrenia: Past, present, and future. *Schizophrenia research. Cognition*, *1*(1), e1-e9. doi: 10.1016/j.scog.2014.02.001

Griffin, J. D., & Fletcher, P. C. (2017). Predictive processing, source monitoring, and psychosis. *Annual review of clinical psychology*, *13*, 265–289. doi: 10.1146/annurev-clinpsy-032816-045145

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *35*(1), 4–26. doi: 10.1038/npp.2009.129

Haralanova, E., Haralanov, S., Beraldi, A., Möller, H.-J., & Hennig-Fast, K. (2012). Subjective emotional over-arousal to neutral social scenes in paranoid schizophrenia. *European archives of psychiatry and clinical neuroscience*, *262*(1), 59–68. doi: 10.1007/s00406-011-0227-1

Holt, D. J., Titone, D., Long, L. S., Goff, D. C., Cather, C., Rauch, S. L., … Kuperberg, G. R. (2006). The misattribution of salience in delusional patients with schizophrenia. *Schizophrenia research*, *83*(2-3), 247–256. doi: 10.1016/j.schres.2005.12.858

Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., & Kapur, S. (2012). The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Archives of general psychiatry*, *69*(8), 776–786. doi: 10.1001/archgenpsychiatry.2012.169

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version iii–the final common pathway. *Schizophrenia bulletin*, *35*(3), 549–562. doi: 10.1093/schbul/sbp006

Howes, O. D., McCutcheon, R., Owen, M. J., & Murray, R. M. (2017). The role of genes, stress, and dopamine in the development of schizophrenia. *Biological psychiatry*, *81*(1), 9–20. doi: 10.1016/j.biopsych.2016.07.014

Jensen, J., Willeit, M., Zipursky, R. B., Savina, I., Smith, A. J., Menon, M., … Kapur, S.

(2008). The formation of abnormal associations in schizophrenia: neural and behavioral evidence. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *33*(3), 473–479. doi: 10.1038/sj.npp.1301437

Jozefowiez, J. (2012). Neuropsychology of learning. In N. M. Seel (Ed.), *Encyclopedia of the sciences of learning* (pp. 2459–2468). New York: Springer.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *The American journal of psychiatry*, *160*(1), 13–23. doi: 10.1176/appi.ajp.160.1.13

Knutson, B., Adams, C., Fong, G., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience*, *21*, RC159:5.

Maia, T. V., & Frank, M. J. (2017). An integrative perspective on the role of dopamine in schizophrenia. *Biological psychiatry*, *81*(1), 52–66. doi: 10.1016/j.biopsych.2016.05.021

Mathys, C. D., Lomakina, E. I., Daunizeau, J., Iglesias, S., Brodersen, K. H., Friston, K. J., & Stephan, K. E. (2014). Uncertainty in perception and the hierarchical gaussian filter. *Frontiers in human neuroscience*, *8*, 825. doi: 10.3389/fnhum.2014.00825

McElreath, R. (2020). *Statistical rethinking: A bayesian course with examples in r and stan* (Second edition ed.).

Modinos, G., Allen, P., Zugman, A., Dima, D., Azis, M., Samson, C., … McGuire, P. (2020). Neural circuitry of novelty salience processing in psychosis risk: Association with clinical outcome. *Schizophrenia bulletin*, *46*(3), 670–679. doi: 10.1093/schbul/sbz089

Morean, M. E., de Wit, H., King, A. C., Sofuoglu, M., Rueger, S. Y., & O'Malley, S. S. (2013). The drug effects questionnaire: psychometric support across three drug types. *Psychopharmacology*, *227*(1), 177–192. doi: 10.1007/s00213-012-2954-z

Murray, G. K., Corlett, P. R., Clark, L., Pessiglione, M., Blackwell, A. D., Honey, G., … Fletcher, P. C. (2008). Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Molecular psychiatry*, *13*(3), 239, 267-76. doi: 10.1038/sj.mp.4002058

Nalborczyk, L., Batailler, C., Loevenbruck, H., Vilain, A., & Bürkner, P.-C. (2017). *An introduction to bayesian multilevel models using brms: A case study of gender effects on vowel variability in standard indonesian.* Open Science Framework. doi: 10.17605/OSF.IO/DPZCB

Nassar, M. R., Wilson, R. C., Heasly, B., & Gold, J. I. (2010). An approximately bayesian delta-rule model explains the dynamics of belief updating in a changing environment. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *30*(37), 12366–12378. doi: 10.1523/JNEUROSCI.0822-10.2010

Nicholls, M. E. R., Thomas, N. A., Loetscher, T., & Grimshaw, G. M. (2013). The flinders handedness survey (flanders): a brief measure of skilled hand preference. *Cortex; a journal devoted to the study of the nervous system and behavior*, *49*(10), 2914–2926. doi: 10.1016/j.cortex.2013.02.002

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human brain mapping*, *15*(1), 1–25. doi: 10 .1002/hbm.1058

Nour, M. M., Dahoun, T., Schwartenbeck, P., Adams, R. A., FitzGerald, T. H. B., Coello, C., … Howes, O. D. (2018). Dopaminergic basis for signaling belief updates, but not surprise, and the link to paranoia. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(43), E10167-E10176. doi: 10.1073/pnas.1809298115

O'Daly, O. G., Joyce, D., Stephan, K. E., Murray, R. M., & Shergill, S. S. (2011). Functional magnetic resonance imaging investigation of the amphetamine sensitization model of schizophrenia in healthy male volunteers. *Archives of general psychiatry*, *68*(6), 545–554. doi: 10.1001/archgenpsychiatry.2011.3

O'Daly, O. G., Joyce, D., Tracy, D. K., Azim, A., Stephan, K. E., Murray, R. M., & Shergill, S. S. (2014). Amphetamine sensitization alters reward processing in the human striatum and amygdala. *PloS one*, *9*(4), e93955. doi: 10.1371/journal.pone.0093955

O'Daly, O. G., Joyce, D., Tracy, D. K., Stephan, K. E., Murray, R. M., & Shergill, S. (2014). Amphetamine sensitisation and memory in healthy human volunteers: a functional magnetic resonance imaging study. *Journal of psychopharmacology (Oxford, England)*, *28*(9), 857–865. doi: 10.1177/0269881114527360

Rich-Edwards, J. W., Kaiser, U. B., Chen, G. L., Manson, J. E., & Goldstein, J. M. (2018). Sex and gender differences research design for basic, clinical, and population studies: Essentials for investigators. *Endocrine reviews*, *39*(4), 424–439. doi: 10.1210/er.2017 -00246

Roiser, J. P., Howes, O. D., Chaddock, C. A., Joyce, E. M., & McGuire, P. (2013). Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis.

Schizophrenia bulletin, *39*(6), 1328–1336. doi: 10.1093/schbul/sbs147

Roiser, J. P., Stephan, K. E., den Ouden, H. E. M., Barnes, T. R. E., Friston, K. J., & Joyce, E. M. (2009). Do patients with schizophrenia exhibit aberrant salience? *Psychological medicine*, *39*(2), 199–209. doi: 10.1017/S0033291708003863

Romaniuk, L., Honey, G. D., King, J. R. L., Whalley, H. C., McIntosh, A. M., Levita, L., … Hall, J. (2010). Midbrain activation during pavlovian conditioning and delusional symptoms in schizophrenia. *Archives of general psychiatry*, *67*(12), 1246–1254. doi: 10.1001/archgenpsychiatry.2010.169

Schlagenhauf, F., Huys, Q. J. M., Deserno, L., Rapp, M. A., Beck, A., Heinze, H.-J., … Heinz, A. (2014). Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. *NeuroImage*, *89*, 171–180. doi: 10.1016/j.neuroimage.2013.11.034

Schlagenhauf, F., Rapp, M. A., Huys, Q. J. M., Beck, A., Wüstenberg, T., Deserno, L., … Heinz, A. (2013). Ventral striatal prediction error signaling is associated with dopamine synthesis capacity and fluid intelligence. *Human brain mapping*, *34*(6), 1490–1499. doi: 10.1002/hbm.22000

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of neurophysiology*, *80*(1), 1–27. doi: 10.1152/jn.1998.80.1.1

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The mini-international neuropsychiatric interview (m.i.n.i.): the development and validation of a structured diagnostic psychiatric interview for dsm-iv and icd-10. *The Journal of clinical psychiatry*, *59 Suppl 20*, 22-33;quiz 34-57.

Sims, A. (2017). The problems with prediction: Philosophy and predictive processing. doi: 10.15502/9783958573246

Strauss, G. P., Waltz, J. A., & Gold, J. M. (2014). A review of reward processing and motivational impairment in schizophrenia. *Schizophrenia bulletin*, *40 Suppl 2*, S107-16. doi: 10.1093/schbul/sbt197

Sun, J., Walker, A. J., Dean, B., van den Buuse, M., & Gogos, A. (2016). Progesterone: The neglected hormone in schizophrenia? a focus on progesterone-dopamine interactions. *Psychoneuroendocrinology*, *74*, 126–140. doi: 10.1016/j.psyneuen.2016.08.019

Taylor, S. F., Phan, K. L., Britton, J. C., & Liberzon, I. (2005). Neural response to emotional salience in schizophrenia. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *30*(5), 984–995. doi: 10.1038/sj.npp.1300679

Turi, Z., Bjørkedal, E., Gunkel, L., Antal, A., Paulus, W., & Mittner, M. (2018). Evidence for cognitive placebo and nocebo effects in healthy individuals. *Scientific reports*, *8*(1), 17443. doi: 10.1038/s41598-018-35124-w

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological medicine*, *39*(2), 179–195. doi: 10.1017/S0033291708003814

Waltz, J. A., & Gold, J. M. (2007). Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. *Schizophrenia research*, *93*(1-3), 296–303. doi: 10.1016/j.schres.2007.03.010

Weidenauer, A., Bauer, M., Sauerzopf, U., Bartova, L., Nics, L., Pfaff, S., … Willeit, M. (2020). On the relationship of first-episode psychosis to the amphetamine-sensitized state: a dopamine d2/3 receptor agonist radioligand study. *Translational psychiatry*, *10*(1), 2. doi: 10.1038/s41398-019-0681-5

Weidenauer, A., Bauer, M., Sauerzopf, U., Bartova, L., Praschak-Rieder, N., Sitte, H. H., … Willeit, M. (2017). Making sense of: Sensitization in schizophrenia. *The international journal of neuropsychopharmacology*, *20*(1), 1–10. doi: 10.1093/ijnp/pyw081

Winton-Brown, T. T., Fusar-Poli, P., Ungless, M. A., & Howes, O. D. (2014). Dopaminergic basis of salience dysregulation in psychosis. *Trends in neurosciences*, *37*(2), 85–94. doi: 10.1016/j.tins.2013.11.003

Winton-Brown, T. T., Schmidt, A., Roiser, J. P., Howes, O. D., Egerton, A., Fusar-Poli, P., … McGuire, P. (2017). Altered activation and connectivity in a hippocampal-basal ganglia-midbrain circuit during salience processing in subjects at ultra high risk for psychosis. *Translational psychiatry*, *7*(10), e1245. doi: 10.1038/tp.2017.174

Wise, R. A. (2004). Dopamine, learning and motivation. *Nature reviews. Neuroscience*, *5*(6), 483–494. doi: 10.1038/nrn1406