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„The Effects of Amphetamine-induced Sensitization and its Relation to Stress, Reward Processing and Decision Making "

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1 Abstract

The triggering and relapse of psychosis in schizophrenia is thought to occur as an etiologic consequence of a hyperresponsive dopaminergic system, resulting in aberrant reward and salience processing as well as a pathologic response to common life stressors. Using a double blind placebo controlled study design, we examined the effect of an amphetamine sensitization regimen, modelling the hyperdopaminergic state found in psychotic individuals on the mean prediction error in a reward based predictive inference task. We further evaluated the effects of acute amphetamine administration, as well as exposure to a minor psychosocial stressor on sensitized healthy male participants (N=9). Using fMRI, we also tested for neural differences resulting from our sensitization manipulation. Additionally, we evaluated how their subjective drug experience as well as physiological measures, such as heart rate and blood pressure were affected by the participants hyperresponsive dopamine system, as a consequence of the amphetamine sensitization regimen. Our results point towards a negative effect of sensitization on the mean prediction error, resulting in increased task performance but were also associated with large uncertainty. Stress and acute amphetamine administration appeared to result in a positive effect on the mean prediction error resulting in worse performance but were also associated with uncertainty. Heart rate did not appear to be affected by our sensitization regimen, while blood pressure showed an effect indicating a small increase in diastolic blood pressure. We found no significant neural differences pre- and post-sensitization in our subjects.

2 Introduction

Mental disorders called psychoses, affect the people suffering from it through severe disturbances in perception, emotional expression, social relationships, and motor behavior as well as a severely distorted view of reality (Meyer, 2019). The most commonly associated syndrome with psychosis is schizophrenia. People suffering from schizophrenia demonstrate a wide variety of symptoms such as hearing voices that don't exist, unrealistic ideas and beliefs and impaired communication (Meyer, 2019). While the symptoms of schizophrenia can usually be well controlled through antipsychotic medication, approximately 30% of the people suffering from schizophrenia will spend a significant portion of their lives in psychiatric hospitals, where they account for a majority of the total hospitalization (Meyer, 2019). Scientists investigation the

etiology of schizophrenia found genetic variables, exposure to stress, and abnormal dopaminergic salience processing to be some of the major underlying factors (Howes & Kapur, 2009). However, the precise nature of the interaction of these factors is a complex topic whose answers need to rely on multidisciplinary and multimethodological approaches, one of which was used in this thesis.

2.1 Schizophrenia and Psychosis

Schizophrenia is a complex, chronic mental disorder that requires the presence of psychosis as a defining feature. Psychosis itself is a syndrome which entails a mixture of various symptoms. At the most fundamental level psychosis describes delusions and hallucinations. However, psychosis commonly includes disorganized speech, disorganized behavior, and gross distortions of reality (Stahl, 2008). As a consequence, psychosis can be understood as a group of symptoms that impair a person's mental capacity, affective response, their ability to recognize reality and their capacity to relate to and communicate with others. Psychosis is usually associated with motor disturbances and perceptual distortions, such as hallucinatory voices causing the patients distress (Stahl, 2008). The patients report voices that accuse, blame, or threaten them. Other perceptual distortions include hallucinations of vision, touch taste or odor. Perceptual distortions also often cause the patients to report that familiar things and people appear differently. Peculiar physical behavior in psychotic patients stems from motor disturbances, which display themselves as odd positions, overt signs of tension, inappropriate facial expressions, repetition of peculiar gestures as well as talking, muttering, or mumbling to themselves (Stahl, 2008). The psychotic symptoms of schizophrenia are referred to as the positive symptoms of the disorder because they indicate an excess of function. These positive symptoms are the target of antipsychotic drug treatments (Stahl, 2008). Schizophrenic patients also display a variety of negative symptoms that denote a reduction compared to their normal functioning. Common negative symptoms are blunted affect, apathetic social withdrawal, anhedonia, emotional withdrawal, and attentional impairment. The severity of the negative symptoms is associated with poor social functioning and long periods of hospitalization (Stahl, 2008).

2.2 Dopamine in schizophrenia and psychosis

Dysfunctional dopamine processing has long been established as a key factor in schizophrenia and psychosis. The most widely accepted theory of schizophrenia has already been established

over four decades ago and is called the dopamine hypothesis of schizophrenia (Howes et al., 2017). It originated as a result of two major findings. First, clinical studies were able to establish that dopaminergic agonists and stimulants could worsen psychotic symptoms in patients with schizophrenia (Howes & Kapur, 2009). Second, was the discovery that antipsychotic drugs affect the dopamine system, specifically through their affinity for the dopamine d2 receptor (Howes et al., 2017).

Since then research has been able to identify specific regions in which dopamine levels differ in schizophrenic patients compared to the healthy population (Howes & Kapur, 2009). Dopamine concentrations are usually regulated through tonic and phasic activation of dopaminergic neuron. Baseline dopamine levels are regulated by tonic activation while phasic activation regulates brief spikes of dopamine levels. These mechanisms have been found to be dysregulated in psychosis (Maia & Frank, 2017). Among the dysregulated regions are three dopaminergic pathways in the brain, the mesolimbic dopamine pathway, the mesocortical dopamine pathway and the nigrostriatal dopamine pathway. The mesolimbic pathway projects from dopaminergic cell bodies in the ventral tegmental area of the brainstem to axon terminals in the nucleus accumbens and the ventral striatum (Advokat et al., 2014). This pathway plays an important role in regulating behavior as it is particularly important for motivation, pleasure, and reward (Stahl, 2008). It is believed that dopaminergic hyperactivity in the mesolimbic pathway mediates the positive symptoms of psychosis regardless of whether the psychosis results from schizophrenia or is possibly drug induced (Stahl, 2008). While the causes of mesolimbic dopamine hyperactivity have not been clearly identified, current theories assume that its results as a downstream consequence of dysfunctional glutamate activity in the prefrontal cortex and the hippocampus (Stahl, 2008). The mesocortical dopamine pathway also begins from cell bodies in the ventral tegmental area but it extends to the prefrontal cortex where it branches to the dorsolateral prefrontal cortex and the ventromedial prefrontal cortex (Julien et al., 2011). It is thought that the dorsolateral branch of this pathway regulates cognition and executive function while the ventromedial branch is involved in the regulation of emotion and affect (Stahl, 2008). Unlike the mesolimbic pathway, studies have identified a reduction of dopaminergic activity in this pathway for patients of schizophrenia and psychosis (Stahl, 2008). It is believed that dopaminergic hypoactivity in this pathway may be responsible for the cognitive and negative symptoms displayed by psychotic patients. The nigrostriatal dopamine pathway projects from the

substantia nigra to the striatum and is part of the extrapyramidal nervous system and plays a key role in the regulation of movements (Stahl, 2008). Dysregulated dopamine in this pathway results in a variety of movement disorders such as chorea, dyskinesias, and tics (Stahl, 2008).

2.3 Dopamine and psychosocial stress in the etiology of schizophrenia

Dopaminergic dysregulation, however, does not seem to begin with the onset of psychosis. Research has been able to show that clinical high risk (CHR) individuals that progress to psychosis displayed elevated dopamine synthesis capacity that was positively associated with the severity of their prodromal-type symptoms (Howes et al., 2009). Their dopamine synthesis capacity also increased as they progressed into acute psychosis. However, unlike in schizophrenia, the CHR showed no differences in baseline synaptic dopamine levels compared to healthy controls. However, following dopamine depletion CHR reported symptomatic improvements (Bloemen et al., 2013).

These findings lead to the conclusion that dopaminergic functioning is already dysregulated in prodromal type individuals that progress to schizophrenia, but not as strongly as in patients suffering from schizophrenia. Therefore, it seems likely that an initial dysregulation continually increases from prodrome to psychosis (Howes et al., 2012).

Psychosocial stress is another factor that increases the risk of schizophrenia since acute stress seems to trigger psychotic symptoms (Day et al., 1987) and impaired stress tolerance is associated with prodromal symptoms (Reininghaus et al., 2016). The effects of chronic stress on the dopamine system seem to vary depending on the precise region as well as the nature of the stress. In the animal model chronic exposure to stress led to reduced baseline levels of dopamine in frontal areas but an increased activity in response to acute stress (Howes et al., 2017). Another study investigating healthy individuals has also been able to show a positive connection between childhood adversity and cortical dopamine release in response to a stress task (Oswald et al., 2014). Regarding the striatal areas, greater dopamine release has been observed in response to acute social stress in CHR and patients suffering from schizophrenia (Soliman et al., 2008).

The diathesis-stress model of schizophrenia suggests that the disorder develops because of an exposure to stress that acts on a pre-existing vulnerability such as genetic factors or early environmental insults. Genetic studies enable an identification of potential molecular

mechanisms underlying the disorder. “A recent systematic pathway analysis of the psychiatric Genomics Consortium’s enlarged sample (PGC2) identified the top pathway for genes associated with schizophrenia to be for the dopaminergic synapse” (Howes et al., 2017).

A study by Mizrahi et al. (2012) investigated the neural events that result in an exaggerated response to external stressors. A considered mechanism for this stress increased neural activation is a sensitization of the mesolimbic dopamine system through a continuous exposure to external stressors (Mizrahi et al., 2012). In line with this animal model it has been shown that a repeated exposure to stressors leads to reduced cortical baseline dopamine activity and sensitization of the mesolimbic system (Hollon et al., 2015). A sensitized dopamine system is thought to be hyperresponsive to external stimuli and responds with excessive levels of dopamine release even to stressors that would result in a moderate stress response under normal circumstances (Mizrahi et al., 2012). In a PET study they compared the stress induced dopamine release of 12 clinical high risk, 10 antipsychotic-naïve subjects with schizophrenia, and 12 healthy subjects. Stress was induced using a validated psychosocial stress task, the Montreal Imaging Stress Task (MIST). They found the clinical high risk group and the schizophrenia group to show an increased stress response in the associative compared to the healthy subjects, revealing a sensitized dopaminergic response to stress in CHR and schizophrenic patients (Mizrahi et al., 2012). This suggests how a continuous exposure to stress could act upon a genetic vulnerability in the dopamine system of schizophrenic patients and sensitize their dopamine system to react with an exaggerated response. In accordance with this idea of an endogenous dopamine sensitization resulting in an increased stress response a recent longitudinal study has been able to show an age effect of cortisol in CHR in which their cortisol levels increase throughout the adolescent/early adult years (Walker et al., 2013).

In the set of genes that are associated with schizophrenia, however, are not only those that affect dopamine receptors. Both Glutamate receptor subtypes AMPA and NMDA are included as well (Howes et al., 2017). Another analysis that focused on a set of 11 genes, that relate to dopamine transmission directly, found an association with single nucleotide polymorphisms (SNP) in the vicinity of the gene DRD2 (Howes et al., 2017) which codes for the dopamine receptor d2. This finding is relevant to the understanding of the role of dopaminergic neurotransmission in the disorder and the identification of potential mechanisms. It is however also possible that the SNP

at DRD2 modulates the function of another gene either in cis or trans direction of DRD2 itself (Howes et al., 2017). It is suggested that further research needs to investigate how and at what developmental stage this association of the SNP at DRD2 with schizophrenia might play an etiologic role for the dopamine dysfunction observed in patients with schizophrenia.

Interactions between genes and psychosocial risk factors have also been shown to be relevant for the development of schizophrenia. Specifically, genes that may mediate the relationship between stress exposure, dopaminergic function, and psychosis. Catechol-O-methyl-transferase (COMT) for example is a dopamine catabolic enzyme that is located in one of the strongest identified genetic risk factors for schizophrenia (Bassett & Chow, 2008). COMT contains a functional polymorphism in which the amino acids valine (val) and methionine (met) can be substituted. A study investigating stress induced cortical dopamine release found the met allele to be associated with reduced dopamine release and a greater subjective stress response (Howes et al., 2017). Another functional val met polymorphism in brain derived neurotrophic factor has also been investigated. Met carriers of this polymorphism have shown greater striatal dopamine release in response to a pain stressor than carriers of the Val allele (Peciña et al., 2014). DISC1 (disrupted in schizophrenia 1) is one of the best studied loci linked to an increased risk of schizophrenia. Animal models of this locus have shown that alterations in DISC1 can lead to impaired development of mesocortical dopaminergic neurons (Howes et al., 2017). Further, adolescent stress induced by isolation in the animal model has been shown to only lead to behavioral abnormalities in mice with mutations in DISC1 (Howes et al., 2017).

These findings together identify an increase in striatal dopamine synthesis and release as the main source of dopaminergic dysfunction in schizophrenia. This dysfunction is also present in the prodrome and therefore, together with stress, the mediating effects of genes and environmental factors, plays a causal role in the development of psychosis.

2.4 Dopamine and reward processing

A mechanism through which dopaminergic dysregulation results in the symptoms commonly shown by psychotic individuals is theorized to stem from dopamine's role in reward processing (Strauss et al., 2014). Reward as a concept came from early theories of associative learning, namely conditioning. Pavlovian conditioning involves connecting a conditioned stimulus that is associated with a reward with a neutral unconditioned stimulus (Berridge, 2012). Instrumental

conditioning happens between an action and its consequence in the environment (Wise, 2004). Rewards as they are understood in conditioning correspond to external factors that initiate reward-seeking-behavior (Wise, 2004). In reward processing, however it describes the subjectively ascribed value of objects or internal states that motivate goal-directed behavior (Winton-Brown et al., 2014).

The role of dopamine in reward processing has been studied in a series of animal studies using classic reward based learning tasks. It was found that dopaminergic neurons were sensitive to the unexpected absence or presence of rewards (Schultz, 1998). These dopaminergic responses have been interpreted as reward prediction errors. These dopaminergic responses appear whenever a predicted outcome does not match the actual outcome in the organisms environment (Schultz, 1998). The prediction error signal is hypothesized to serve as a global learning signal, propagating to other reward-processing brain regions through which it would facilitate decision-making and learning. Subsequent studies with human subjects have been able to confirm behavioral, 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 et al., 2014). A useful framework for understanding how aberrant dopaminergic prediction error signaling leads to the positive symptoms of psychosis such as hallucinations is the predictive processing framework. Predictive processing, also called predictive coding describes groups of models that view the brain as an organ of predictive inference (Griffin & Fletcher, 2017). Theories in the predictive processing framework postulate that the brain constantly matches incoming sensory inputs with prior top-down predictions (Clark, 2013). The discrepancy between the top-down prediction and the sensory input is thought to send a signal throughout the brain, which in turn results in an adjustment of future predictions. Future predictions should then in turn lead to a lower discrepancy between the predicted and the actual sensory input (Clark, 2013). In order to make such predictions, however the brain needs to be able to make associations. In simple associative learning models such as the Rescorla Wagner Model this is done by error minimization (Griffin & Fletcher, 2017). However, since the world is not static simply trying to minimize the prediction error is not enough as there are conditions under which a model should not be updated despite an inaccurate prediction. Accordingly, such a model needs to tolerate inaccuracy, which in turn makes the model less sensitive. A less sensitive model on the other hand might cause problems in in making efficient adjustments to

environmental volatility. The model needs to find a way to discern situations in which it needs to maintain expectations, when to update them or when to generalize them in order to maximize its predictive accuracy.

Dopaminergic neurons in the midbrain region have not only been found to signal the strength of the prediction error (Schultz, 1998), but also to be involved in signaling the precision (Fiorillo et al., 2003) as well as the quantity of meaningful information of incoming stimuli that cause shifts in belief (Schwartenbeck et al., 2016). These functions serve the brain to model the regularities of its environment as sensitively as possible and reduce the possibility of premature and unnecessary updating (Griffin & Fletcher, 2017). In such a model aberrant dopaminergic processing would then lead to disrupted prediction error processing. Research comparing healthy subjects to subjects with delusional beliefs indeed has been able to identify frontal cortical responses indicating disrupted prediction error processing in delusional subjects (Corlett et al., 2007). Furthermore, it was found that the extent of the disruption was significantly linked to the individuals propensity to form delusional beliefs (Corlett et al., 2007).

2.5 Dopamine and Salience processing in psychosis

Aside from the prediction error, dopamine has also been suggested to be involved in the processing of the incentive salience of stimuli (Robinson, 1993). In order for humans to operate in complex changing surroundings they must identify stimuli and select how to respond to them. The vast amount of perceptual input stands opposed to limited cognitive and motor resources of the individual. Allocating these resources requires attention, filtering, sensory and behavioral orientation, motivation, action selection, and execution (Winton-Brown et al., 2014). Stimuli are selected based on their saliency; their features are compared to the context they appear in. Salient stimuli can be largely independent of the organism's internal state, such as loud bangs that naturally draw attention to themselves. Most salience processing however happens internally. The features of the stimulus interact with the individuals' internal factors such as goals, beliefs and history to determine the most salient stimulus for the individual in its current time and place (Winton-Brown et al., 2014).

Dopamine has been linked to salience processing in a number of studies. There is evidence from a study using PET and MRI measures that found associations between dopamine synthesis capacity and greater salience network connectivity, while also showing dopamine release

capacity to be linked to weaker salience network connectivity (McCutcheon et al., 2019). Novelty has been conceptualized as an important factor in salience processing (Bunzeck & Düzel, 2006). Studies have been able to establish that novel stimuli are associated with fMRI activations in the dopaminergic midbrain (Bunzeck & Düzel, 2006) and also improve memory formation (Schott et al., 2004; Winton-Brown et al., 2014; Wittmann et al., 2007). Furthermore, emotional stimuli that are also highly salient for humans and their processing have also been observed to be modulated by presynaptic dopaminergic function in the midbrain (Jabbi et al., 2013). While it has been attempted to fit these observations into a reward framework, more recent animal research points towards functionally distinct subgroups of dopaminergic neurons that may code for either salience or reward prediction errors (Winton-Brown et al., 2014).

But then how does altered dopaminergic salience and prediction error processing lead to delusions and hallucinations? In healthy individuals, dopamine mediates the process of salience acquisition and expression, but it does not create the process. In psychosis however, dysregulated dopamine transmission leads to stimulus independent release of dopamine (Kapur, 2003). In the psychotic individual their normal process of contextually driven salience is taken over by aberrant assignment of salience to external objects and internal representations (Kapur, 2003). In this framework the psychotic individual develops delusions as a top-down cognitive explanation for their experiences of aberrant salience in order to understand their misattributed salience (Kapur, 2003). Delusions and hallucinations are the result of the individuals' own explanations for his experiences of aberrant salience that emerge over time. These explanations stem from the individual and are therefore largely affected by their social, cultural, and personal background. This offers an explanation for how dopaminergic dysfunction can result in the wide variety of different clinical manifestations of psychosis that can be observed in different cultures and individuals (Howes & Kapur, 2009).

2.6 Amphetamines

Amphetamine is the parent compound of a family of synthetic psychostimulants that are derived from the beta-phenylethylamine (phenethylamine) core structure (Carvalho et al., 2012). In Amphetamine a hydrogen on the alpha carbon of phenethylamine is replaced with a methyl group giving it its name, alpha-methyl-phenethylamine. It exists in two Isomers, the less potent levoamphetamine (l-amphetamine) and the three to four times more potent dextroamphetamine

(d-amphetamine) (Advokat et al., 2014). Amphetamine is structurally related to Dopamine whose chemical name is dihydroxy-phenethylamine. Amphetamine produces a variety of effects on both the central nervous system (CNS) as well as the autonomous nervous system (ANS). Amphetamine is also called a sympathomimetic agent because it mimics the actions of Adrenaline (Epinephrine) which also belongs to the substituted phenethylamines. As such amphetamine produces symptoms of the normal alerting response such as vasoconstriction, tachycardia and hypertension (Julien et al., 2011). Historically Amphetamine has been used as a treatment for a variety of medical issues such as obesity and Parkinsons disorder (Seiden et al., 1993), however, today it is mostly used for the treatment of Attention-Deficit-Hyperactivity-Disorder (ADHD) and Narcolepsy (Meyer, 2019).

2.7 Effects

Pharmacological response to amphetamine varies with dose and route of administration. Generally, the effects produced by amphetamine can be categorized as effects produced by low to moderate doses (2.5-20mg d-amphetamine), moderate doses (20-50mg d-amphetamine) and high doses (>50mg d-amphetamine) (Advokat et al., 2014). Low doses increase blood pressure, heart rate, relax bronchial muscle and produce further responses from the bodies alerting response (Advokat et al., 2014). In the CNS amphetamine acts as a strong stimulant and produces a variety of subjective effects such as alertness, euphoria, excitement, wakefulness, reduction of fatigue and loss of appetite. It also produces an increase in mood, motor and speech activity and a feeling of power (Julien et al., 2011). It is also notable that some of the subjective effects produced by amphetamine such as euphoria and arousal are related to the users personality traits like impulsivity (Kirkpatrick et al., 2013). Moderate doses of amphetamine induce additional effects such as stimulation of respiration, tremors, restlessness, as well as a further increase in motor activity, insomnia, and agitation. As dosage increases further the previous reactions increase in intensity and can be accompanied by de novo production of anxiety disorders, obsessive behaviors, panic disorders, paranoia leading up to possible paranoid psychosis (Bramness et al., 2012).

2.8 Pharmacodynamics

Due to its structural similarity to the monoamine neurotransmitters amphetamine works as an indirect agonist of the catecholaminergic system (Meyer, 2019). Amphetamine stimulates both

the alpha and beta noradrenergic receptors in the body and brain (Urman-Yotam & Ostacher, 2014). Amphetamine increases dopamine in the synaptic cleft through several related mechanisms. Firstly, amphetamine interacts with the dopamine transporter (DAT), inhibiting it and thereby blocking the reuptake of dopamine into the presynaptic nerve terminal. DAT also transports the amphetamine to the inside of the nerve terminal. Inside of the nerve terminal amphetamine interacts with the vesicular monoamine transporter 2 (VMAT2) through which it enters the synaptic vesicle. This causes the vesicle to release the stored dopamine into the cytosol, thereby increasing dopamine concentration inside the nerve terminal. Amphetamine also binds to the intracellular site of DAT where it reverses its direction. This causes DAT to move dopamine from inside of the cell to the synaptic cleft. Large doses of amphetamine also block the enzyme Mono Amino Oxidase (MAO) inside of the cell. This prevents the breakdown of dopamine inside the nerve terminal, further increasing its concentration there. Amphetamine also exerts comparable effects on the norepinephrine transporter (NET) (Advokat et al., 2014).

2.9 Amphetamine induced Psychosis

In schizophrenia patients amphetamine has been shown to induce psychotic symptoms at doses that would cause mild euphoria in healthy subjects at best (Lieberman et al., 1987). However, psychotic symptoms can also be observed following amphetamine administration in individuals that are not affected by the disorder (Bramness et al., 2012). Amphetamine induced psychosis can occur in two forms, toxic psychosis and repeated-use psychosis (Seiden et al., 1993). Toxic psychosis usually follows a single large dose of amphetamine and is characterized by confusion and disorientation (Seiden et al., 1993). Repeated-use psychosis occurs after continuous high-dose use (500-100mg/day) but can also occur following lower-dose use (0.3-1.2 mg/kg, or 20-80mg/day) and is characterized by an increase in motor activity, repetitive and compulsive behavior, social withdrawal, delusions of persecution and paranoia, lack of concentration, disorganization of thoughts and auditory hallucinations (Bramness et al., 2012; Seiden et al., 1993). While some of the thought disorders that accompany psychosis in schizophrenia, such as splitting and loosening of associations, a concreteness of abstract thought and an impairment in goal-directed thought appear less pronounced in amphetamine induced psychosis (Yui et al., 2000) distinguishing both types of psychosis based on their acute symptoms is still very difficult (Bramness et al., 2012; Srisurapanont et al., 2011). These strong similarities between

amphetamine induced psychosis and psychosis in schizophrenia have led to the theory, that amphetamine induced psychosis might be used as a model for paranoid psychosis in schizophrenia (Snyder, 1976).

2.10 Amphetamine sensitization

In researching salience and reward processing in psychotic individuals however, it is quite difficult to quantify the role of dopamine processing as opposed to other factors. It is, for example, difficult to generalize findings on psychotic patients, because a lot of them take, or have taken drugs of use or abuse, that potentially alter dopamine transmission (Howes & Kapur, 2009). Another point to consider is that fMRI studies only represent functional activation in brain regions involved in dopamine transmission, not the direct action of dopamine on the neurological process (Winton-Brown et al., 2014). In order to make more direct causal observations about the role of dopamine processing in psychosis a method, named the amphetamine sensitization model, has been developed (Weidenauer et al., 2017). Sensitization describes a non-associative learning process in which continuous exposure to a stimulus results in a steady increase in the behavioral and neurochemical response (Weidenauer et al., 2017). In a pharmacological context sensitization expresses an alteration in the dose/response relationship and can be thought of as the opposite of the more commonly known term drug tolerance. While a development of drug tolerance describes a diminished response to a certain dose in continuous administration, sensitization describes an increased response to the dose (Weidenauer et al., 2017). Sensitization has been described for most drugs of abuse such as cocaine, opiates, nicotine but most relevant for the current subject, amphetamines (Weidenauer et al., 2017). In studies, sensitization to repeated administration of amphetamine showed a progressive increase in striatal dopamine release in sensitized individuals (Boileau et al., 2006; Booij et al., 2016). Another recent PET study by Weidenauer et al. (2020) used Boileau et al. (2006)´s sensitization scheme and showed that post sensitization, stimulant naïve healthy subjects display indistinguishable levels of dopamine release compared to unmedicated first-episode psychotic patients. They also found a negative correlation between prefrontal cortical volume and dopamine release for their healthy subjects. This correlation was however, not found for the psychotic patients and disappeared post sensitization. These alterations of dopaminergic function are thought to approximate the state of aberrant dopamine processing found in in

psychotic or CHR subjects. The increased response from amphetamine sensitization is further matched by increased behavioral measures, such as the rate of eye blinking, ratings of euphoria or focus as well as increased plasma cortisol secretion (Farré et al., 2004; Strakowski, 2001). It is notable that these effects are rather long lasting. Even at low doses, amphetamine sensitization has been shown to increase dopamine release and the psychomotor response of healthy male subjects for periods of up to one year (Boileau et al., 2006). Additionally, the amphetamine sensitization model has also been used to research dopamine's function in working memory (Owen G. O'Daly, Joyce, Tracy, Stephan, et al., 2014) as well as reward processing (Owen G. O'Daly, Joyce, Tracy, Azim, et al., 2014). These studies identified altered dopaminergic activation patterns in sensitized healthy subjects matching those displayed by psychotic patients. During memory encoding sensitized subjects displayed an increased BOLD response within the medial temporal lobe as well as in the midbrain, near the substantia nigra/ventral tegmental area (Owen G. O'Daly, Joyce, Tracy, Stephan, et al., 2014). An increased BOLD response from the ventromedial caudate in sensitized subjects has also been observed during reward anticipation, while a decreased response in the dorsal striatum has been observed during decision making (Owen G. O'Daly, Joyce, Tracy, Azim, et al., 2014). Additionally, the amygdala displayed a blunted reward outcome response. Neither study could find effects of sensitization on physiological measures, but found effects of sensitization on the subjective response to amphetamine (Owen G. O'Daly, Joyce, Tracy, Azim, et al., 2014; Owen G. O'Daly, Joyce, Tracy, Stephan, et al., 2014). These results suggest the amphetamine sensitization model to be a promising way of investigating the role of aberrant dopaminergic function and its effects on salience and reward processing in healthy subjects, while simultaneously avoiding the confound of drug treatment in psychotic subjects or the interpretative disconnect between BOLD activation and dopaminergic action.

2.11 Study rationale and hypothesis

Previous studies investigating the connection between dopamine dysregulation and aberrant prediction error and salience processing have relied mostly on correlational evidence. Furthermore, the correlational data obtained in these studies frequently relied on the endogenous dopamine dysregulation present in psychotic subjects (Winton-Brown et al., 2014). In order to obtain a better understanding of how symptoms in schizophrenia relate to the neurobiological

deficits in patients it is crucial to learn more about the hypersensitive dopaminergic state, its relation to stress, and its causal effects on salience and reward processing. Consequently, our aim was to causally investigate whether increasing striatal sensitivity by inducing a mild sensitization to amphetamine in healthy volunteers would lead to aberrant reward and salience processing. Additionally, we were interested in whether sensitized participants would respond more strongly to a mild stressor and how that would affect their reward processing. To investigate this we conducted a double-blind, placebo controlled study. We used fMRI to collect data on neural activity of healthy subjects whose dopamine levels were manipulated with an amphetamine sensitization regime, an acute amphetamine challenge, and a mild stressor, while they completed a reward-based reversal variant of the predictive inference task by Nassar et al. (2010). This task requires participants to predict outcomes while considering different sources of uncertainty rather than selecting a choice between different options (Nassar et al., 2010). On one of the testing days participants were also exposed to a mild psychosocial stressor, the Montreal Imaging Stress Task (Tomova et al., 2017)

We hypothesized that sensitized participants will show a reduced performance in the reward based predictive inference task due to their aberrant salience and reward processing. They will attribute more meaning to random fluctuations in stimulus outcome contingencies as a result of their blunted prediction error response to relevant cues and exaggerated prediction error response to random cues. We also expected to find stronger effects in sensitized subjects under an acute amphetamine challenge. Additionally, we expected the exposure to a mild psychosocial stressor to negatively impact the subject's performance and this effect to be stronger for sensitized subjects.

In line with previous research (Strauss et al., 2014; Subramaniam et al., 2015), we further hypothesized that sensitized participants in the treatment group would show decreased activation in the striatum during reward anticipation and that this effect would be stronger post sensitization as compared to pre-sensitization.

3 Methods

3.1 Sample:

This thesis was contained in a larger study. Originally a sample size of 50 participants was planned. However, due to the COVID-19 crisis the study had to be ended prematurely, resulting in complete datasets from only 9 participants. All participants were male, as females were excluded from the study to avoid confounds from the menstrual cycle, which has been shown to affect dopamine levels (Dreher et al., 2007). The participants were aged between 21 and 30 years old. In general, the age range during recruitment was restricted to the ages from 18 - 35. The reason for this was that our interest in amphetamine sensitization was primarily due to its similarities to the hypersensitive dopaminergic state seen in first episode schizophrenia patients. All participants were recruited from an existing participant pool. They were all native German speakers. Further, they had to be right-handed, which was confirmed using Flinders Handedness survey (Nicholls et al., 2013). Additionally, the participants were all subjected to a general physical examination as well as a neuropsychological assessment in order to assure that they were all in good health. Participants had to show no psychiatric conditions which was verified using the Mini-International Neuropsychiatric Interview (M.I.N.I. German Version 5.0.0; Sheehan et al., 1998). They also had to show no abnormalities in laboratory screenings which included thyroid urinalysis, blood cell count, serum electrolytes as well as liver and kidney function. Their electrocardiogram was not allowed to show any cardio-vascular abnormalities and blood pressure and pulse had to be in a normal range. Participants had to show no use of illegal drugs (defined as less than five life-time exposures to psychoactive substances) or alcohol abuse as declared by their anamnesis. This was further confirmed via urine drug screening (nicotine was excluded). Participants also had to be MR scanner compatible. Participants all gave their informed consent. For their participation in the study the participants were all compensated with a flat fee of 340€. Additionally, they could earn an additional reward up to 110€ based on their completion of and performance in the tasks.

3.2 Study Design:

For this pharmacological study a randomized, double-blind, placebo-controlled study design was chosen in combination with an amphetamine sensitization and an amphetamine challenge paradigm. Participants were randomly assigned to either the amphetamine group (n = 8) or the placebo group (n = 1) and were subjected to an amphetamine sensitization scheme. Following the sensitization, both groups of participants received a dose of amphetamine. The study was

conducted partially at the Psychiatric Clinic of the Medical University of Vienna as well as the Dental Clinic of the Dental Medical University of Vienna. Due to this thesis being part of a larger study, not all tasks and measurements completed by the participants will be reported here.

3.3 D-Amphetamine sensitization and Amphetamine Challenge

A previously established D-Amphetamine dosing scheme (Boileau et al., 2006) was used in order to sensitize participants. Approximately 0.4mg of D-Amphetamine per kilogram of body weight was administered on three consecutive testing days with a minimum of 48 hours between individual administrations. Administration was oral in the form of 5mg Attentin ® capsules. This scheme allowed us to maintain a fairly uniform dosage for participants of varying body weights (Table 1). Participants in the placebo group received Mannitol following the same scheme. Both Amphetamine and placebo were administered in pharmacological capsules. On the last day of participation between 14-21 days after their third administration, subjects from the amphetamine as well as the placebo group both received Amphetamine following the same dosage scheme as used for sensitization. Administration always took place at the Psychiatric Clinic of the Medical University of Vienna.

Table 1. Amphetamine 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)

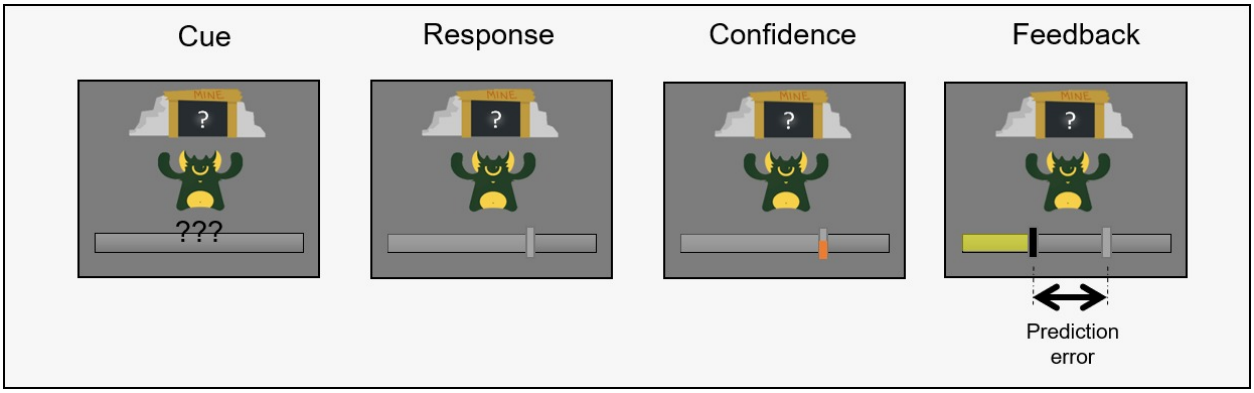
3.4 Reward Based Predictive Inference Task

The main task analyzed in this thesis was an adaptation of an earlier predictive inference task (Nassar et al., 2010) that imitates changes in a dynamic environment. During our task participants were instructed to predict a number between 0-100 on a horizontal bar which represented an amount of money which could be earned. After their prediction they were shown

the actual output and could update their prediction on subsequent trials. The output number was drawn from a normal distribution. During a trial-block, the mean and variance of the distribution from which the output was drawn changed several times. The changes in the distribution were based on a noisy process that manipulated the volatility of the environment described as a change in mean as well as the reliability of the outcome represented by a change in variance. The probability of a change of the distributions mean (experimental reversal) was set 0.1 following the first three trials. A new mean was drawn from a uniform distribution within an interval between 0 to 90 after an experimental reversal. One a reversal occurred the variance of the distribution could change with a probability of 0.4 to either a high variance (SD = 15) or a low variance (SD = 5). The subjects had to do one practice block and one test block consisting of 240 trials on 5 different study days. These blocks were completed on a standard desktop computer using a mouse and keyboard. During testing days which included MR scans the participants completed two blocks consisting of 120 trials each while inside the MR scanner. The task was displayed on an MR compatible screen and responses were collected using a response box. Scanning was stopped in between blocks to allow the participants to rest a bit if they desired so. Each individual block began with an initial display of a white fixation dot in the center of the screen on a black background which was presented for three seconds. Each individual trial consisted of two distinct phases, a prediction phase, and a feedback phase. During the prediction phase participants had to predict the next number which would appear in the subsequent feedback phase. Their prediction was made by moving a small vertical bar on a larger horizontal bar. When confirming their choice, the participants also had to rate their confidence in their own prediction. This was done by holding the confirmation button after selecting their choice for a longer period of time corresponding to how confident they were in their prediction. In order to give participants a visual cue of their estimate of their confidence the small vertical bar would fill up in orange from bottom to top. Filling the small bar completely reflected the participants complete certainty in their own prediction. Whenever the participants confidence ratings appeared inadequate twice in a row a message of “Confidence rating!!!” appeared on the screen to remind them. Inadequate confidence ratings were defined as either low confidence ratings despite a small difference between prediction and feedback as well as high confidence ratings despite a large difference between prediction and feedback. The confidence ratings, however, are not a part of this thesis. Trials were also time restricted to 20 seconds. Participants were shown a

red line at the top of the screen which indicated their remaining time for the current trial. If the participants exceeded the set time per trial a short message reading “Too Slow” popped up on the screen and the next trial started. After participants selected their prediction, it was displayed for 0.3 seconds before the feedback phase started. The inter stimulus interval between the prediction and feedback was jittered between 1.5 and 2.5 seconds in which a white fixation dot in the center of the screen was shown on a black background. During the feedback phase the same horizontal bar appeared on the screen as during the prediction phase. During this phase however, the participants prediction was shown as a vertical black bar and the actual outcome was presented as a vertical grey bar. This allowed participants to see their prediction error which was the difference between their prediction and the actual outcome. The feedback screen was shown for one second followed by an inter trial interval of 0.1 seconds during which the white fixation dot on the black background was shown on the screen again. The display of a typical trial can be seen in Figure 1.

Figure 1. Sequence of Stimuli during a trial



3.5 Montreal Imaging Stress Task (MIST)

Participants were introduced to a mild stressor in the form of a version of the MIST that was adapted by Tomova et al. (2017). The task consists of a mental arithmetic challenge under limited time and an additional social evaluative threat. Social stress is induced in the participants by the experimenter, who gives them negative feedback following their negative performance and informs them that their data would be unusable unless they improved their performance. In addition, subjects also received real-time feedback on the top of the screen indicating their performance to be below their group average.

3.6 Drug effects questionnaire (DEQ)

To measure participants subjective experience of the administered drug, the "Drug Effects Questionnaire" (Morean et al., 2013), was used. Participants rate their subjective experience of the drug on four different scales. Those scales being 1. "Feeling the effect of the drug" (feel), 2. "Feeling high" (high), 3. "Liking the effect of the drug" (like) and 4. "Wanting more of the drug" (more). Responses are collected on a visual analogue scale ranging from 1 to 10 with the anchors corresponding to "not at all" =1 and "extremely" =10. The participants completed the DEQ ten minutes before drug administration, right after drug administration and repeatedly in 30-minute intervals after administration until they were discharged on the respective days.

3.7 Task Instructions

All task instructions were given in German. Participants received full instructions before their first practice run and short instructions prior to every testing block. In order to increase participants engagement, the instructions were embedded into a story. Participants were told that they would visit a foreign planet on which they encountered an Alien. This Alien would be going to various mines on the planet to mine for gold. This alien would ask the participants to estimate how much gold it would be bringing back from the mine every day. One day corresponding to one individual trial. If the estimated gold was close to the actual gold the alien returned with, it would be willing to share some of its gold with the participants. Participants estimates were given on the horizontal bar during the prediction phase while the aliens mined gold were shown on the same bar during the feedback phase. In order to reinforce the connection between the task and the story, an image of an Alien and a mine were included in the stimuli (see Figure 1). Similar to the original task (Nassar et al., 2010), participants were informed that the mines would differ in the daily average of gold that could be returned from there and how difficult it would be for the alien to mine the gold. This meant that returns between trials would fluctuate more for some mines than others. Participants were also told that the alien would sometimes change the mines without informing the participants. This was included in order to reduce participants uncertainty about the task structure. The thought behind these instructions was to allow participants to assess whether changes in returns stemmed from noise, meaning the variance within the distribution from which the number was drawn or from an experimental reversal (Nassar et al., 2010). To increase participants investment into the task, each individual trial was

associated with a monetary reward. The amount of reward was based on two factors. The first being the size of their prediction error. Smaller prediction errors resulting in larger rewards. The second factor was the actual outcome, represented by the amount of gold the alien returned with. As a consequence of this, participants were advised to try to predict the average return of a mine to maximize their reward.

3.8 Physiological measures

Subjects Heart rate as well as systolic and diastolic blood pressure were measured at pre-dose about 10 minutes and 1 minute before administration. Measurements also continued in 30-minute intervals following Amphetamine administration until the participants were discharged on the respective days. Appropriate medication for the unlikely event of an excessive raise in blood pressure defined as higher than 180 mmHg systolic was kept ready at hand.

3.9 MINI-International Neuropsychiatric Interview (MINI-Plus)

The M.I.N.I.-Plus (Sheehan et al., 1998) is a structured diagnostic interview developed in cooperation by psychiatrists and clinicians from the United States and Europe, for DSM-IV and ICD-10 psychiatric disorders. The Interview was designed to meet a need for a short but accurate structured psychiatric interview for clinical trials and epidemiology studies and can be completed in approximately 20 minutes.

3.10 FMRI Data Acquisition

All Neuroimaging data was obtained at the Neuroimaging Center of the University of Vienna at the Dental Clinic of the Vienna Medical University. Functional neuroimaging data was obtained using a 3 Tesla Magnetom Skyra MRI system (Siemens Medical, Erlangen, Germany) equipped with a 32-channel head coil and a high-performance gradient system allowing for fast, high-resolution whole-brain multiband echoplanar imaging. The parameters used for image acquisition were: echo time (TE)/repetition time (TR) = 34/704 ms, flip angle = 50°, interleaved acquisition, 32 axial slices coplanar to the line connecting anterior and posterior commissures, field of view = 210 mm, matrix size = 96x96, voxel size = 2.2x2.2x3.5 mm. Additionally structural images were acquired using a magnetization-prepared rapid gradient-echo sequence (TE/TR = 2.29/2300 ms, 176 sagittal slices, voxel size = 0.9x0.9x0.9 mm, flip angle = 8°, field of view = 240 mm).

3.11 Experimental Procedure

Subjects participated for 8 study days (see table 2). The first day (B1) as well as the fifth day(B2) consisted of strictly behavioral testing, during which the participants completed a variety of tasks including the predictive inference task analyzed in this thesis. Sensitization began on the second study day (A1) during which the participants received their first dosage of Amphetamine or Placebo respectively. Additionally, the participants completed the same tasks as they did on both behavioral testing days (B1 & B2). This day also included the first MR scanning session in which the participants completed two blocks of the predictive inference inside of the MR scanner. The third (A2) and fourth (A3) days of the study consisted of strict sensitization days on which the participants received their second and third dose of either amphetamine or placebo. During the sixth study day (M1) participants were subjected to another scanning session during which they completed the predictive inference task as well as the MIST while lying in the MR scanner. The seventh study day of the study (A4) was identical to the second day (A1), the only difference being that both groups received Amphetamine on this day. All study days with the exception of M1, began between 9AM and 11AM at the Psychiatric Clinic of the Medical University of Vienna. These times were chosen in order to keep the participants hormone levels comparable. On both sensitization days (A2 & A3) participants received their respective dose of Amphetamine or placebo 15 minutes after their arrival. Participants baseline physiological data were measured ten minutes prior to drug or placebo administration. Starting with the administration the physiological data was measured repeatedly in 30-minute intervals (0,30,60 and 90 minutes post administration). Physiological data was measured using an electronic sphygmomanometer. Participants also completed the Drug Effects Questionnaire at the same intervals. Participants whose physiological measures showed no abnormalities were discharged 90 minutes after drug administration on both sensitization days (A2 & A3). On the testing days A1 and A4 participants were instructed to arrive with an empty stomach to ensure similar absorption speeds across all participants. Upon their arrival a urinalysis test was performed to check for any use of illicit drugs. Participants who tested positive were excluded from further participation in the study. Participants were also questioned whether they had consumed alcohol within the previous 24 hours of testing and their testing day was rescheduled if they responded that they had consumed alcohol. Physiological as well as behavioral measures on both days (A1 & A4) were obtained in the same time intervals as on the sensitization days (A2 & A3). After

drug administration participants spent approximately 100 minutes completing various tasks. Following task completion, a research assistant guided the participants on foot for a distance of roughly 900meters from the Psychiatric Clinic of the Medical University of Vienna to the Neuroimaging Center of the University of Vienna. Collection of physiological measures as well as the DEQ continued upon arrival approximately 120, 215 and 250 minutes post drug administration. Prior to scanning participants had to fill out an MR safety questionnaire. MR scanning began about 150 minutes following drug administration, during which the participants completed two blocks of the reward based predictive inference task. This timeline was chosen to ensure that participants would be completing the reward based predictive inference task inside the scanner during peak blood amphetamine concentration (Weidenauer et al., 2020). Participants were discharged approximately 250 minutes post drug administration. Testing days B1, B2 and M1 did not require any specific regulations as no drug administration occurred on these days.

Table 2. Testing Schedule

	Sensitisation period			Washout period	Post-sensitisation period	
0 D	1 D	3 D	5 D	~ 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. The table indicates what data was obtained on which day of the study as well as the timeframes in between individual sessions.

4 Analysis

The following section contains a more detailed descriptions of the methods used in this thesis as well as the rationale for the data analysis. First an overview of Bayesian Multilevel Modelling is given, which was used to analyze the subjective measures of amphetamine sensitization and the measured physiological data of the participants. Behavioral data from our task was also analyzed using Bayesian Multilevel Modelling. Our behavioral data was first prepared in MATLAB[1] and

[1] Version 9.4.0.813654 (R2018a), The MathWorks Inc, Natick, Massachusetts, US

subsequently analyzed in R[2]. Physiological and behavioral data was analyzed only in R. fMRI analysis was done exclusively using MATLAB.

4.1 Bayesian Multilevel Modelling

Since our final number of participants consisted only of a fraction of our planned sample size and this fraction having an uneven distribution of participants from the amphetamine and placebo-group we chose to use Bayesian Multilevel models for the analysis. This approach is particularly useful when analyzing repeated measurements as well as unequal sample sizes (Nalborczyk et al., 2019) both of which apply to our data. These Multilevel Models (MLMS) can be characterized as a hierarchical regression analysis since the parameters of one regression model are being modeled as outcomes of another regression model. To create our MLMs the brms package in R was used (Bürkner, 2017). Brms itself fits MLMs by using the probabilistic programming language Stan. Stan on the other hand uses Markov Chain Monte Carlo (MCMC) algorithms as well as the No-U-Turn-Sampler (NUTS) to draw samples from the posterior distribution as opposed to approximating the posterior distribution directly (Bürkner, 2017). This procedure results in a description of the predictors effects as a mean and a standard deviation of the posterior distribution as well as a two sided 95% credible interval (CrI) of the mean. These CrI can be interpreted as probability statements as opposed to confidence intervals obtained when using a frequentist approach (Nalborczyk et al., 2019). The 95% CrI represents a probability of 0.95 that the credible interval contains the population value of the specific estimate, based on the data, the model, and its priors. The CrI also contains information regarding the certainty of the model estimate based on its width. A narrow CrI representing a higher certainty and a wider CrI representing a lower certainty.

We also included an equivalent to Cohen's *d* used in MLMs, δt. This represents 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., 2019). δt is reported similarly to each predictors' effects from the prior paragraph. To check for negative or positive probability effects, we also checked the percentage of the posterior distribution of each estimate higher and lower than zero.

[2] Version 3.6.3, R Core Team, Vienna, Austria, https://www.R-project.org

4.2 Assessment of Sensitization

In order to assess whether amphetamine sensitization was successful we checked the effects of sensitization and amphetamine administration on the self-reported drug effects as well as the physiological measures that were taken on testing days (A1, A2, A3 and A4). Subjective drug effects were obtained through the DEQ while the physiological measures taken were the heart rate (HR), systolic blood pressure (sBP) and diastolic blood pressure (dBP). All measures were analyzed with the same MLMs using the model:

Response variable ~ session + sensitized + amphetamine +(session|ID)

Dummy coding was used for sensitization where 1= sensitized (session A4) and 0 = not sensitized (session A1, A2 and A3). Amphetamine was also dummy coded with 0= no amphetamine/placebo group and 1= amphetamine group. The sessions themselves were coded as categorical predictors with 4 levels corresponding to the sessions (1= A1, 2=A2, 3=A3, 4=A4). The amphetamine administration was included as a predictor because of our interest in the effects of acute amphetamine after sensitization (A4) when both groups received amphetamine and their DEQ and physiological measures were obtained. Unlike for the behavioral and fMRI data analyses no extensive model fitting was done as these serve only to check whether sensitization worked.

4.3 Physiological measures

Prior to model analysis the difference between the baseline and the most distant value for HR, sBP and dBP were calculated individually for each participant during each separate session. This calculated difference could be either a positive or negative value. This data was used in the Model described in the previous section. Our expectation was that we would find elevated HR as well as elevated sBP and dBP values in sensitized or amphetamine challenged participants. As in previous research (Boileau et al., 2006; Owen Gareth O'Daly et al., 2011) we expected the effects to be rather small.

4.4 DEQ

Subjective drug effect data was prepared in a similar fashion to the physiological measures we obtained. The difference between the peak reported value and the baseline value was calculated

for every item and every separate session. This data was used in the previously described model. We expected to find elevated self-reports of the drug effects for sensitized and amphetamine challenged participants.

4.5 Behavioral Analysis

The analysis of our data concerned itself primarily with the detection of the effects of sensitization, amphetamine administration, and exposure to a minor stressor on the mean prediction error.

4.6 Hierarchical regression analysis

All variables of interest were assessed using Bayesian MLMs while following a three step procedure suggested by Nalborczyk et al. (2019):

1. Definition of a probability model
2. Computation of the posterior distributions of each parameter that is defined by the model
3. Evaluation of the model fit and the model's predictive performance

All models used data from testing days B1, A1, B2, M1 and A4.

4.7 Model Definition

Table 3. Model Formulas

Model	Model formula
M0	*mean prediction error* ~ + (1|*ID*)
M1	*mean prediction error* ~ + *session* + (1|*ID*)
M2	*mean prediction error* ~ + *session* + *amphetamine* + (1|*ID*)
M3	*mean prediction error* ~ + *session* + *amphetamine* + *sensitized* + *(1|ID)*
M4	*mean prediction error* ~ + *session* + *amphetamine* + *sensitized* + (*session*|*ID*)
M5	*mean prediction error* ~ + *session* + *amphetamine* + *sensitized* + *stress* + *(session|ID)*
M6	*mean prediction error* ~ + *session* + *amphetamine* + *sensitized* + *stress* + *stress* : *sensitized* + *(session|ID)*

Note. Outcome variable is the mean prediction error, ID = subject ID, session = testing day, categorical predictor with five levels, amphetamine = amphetamine administration (0= no

amphetamine/placebo, 1 = amphetamine), sensitized = sensitization status (0 = pre sensitization/placebo, 1 = post sensitization), stress = stress exposure (0 = no exposure, 1 = exposure)

Several models were fit to the data in order to predict our outcome variable the mean prediction error. Constant and varying effects were both included in the models. Population level effects are our constant effects that represent effects that were shared across subjects. Varying effects modeled subject specific variability. All models other than the null model contained a constant effect of session (M1, M2, M3, M4, M5, M6). The predictors amphetamine and sensitization were added to the models in subsequent steps beginning with the effect of amphetamine (M2, M3). In our next model we added a varying effect of session to model the variability of the mean prediction error across subjects (M4). The next model contained another constant effect of stress (M5). To test for an interaction between sensitization and stress we added an interaction effect between those two predictors to our last model (M6). Amphetamine administration, stress, and sensitization predictors were all dummy coded (*amphetamine*: 1 = amphetamine administration, *sensitization*: 1 = sensitized, *stress*: 1 = stressed). Session was modelled as a categorical predictor with five levels (1 =B1, 2 =A1, 3 = B2, 4 =M1, 5 =A4).

4.8 Model fitting

We fit our models using four Markov Chain Monte Carlo (MCMC) chains to approximate the posterior distribution for each model. We ran 1000 iterations per chain of which 200 were used for warmup, resulting in 3200 post-warm-up samples as posterior probability of our model parameters. All models were run using weak uninformative normally distributed priors (N(0,1)). We followed the brms packages suggestions regarding the number of iterations and warm-ups as well as adapt_delta for non-converging chains. Convergence was evaluated by the $\hat{R}$ statistic where $\hat{R}<1.01$ indicates chain convergence. Additionally we evaluated convergence checking each parameters effective sample size of the posterior distribution and through inspection of their trace plots (Nalborczyk et al., 2019).

4.9 Model comparison

Models were compared based on two criteria, first how well they predict unobserved data and second, how well the model fits the observed data. The models' out of sample predictive performance was estimated by the leave one out cross validation procedure in the brms package.

The resulting index (LOOIC) serves as an estimate of the models predictive fit to unobserved data (Nalborczyk et al., 2019). Bayesian R^2 was used to compare model fits to the observed data. We chose the model with the best predictive performance (lowest LOOIC) as the most accurate model unless their predictive performance was similar (difference = <10; Turi et al., 2018). In this case the model that best explained the observed data was chosen as the most accurate model, namely the model that showed the highest Bayesian R^2.

4.10 fMRI Analysis

The Spm12[3] software package in MATLAB was used to pre-process and analyze fMRI data from testing days A1 and A4. Since we had only one participant in the control group, we decided to exclude them in our analysis in hopes of finding an effect of sensitization on reward anticipation, in our small, sensitized sample when comparing participants pre and post-sensitization regimen.

4.11 Pre-processing

Prior to pre-processing our obtained MRI data was converted to the NiFTi format. Within-subject pre-processing steps included slice-time correction, realignment, unwarping, co-registration, and uniform segmentation. Following this our images were spatially normalized to Montreal Neurological Institute (MNI) space and smoothed using a 3D Gaussian kernel of 4mm full-width at half-maximum (FWHM) to allow for between-subject comparison.

First, we used slice-time correction to correct for the differences in image acquisition time between sampled slices that occur from the images being taken in interleaved mode. Our reference slice was recorded in the middle of the sequence (i.e., at TR/2). Since the movement of the subjects resulted in large excessive motion artifacts in the functional images, which can lead to a loss of sensitivity and specificity. To improve sensitivity and specificity, we used realignment and unwarping methods. In the case of realignment, the first scan of the session for each participant was adjusted by 6 parameters (3 degrees for rotations and 3 mm for translations) to the first scan of the first session. Subsequently, all images from a session were realigned to the first image of that session. The movements of the subjects lead to strong geometric distortions, which were corrected by unwarping to correct for susceptibility-by-movement interactions. Co-

[3] Wellcome Trust Centre for Neuroimgaing, London, UK, http://www.fill.ion.ucl.ac.uk/spm

registration was then used to match the anatomical information from the functional images with the structural image to achieve better anatomical localization. Segmentation based on tissue probability maps was performed to separate different tissue types (grey matter and white matter). Bias correction was then used to correct for the inherent intensity heterogeneity of MRI, facilitating normalization. The normalization helps to create a voxel-to-voxel match between the brains of the different subjects, allowing for comparison of brain activity between subjects. T1-weighted anatomical images were transformed and normalized into the MNI template of uniform segmentation. The obtained normalization parameters were then applied to all functional images. Smoothing was used to increase the signal-to-noise ratio by suppressing noise as well as the effects of residual differences in gyral and functional architecture. This resulted in improved normally distributed data, better spatial overlap, and an increase in sensitivity to effects of similar magnitude to the kernel.

4.12 First-level analysis

For the reward based predictive inference task, a general linear model (GLM) was used to calculate statistical parametric maps of BOLD activation. Our first-level models were created for each subject and day of image acquisition. Since we were primarily interested in the effects of amphetamine sensitization on reward anticipation our GLM was conducted using reward anticipation as a regressor of interest. Reward anticipation was defined as the start of the inter-stimulus-interval between the subject's selection and them receiving feedback. Furthermore, we included six realignment parameters as regressors of no interest to account for movement based variance. Prior to fitting the model to the data, regressors were convolved with a canonical hemodynamic response function. A high pass filter with a cut-off frequency of 128Hz was applied to remove low frequency signal drifts. Regressors were corrected for serial correlations through usage of a first order autoregressive model. Consequently, we obtained contrast images between the participants reward anticipation and resting state for each participant on each testing day, ready to be used for the group-level analysis.

4.13 Group-level analysis

We performed whole brain analysis comparing differences between reward anticipation and the resting state with a with a paired samples t-test. We used multiple comparison correction to

control the number of false positives to obtain reliable results. Our statistical maps were corrected by a multiple comparison correction at a family-wise error (FWE) of $p < 0.05$.

As our intent was to examine sensitization effects on reward anticipation, we chose to focus on changes in neural activation in areas that have been implied show aberrant reward processing in previous studies, namely the striatum. ROI Images were created using the WFU_PickAtlas[4] using a predefined anatomical mask of the striatum (caudate, pallidum, putamen). These ROIs were then used as a mask for group level analysis.

5 Results

5.1 Assessment of sensitization

5.2 Sensitization and amphetamine effects on physiological data

We found weak effects of sensitization and amphetamine that were associated with large uncertainties on our physiological measures. Table 4 shows our results for the sensitization and amphetamine effects on heart rate and blood pressure. We found a positive effect of both sensitization ($\beta_{sens} = 0.63, 95\% CrI[-5.28, 5.73]$) and amphetamine administration ($\beta_{amphetamine} = 0.45, 95\% CrI[-5.18, 6.39]$) on our subject's heart rate suggesting that amphetamine administration and sensitization increased the heartbeat. The means of the posterior distribution of the regression coefficients for sensitization and amphetamine were both positive (see Table 4). However, the CrIs' show that they are associated with very high uncertainties since they vary from strongly negative to strongly positive effects. Our results also show that heart rate seems to be almost equally likely to be negatively or positively affected by both sensitization ($P(\beta_{sens} > 0) = 59\%$) and amphetamine administration ($P(\beta_{amphetamine} > 0) = 56\%$). Since the calculated effect sizes for heart rate are close to zero in both cases ($\delta_{tamph} = 0.03;\ \delta_{tsens} = 0.04$), our positive effects of sensitization and amphetamine administration on heart rate remains inconclusive.

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

Table 4. Results of the physiological analysis for Sensitization and Amphetamine

	Sensitization results					
	ß	*low 95%-CrI*	*up 95%-CrI*	*δt*	*low 95%-CrI*	*up 95%-CrI*
HR	0.63	-5.28	5.73	0.04	-0.31	0.33
dBP	1.94	-3.47	6.55	0.16	-0.37	0.77
sBP	0.24	-5.43	6.05	0.01	-0.19	0.21
	Amphetamine results					
	ß	*low 95%-CrI*	*up 95%-CrI*	*δt*	*low 95%-CrI*	*up 95%-CrI*
HR	0.45	-5.18	6.39	0.03	-0.31	0.37
dBP	2.13	-3.95	7.34	0.25	-0.38	0.96
sBP	0.35	-5.40	6.46	0.01	-0.19	0.22

Similar to heart rate we found positive effects for both sensitization and amphetamine on the subjects' systolic blood pressure ($\beta_{sens} = 0.24, 95\%CrI[-5.43, 6.05];\ \beta_{amph} = 0.35, 95\%CrI[-5.40, 6.46]$) . For systolic blood pressure we found weak positive effects ($\delta_{tamph} = 0.01;\ \delta_{tsens} = 0.01$) that were associated with very strong uncertainty for both sensitization($P(\beta_{sens} > 0) = 53\%$) and amphetamine administration ($P(\beta_{amph} > 0) = 54\%$). Since the δ_t values are close to zero and both roughly equally likely to be either positive or negative it seems that neither amphetamine nor sensitization had a noticeable effect on the subject's systolic blood pressure.

Diastolic blood pressure showed the highest means of the posterior distribution of the regression coefficients regarding both amphetamine ($\beta_{amph} = 2.13, 95\%CrI[-3.95, 7.34]$) and sensitization ($\beta_{sens} = 1.94, 95\%CrI[-3.47, 6.55]$). However, both were also associated with wide CrI's reflecting large uncertainty. Our effect sizes for diastolic blood pressure while larger compared to the other measures are still small ($\delta_{tamph} = 0.25;\ \delta_{tsens} = 0.16$). The posterior distribution above zero for sensitization ($P(\beta_{sens} > 0) = 70\%$) and amphetamine ($P(\beta_{amph} > 0) = 76\%$) seem to indicate a positive effect of both sensitization and amphetamine. These results indicate a positive effect of both sensitization and amphetamine administration, however, due to our large uncertainty and small effect sizes the evidence for sensitization effects on blood pressure remain inconclusive.

5.3 Sensitization and amphetamine effects on subjective drug experience

Table 5. Results of the subjective drug experience analysis for Sensitization and Amphetamine

	Sensitization results					
	ß	*low 95%-CrI*	*up 95%-CrI*	*δt*	*low 95%-CrI*	*up 95%-CrI*
feel	1.22	-2.35	4.69	0.35	-0.71	1.33
high	0.87	-2.83	4.42	0.24	-0.69	1.21
like	0.45	-2.71	3.45	0.17	-0.98	1.38
more	0.40	-2.91	3.70	0.16	-1.09	1.40
	Amphetamine results					
	ß	*low 95%-CrI*	*up 95%-CrI*	*δt*	*low 95%-CrI*	*up 95%-CrI*
feel	1.23	-2.48	4.68	0.35	-0.68	1.36
high	1.14	-2.49	4.98	0.31	-0.65	1.32
like	1.19	-1.67	3.87	0.45	-0.58	1.50
more	0.76	-2.04	3.37	0.29	-0.71	1.34

Regarding the subjective drug effects, we found imprecise weak positive effects of sensitization on all four components of the DEQ (see Table 5). Our model and data suggest that sensitization had the strongest effect on the subjective experience of the drug (*feel*: $\beta_{sens} = 1.22, 95\%CrI[-2.35, 4.69];\ \delta_{tsens} = 0.35$), followed by an increased feeling of being high (*high*: $\beta_{sens} = 0.87, 95\%CrI[-2.83, 4.42];\ \delta_{tsens} = 0.24$), liking the drug (*like*: $\beta_{sens} = 0.45, 95\%CrI[-2.71, 3.45];\ \delta_{tsens} = 0.17$), and wanting more of the drug (*more*: $\beta_{sens} = 0.40, 95\%CrI[-2.91, 3.70];\ \delta_{tsens} = 0.16$). However, the large CrIs' that vary from negative to positive effects make our effects very uncertain. The percentage of the posterior distribution above zero seems to indicate a trend towards a positive effect of sensitization on subjective drug experience (*feel*: $(P(\beta_{sens} > 0) = 75\%)$; *high*: $(P(\beta_{sens} > 0) = 68\%)$; *like*: $(P(\beta_{sens} > 0) = 62\%)$; *more*: $(P(\beta_{sens} > 0) = 60\%)$).

The effects of amphetamine administration showed a similar pattern with feel showing the highest mean of the posterior distribution (*feel*: $\beta_{amph} = 1.23, 95\%CrI[-2.48, 4.68];\ \delta_{tamph} = 0.35$), followed by like (*like*: $\beta_{amph} = 1.19, 95\%CrI[-1.67,3.87];\ \delta_{tamph} = 0.45$), high (*high*:

$\beta_{amph} = 1.14, 95\%CrI[-2.49, 4.98];\ \delta_{tamph} = 0.31$) and lastly more (*more*: $\beta_{amph} = 0.76, 95\%CrI[-2.04,3.37];\ \delta_{tamph} = 0.29$). While amphetamine administration showed stronger effects and smaller CrIs' than sensitization on all four components of the subjective drug measure, the CrIs' also include the possibility of either negative or positive effects reflecting uncertainty. The percentage of the estimated distribution above zero (*feel*: $\big(P(\beta_{amph} > 0) = 74\%\big)$; *high*: $\big(P(\beta_{amph} > 0) = 72\%\big)$; *like*: $\big(P(\beta_{amph} > 0) = 81\%\big)$; *more*: $\big(P(\beta_{amph} > 0) = 72\%\big)$), displays a tendency toward a positive effect of amphetamine administration on the four DEQ components.

The predictor amphetamine in our model controlled for the acute effects of amphetamine administration. Our model nonetheless showed a trend towards a positive effect of sensitization on the subjective drug experience. While the large uncertainty in effect sizes urges for a cautious interpretation, we interpret these results as a possible indicator that our sensitization was successful regarding the subjective drug experience.

Our model and data suggest that sensitization showed a tendency to increase heart rate, associated with large uncertainty and diastolic blood pressure. All four components of the subjective drug experience also appear the have been affected by sensitization, while controlling for the acute effect of amphetamine administration and displaying a tendency towards a positive effect. Consequently, it seems a reasonable assumption that our sensitization regimen was to some degree successful, even though there are reservations due to the uncertainty of our effects.

5.4 Behavioral results

We report behavioral results for model 5 since it showed the highest predictive performance to yet unobserved data (*LOOIC* = 64.99) and also best explained the observed data (*Bayes* R^2 = 0.95). Results of our analysis for all models is shown in table 6.

Table 6. Results of the model comparison

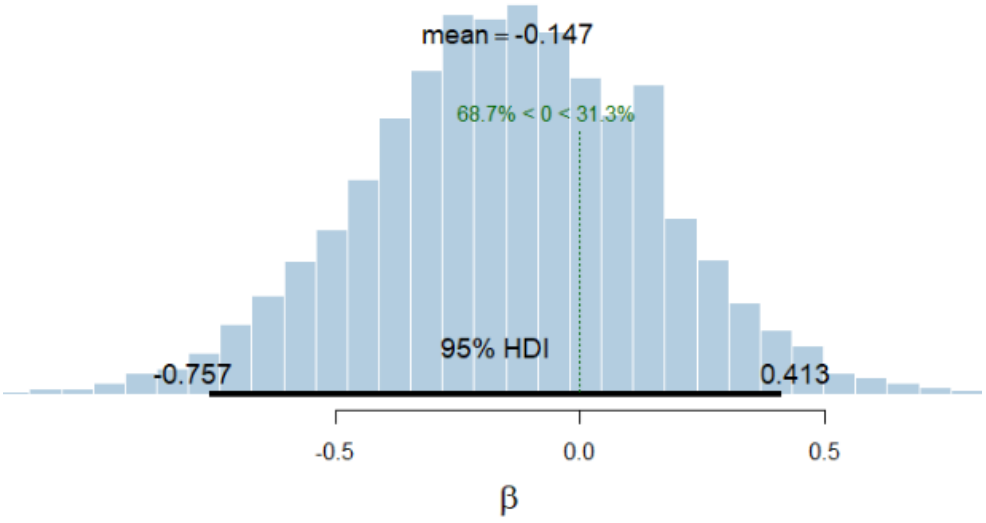
Model	LOOIC	LOOIC SE	Δ LOOIC	Δ LOOIC SE	Bayes R^2	Bayes R^2 SE
M5	64,99	15,36	0,00	0,00	0,95	0,03
M4	68,44	16,71	3,51	1,35	0,94	0,03
M6	69,78	16,28	4,79	0,92	0,94	0,03
M3	77,10	20,99	12,11	5,63	0,85	0,03
M2	77,23	24,20	12,24	8,84	0,85	0,03
M1	82,52	26,21	17,53	10,85	0,82	0,03

Note, LOOIC = leave-one-out information criterion as calculated through LOO cross validation procedure; SE = Standard Error

5.5 Sensitization effects on the mean prediction error

Our results for the sensitization effects on task performance can be seen in Figure 2.

Figure 2. *Posterior distribution of sensitization in model 5*



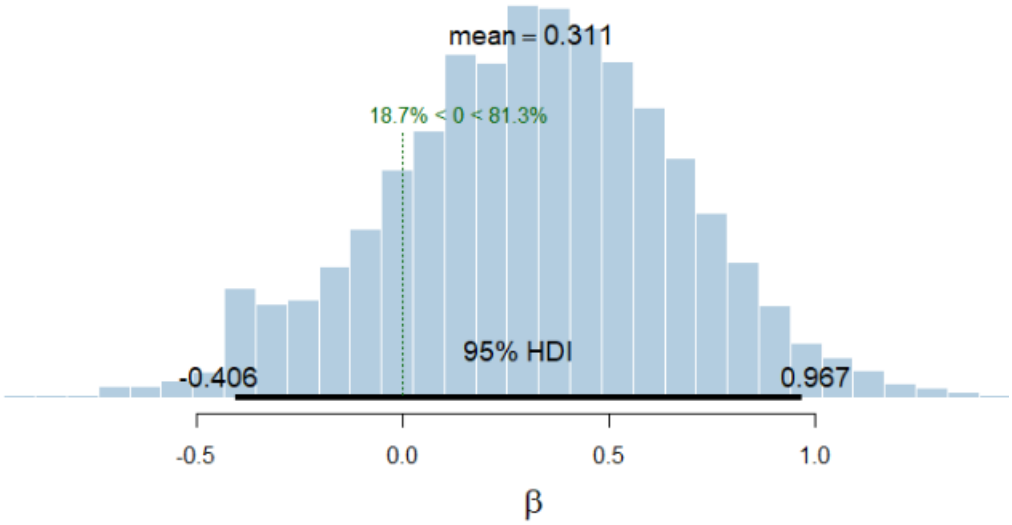
Note. Histogram of posterior samples of the slope for sensitization, as estimated by model 5. HDI = highest density interval

Our results indicate a negative effect of sensitization on the mean prediction error ($\beta_{sens} = -0.15, 95\% CrI[-0.76, 0.41]$). Since we used the normalized mean prediction error in our analysis, a negative mean of the posterior distribution indicates an effect that is positive for task

performance due to the reduction in prediction errors. While the effect we detected is likely to be negative ($P(\beta_{sens} < 0) = 68.70\%$), the CrIs still indicate a certain degree of uncertainty due to both positive and negative values they span. Our calculated effect size δ_t showed a weak negative effect on the mean prediction error ($\delta_{tsens} = -0.12, 95\% CrI[-0.61, 0.34]$). As a result, our data and model point towards a weak negative effect of sensitization on the mean prediction error in the reward based predictive inference task, albeit with a certain degree of uncertainty.

5.6 Amphetamine effects on the mean prediction error

Figure 3. Posterior distribution for amphetamine in model 5



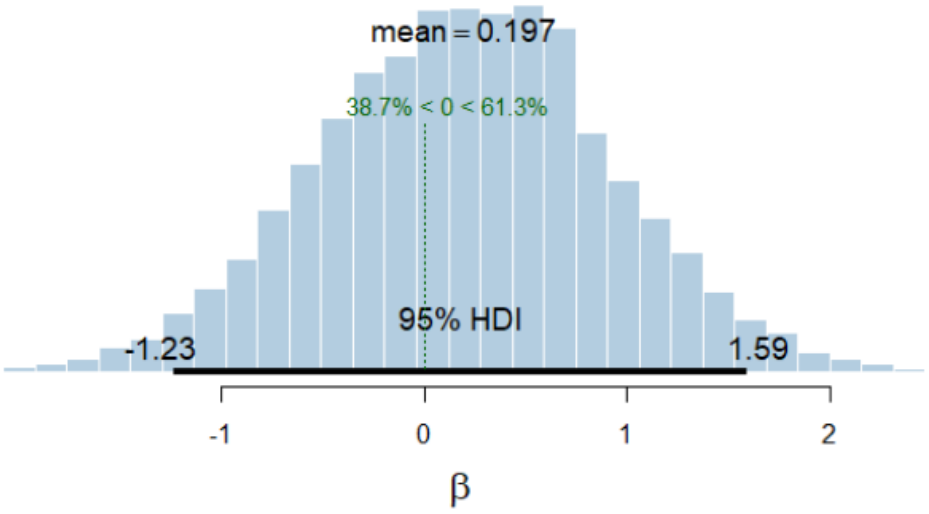
Note. Histogram of posterior samples of the slope for amphetamine administration, as estimated by model 5. HDI = highest density interval

Figure 3 shows the posterior distribution for the effect of amphetamine administration on the mean prediction error. The mean of our posterior distribution points towards a positive effect of amphetamine administration on the mean prediction error ($\beta_{amph} = 0.31$, $95\% CrI[-0.41, 0.97]$) resulting in a negative effect on task performance. This effect was the strongest we discovered in our model and was found to be of medium strength ($\delta_{tamph} = 0.25, 95\% CrI[-0.33, 0.80]$) and associated with a degree of uncertainty. The fact that the

majority of the posterior distribution of the effect of amphetamine administration on the mean prediction error is above zero $\left(P\left(\beta_{amph} > 0\right) = 81.30\%\right)$ adds further notion for this positive effect.

5.7 Stress effects on the mean prediction error

Figure 4. Posterior distribution for stress in model 5



Note. Histogram of posterior samples of the slope for amphetamine administration, as estimated by model 5. HDI = highest density interval

The result of our analysis suggests a positive effect of a mild psychosocial stressor on the mean prediction error, that also results in decreased performance in the reward based predictive inference task ($\beta_{stress} = 0.20, 95\% CrI[-1.23, 1.59]$). The wide positive and negative CrIs indicate large uncertainty regarding this effect. Additionally, the posterior distribution shows the likelihood for the effect to be either positive or negative to be similar ($P(\beta_{stress} > 0) = 61.30\%$). Our calculated effect size ($\delta_{stress} = 0.16, 95\% CrI[-1.01, 1.30]$). further suggests this effect to be weak and imprecise.

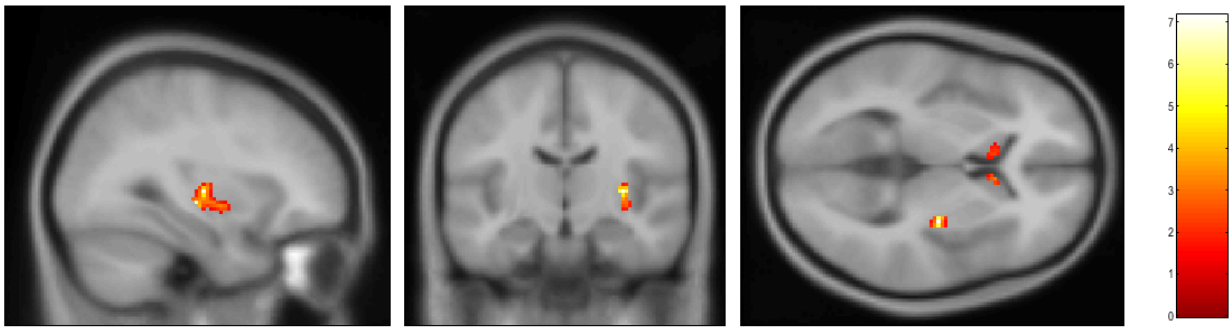
Since our Model 6, which contained a varying effect for stress and sensitization showed worse predictive performance and worse performance at explaining our current data than a simpler model (Model 5) that contained both stress and sensitization as fixed effects (see Table 6). We necessarily conclude that we could not detect an effect of interaction between exposure to a minor psychosocial stressor and sensitization. However, due to the small sample size of our

control group (N=1) it is very conceivable that we did not observe such an effect despite its existence.

5.8 fMRI results

We did not find any significant differences in striatal neural response for reward anticipation between session A1 and session A4. No clusters survived the pairwise family error correction ($p_{FWE} > 0.05$). Consequently, we can only conclude that we did not find any evidence for an altered neural response as a consequence of amphetamine sensitization in our ROIs. Consequently, we additionally extracted the mean contrast estimates for all subjects averaged on each individual testing day over our ROI without the $p_{FWE} > 0.05$ and instead at $p < 0.05$. The uncorrected results in our ROI for session A1 can be seen in Figure 5. We then ran a paired-samples t-test using the obtained mean contrast estimates in order check for differences in striatal activation between A1 and A4. No significant differences were found using this approach either ($t(6) = -1.24$, $sd = 1.65$, $p = 0.26$).

Figure 5. Striatal BOLD activity during A1 at $p<0.1$



Note, the figure displays non-significant differences in striatal activity during session A1 in the sagittal, coronal, and horizontal plane, prior to threshold cluster correction

6 Discussion

In this study we were interested in the effects of amphetamine sensitization, acute amphetamine administration, as well as stress on the prediction error. We hypothesized that sensitization, amphetamine administration, and stress would all result in stronger attribution of salience and therefore a higher average prediction error and that the effect of stress would be stronger in sensitized participants. We found a weak negative effect of sensitization on the prediction error, resulting in better task performance. We found a weak positive effect of stress and a medium

strength effect of amphetamine administration on the prediction error resulting in decreased task performance. Furthermore, we observed no interaction between stress and the sensitized state.

Our results are consistent with prior findings, in which sensitization by amphetamine has been found to enhance the subjective responsiveness to the administered drug but did not have any large effects on the subjects physiological measures (Owen G. O'Daly, Joyce, Tracy, Azim, et al., 2014; Owen G. O'Daly, Joyce, Tracy, Stephan, et al., 2014). However, all effects we were able to identify were generally accompanied by large uncertainty. Nonetheless, we can assume that our amphetamine sensitization regimen led to some of the desired results, seeing as our findings regarding subjective drug measures and physiological data were largely in line with the results of previous research.

Our Behavioral results regarding sensitization showed an effect of the opposite direction of our expected results. While we expected amphetamine induced sensitization to lead to an increase in prediction error, as a result of the subjects' aberrant salience processing. Our findings, however, point towards a reduction of the prediction error, which then in turn would correspond to improved salience processing. Nonetheless, due to the large amount of uncertainty associated with our results they need to be considered preliminary at best. It is quite possible that the reason for the contradiction between our expected results and our actual results regarding sensitization might lie in our control group. As it consisted only of a single subject it is quite possible that our control group simply had a lower performance than the subjects of our sensitization group which then in turn would lead us to the assumption that natural differences in performance would be interpreted as a result of our sensitization regimen.

The effects of amphetamine administration and stress on the other hand were in line with previous research as well as our predicted results. Amphetamine administration as well as stress were both associated with an increased prediction error, supporting the notion that an increase in striatal synaptic dopamine levels results in a negative effect on reward processing.

While the model that showed the best fit to our data and the highest predictive performance ended up not including a varying effect for stress and sensitization, based on previous research we think it highly likely that such an effect might be found if the sample contained a larger control group than ours (N=1).

Our outcome variable for the behavioral analysis was the normalized mean prediction error per session. In order to enhance the inferences that could be drawn from our data, it might be conceivable to have a closer look at the subjects' trial-by-trial behavior. Specifically, their subjective measures of confidence could be included in such an analysis in order to conceptualize differences in the subjective experience of reward prediction and anticipation as opposed to the actual accuracy of the subjects' predictions.

Our fMRI analysis also showed no significant striatal differences during reward anticipation comparing pre and post sensitization states. These differences have been shown in prior research in individuals with psychosis (Strauss et al., 2014; Subramaniam et al., 2015). As a consequence, it appears highly likely that our subject count was simply too low to find any statistically significant differences in striatal neural activity.

6.1 Future perspective and limitations

This thesis has several limitations, the most important of which is our very small sample size and the grossly uneven distribution of participants from the experimental group and the control group. No comparison in which an entire group consists of a single individual can claim to be full of relevant information. Consequently, it comes as no surprise that the results from our behavioral analysis are partly in the opposite direction of our expectation, while simultaneously being associated with small effect sizes and large CrIs'. This problem is only exacerbated in our fMRI analysis, as we only had data from two scanning sessions both of which happened under the influence of amphetamine for a large majority of our sample.

Another major shortcoming of our study is that we only tested male volunteers. There is evidence for sex differences in schizophrenia (Sun et al., 2016). While it seems reasonable to exclude female subjects from a study such as ours due to the established link between the hormonal cycle and reward learning (Dreher et al., 2007), the generalizability of such studies to schizophrenic patients suffers greatly because a large part of the schizophrenic population consists of women.

A further feasible way to improve studies such as ours would to account for further variables such as working memory and personality dimensions. Since our task was rather complex compared to simple reinforcement learning tasks, which already are affected by the subjects

working memory capacity (Deserno et al., 2016), it seems unlikely that his would not be modulating factor in task performance during the reward based predictive inference task. Personality dimensions have also been found to affect the subjective drug experience produced by amphetamines (Kirkpatrick et al., 2013) and have also been shown to predict a subjects proneness to sensitization (Boileau et al., 2006). Research has also been able to identify personality types that are associated with schizophrenia (Camisa et al., 2005). Therefore, controlling the personality type during such a study might deliver important insights into the connections between dopamine processing, schizophrenia, and personality.

6.2 Conclusion

Our aim with this thesis was to investigate the role of dopamine hypersensitivity on the behavioral and neural aspects of reward based learning processes. In order to achieve this, we applied a multi-methodological approach combining pharmacological manipulation of healthy volunteers' dopamine levels, fMRI and a reward based learning task. Unfortunately, the effects of amphetamine sensitization we could find from our behavioral and neural data was very limited, likely as a consequence of our small and uneven sample size resulting from the COVID-19 pandemic. In order to be able to make conclusions about the hypothesized links between reward learning, dopamine and psychosis future studies should strive to use a similar multi-methodological approach, with much larger sample sizes.

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8 Appendix

8.1 German Abstract

Es wird angenommen, dass die Auslösung und der Rückfall von Psychosen bei Schizophrenie eine ätiologische Folge eines hyperreaktiven dopaminergen Systems ist, das zu einer abnormen Belohnungs- und Aufmerksamkeitsverarbeitung sowie zu einer pathologischen Reaktion auf alltägliche Stressfaktoren führt. Anhand eines doppelblinden, placebokontrollierten Studiendesigns untersuchten wir die Auswirkungen einer Amphetamin-Sensibilisierung, die den hyperdopaminergen Zustand psychotischer Personen nachahmt, auf den durchschnittlichen Vorhersagefehler, in einer belohnungsbasierten prädiktiven Inferenzaufgabe. Darüber hinaus untersuchten wir die Auswirkungen einer akuten Verabreichung von Amphetamin sowie einer Exposition gegenüber einem geringfügigen psychosozialen Stressor bei sensibilisierten männlichen Teilnehmern (N=9). Mithilfe von fMRI testeten wir auch auf neuronale Unterschiede, die sich aus unserer Sensibilisierungsmanipulation ergaben. Darüber hinaus untersuchten wir, wie die subjektive Drogenerfahrung sowie physiologische Messwerte wie Herzfrequenz und Blutdruck durch das hyperreaktive Dopaminsystem der Teilnehmer infolge der Amphetamin-Sensibilisierung beeinflusst wurden. Unsere Ergebnisse deuten auf eine negative Auswirkung der Sensibilisierung auf den mittleren Vorhersagefehler hin, was zu einer erhöhten Aufgabenleistung führte, aber auch mit einer großen Unsicherheit verbunden war. Stress und akute Amphetaminverabreichung schienen sich positiv auf den mittleren Vorhersagefehler auszuwirken, was zu einer schlechteren Leistung führte, aber auch mit Unsicherheit verbunden war. Die Herzfrequenz schien durch unser Sensibilisierungsschema nicht beeinflusst zu werden, während der Blutdruck einen Effekt zeigte, der auf einen geringen Anstieg des diastolischen Blutdrucks hindeutete. Wir fanden bei unseren Probanden keine signifikanten neuronalen Unterschiede vor und nach der Sensibilisierung.

8.2 Model results Model 6

Table A1

Model	Formula											
M6	*mean prediction error*	~	+	*session*	+	*amphetamine*	+	*sensitized*	+	*stress*		
			+	*stress*	:	*sensitized*	+	*(session|ID)*				

Note. Model definition of Model 6

Table A2

ß	***Estimate***	***l-95%CrI***	***u-95%CrI***
Intercept	-0,10	-0,67	0,47
session2	0,22	-0,41	0,87
session3	0,14	-0,42	0,69
session4	-0,36	-1,30	0,60
session5	0,24	-1,20	1,69
sensitized	-0,14	-0,73	0,46
stress	0,24	-1,20	1,68
amph_admin	0,32	-0,40	1,01
sensitized:stress	-0,16	-1,04	0,74

Note. Intercept = B1, session2 = A1, session3 = B2, session4 = A4, session5 = M1, l-95%CrI = lower end of the credible interval of the estimated parameter of the posterior distribution, u-95%CrI = upper end of the credible interval of the estimated parameter of the posterior distribution

8.3 Model results Model 5

Table A3

Model	Formula											
M5	*mean prediction error*	~	+	*session*	+	*amphetamine*	+	*sensitized*	+	*stress*		
			+	*(session|ID)*								

Note. Model definition of Model 5

Table A4

ß	*Estimate*	*l-95%CrI*	*u-95%CrI*
Intercept	-0,09	-0,65	0,46
session2	0,21	-0,39	0,85
session3	0,15	-0,39	0,70
session4	-0,33	-1,25	0,60
session5	0,17	-1,23	1,59
sensitized	-0,15	-0,74	0,43
stress	0,31	-0,39	1,00
amph_admin	0,20	-1,22	1,60

Note. Intercept = B1, session2 = A1, session3 = B2, session4 = A4, session5 = M1, l-95%CrI = lower end of the credible interval of the estimated parameter of the posterior distribution, u-95%CrI = upper end of the credible interval of the estimated parameter of the posterior distribution

8.4 Model results Model 4

Table A5

Model	**Formula**
M4	*mean prediction error* ~ + *session* + *amphetamine* + *sensitized* + (*session*|*ID*)

Note. Model definition of Model 4

Table A6

ß	*Estimate*	*l-95%CrI*	*u-95%CrI*
Intercept	-0,09	-0,65	0,46
session2	0,21	-0,39	0,84
session3	0,15	-0,37	0,69
session4	-0,34	-1,24	0,57
session5	0,36	-0,24	0,94
sensitized	-0,15	-0,74	0,42
amph_admin	0,32	-0,36	0,98

Note. Intercept = B1, session2 = A1, session3 = B2, session4 = A4, session5 = M1, l-95%CrI = lower end of the credible interval of the estimated parameter of the posterior distribution, u-95%CrI = upper end of the credible interval of the estimated parameter of the posterior distribution

8.5 Model results Model 3

Table A7

Model	Formula
M3	*mean prediction error* ~ + *session* + *amphetamine* + *sensitized* + *(*1|*ID)*

Note. Model definition of Model 3

Table A8

ß	***Estimate***	***l-95%CrI***	***u-95%CrI***
Intercept	-0,10	-0,81	0,59
session2	0,06	-0,52	0,68
session3	0,38	-0,16	0,92
session4	-0,28	-1,23	0,67
session5	0,60	0,05	1,15
sensitized	-0,45	-1,02	0,09
amph_admin	0,50	-0,13	1,14

Note. Intercept = B1, session2 = A1, session3 = B2, session4 = A4, session5 = M1, l-95%CrI = lower end of the credible interval of the estimated parameter of the posterior distribution, u-95%CrI = upper end of the credible interval of the estimated parameter of the posterior distribution

8.6 Model results Model 2

Table A9

Model	Formula
M2	*mean prediction error* ~ + *session* + *amphetamine* + (1|*ID*)

Note. Model definition of Model 2

Table A10

ß	*Estimate*	*l-95%CrI*	*u-95%CrI*
Intercept	-0,11	-0,85	0,59
session2	-0,08	-0,66	0,51
session3	0,04	-0,31	0,40
session4	-0,83	-1,52	-0,14
session5	0,27	-0,07	0,59
amph_admin	0,70	0,07	1,35

Note. Intercept = B1, session2 = A1, session3 = B2, session4 = A4, session5 = M1, l-95%CrI = lower end of the credible interval of the estimated parameter of the posterior distribution, u-95%CrI = upper end of the credible interval of the estimated parameter of the posterior distribution

8.7 Model results Model 1

Table A11

Model	**Formula**					
M1	*mean prediction error*	~	+	*session*	+	(1|*ID*)

Note. Model definition of Model 1

Table A12

ß	*Estimate*	*l-95%CrI*	*u-95%CrI*
Intercept	-0,09	-0,81	0,60
session2	0,46	0,09	0,83
session3	0,02	-0,34	0,40
session4	-0,17	-0,55	0,21
session5	0,25	-0,12	0,62

Note. Intercept = B1, session2 = A1, session3 = B2, session4 = A4, session5 = M1, l-95%CrI = lower end of the credible interval of the estimated parameter of the posterior distribution, u-95%CrI = upper end of the credible interval of the estimated parameter of the posterior distribution