Salience and Motivated Behaviour in Schizophrenia

By

Suzanne Rosalie Neumann

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Abstract

Schizophrenia is a long-term psychotic disorder that affects approximately 1% of the population worldwide. Schizophrenia is characterised by negative symptoms, such as anhedonia and social withdrawal, and positive symptoms, such as hallucinations and delusions. The impact of schizophrenia reaches beyond the impaired social and cognitive function of the individual, affecting families and wider communities. Therefore, despite its low prevalence, there is a long history of multidisciplinary research investigating the causes of schizophrenia. The effect of antipsychotics in reducing the intensity of symptoms, through their antagonistic effect on dopamine, has led to dopaminergic based theories of schizophrenia. One such theory is based on aberrant salience, the assignment of importance to stimuli that have no intrinsic or learned value or salience. The aberrant salience hypothesis links hyperdopaminergic activation to symptoms of schizophrenia through the intermediary effect of motivational salience. Specifically, it is proposed that hyperdopaminergic activation in schizophrenia creates an aberrant motivational association with a stimulus, leading to cognitive explanations for the unexplained importance that contribute to the development of symptoms. Behavioural and neural evidence supports heightened aberrant salience in schizophrenia, although specific measures of aberrant salience have yielded inconsistent results. There is also a large body of evidence suggesting cognitive functions anchored in dopaminergic activation, such as reward processing and motivated behaviour, are impaired in schizophrenia. To date, however, the assumption that motivational salience mediates the relationship between hyperdopaminergic activation and aberrant salience has not been tested.

The current project sought to elucidate the relationship between aberrant salience and motivational salience. The convergent validity among measures of aberrant salience (Salience Attribution Task and Aberrant Salience Inventory) and motivated behaviour (Effort Expenditure for Rewards Task and Stimulus Chase Task) were investigated in undergraduates. To assess whether aberrant salience, and the underlying relationship with motivational salience, is
unique to schizophrenia, the same measures were completed by individuals diagnosed with schizophrenia, experiencing symptoms of anxiety, or unaffected by mental health. Whereas schizophrenia was associated with heightened aberrant salience, the aberrant salience indices lacked specificity, sensitivity, and convergent validity. Furthermore, whereas schizophrenia was associated with maladaptive motivated behaviour, there was limited evidence supporting a relationship between measures of aberrant salience and motivational salience. The failure to find evidence of such a relationship may be due to issues with the aberrant salience measures or the underlying assumption that motivational salience mediates aberrant salience. Further research is needed to develop measures of aberrant salience that are anchored to known neural systems underlying salience processing.
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>ADDS</td>
<td>Alcohol and Drug Abuse Dependence Screen</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ASI</td>
<td>Aberrant Salience Inventory</td>
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<tr>
<td>BAS</td>
<td>Behavioural activation system</td>
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<tr>
<td>BIS</td>
<td>Behavioural inhibition system</td>
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<tr>
<td>CEN</td>
<td>Central executive network</td>
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<tr>
<td>CWBIS</td>
<td>Carver and White (1994) BIS scale</td>
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<tr>
<td>CWBAS</td>
<td>Carver and White (1994) BAS scales</td>
</tr>
<tr>
<td>DASS</td>
<td>Depression Anxiety Stress Scales</td>
</tr>
<tr>
<td>dlPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<tr>
<td>DMN</td>
<td>Default mode network</td>
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<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders revision 5</td>
</tr>
<tr>
<td>EEfRT</td>
<td>Effort Expenditure for Rewards Task</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalograph</td>
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<tr>
<td>ERP</td>
<td>Event related potential</td>
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<tr>
<td>FEP</td>
<td>First episode psychosis</td>
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<td>FFFS</td>
<td>Flight-fight-freeze system</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases 10th revision</td>
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<tr>
<td>L1SM</td>
<td>SEM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure</td>
</tr>
<tr>
<td>LPP</td>
<td>Late positive potential ERP</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini-International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>mOFC</td>
<td>Medial orbitofrontal cortex</td>
</tr>
<tr>
<td>mPFC</td>
<td>medial prefrontal cortex</td>
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<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NMDAR</td>
<td>N-methyl-D-aspartate receptor</td>
</tr>
<tr>
<td>OFC</td>
<td>Orbitofrontal cortex</td>
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<tr>
<td>PCC</td>
<td>Posterior cingulate cortex</td>
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<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>PID-5A</td>
<td>Nine items comprising the Anxiousness facet of the Personality Inventory for DSM-5</td>
</tr>
<tr>
<td>PLE</td>
<td>Psychotic-Like Experiences scale</td>
</tr>
<tr>
<td>RPE</td>
<td>Reward prediction errors</td>
</tr>
<tr>
<td>RST</td>
<td>Reinforcer sensitivity theory</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SN</td>
<td>Salience network</td>
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<td>SAT</td>
<td>Salience Attribution Test</td>
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<tr>
<td>SCT</td>
<td>Stimulus Chase Task</td>
</tr>
<tr>
<td>TRS</td>
<td>Treatment-resistant schizophrenia</td>
</tr>
<tr>
<td>UHR</td>
<td>Ultra-high risk of psychosis</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>VS</td>
<td>Ventral striatum</td>
</tr>
<tr>
<td>vmPFC</td>
<td>Ventromedial prefrontal cortex</td>
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Chapter One

Introduction

1.1 Background

1.1.1 Schizophrenia

Schizophrenia is a psychotic disorder that affects thought and behaviour (Barbato, 1996). Schizophrenia is characterised by negative and positive symptoms. Negative symptoms refers to symptoms of diminished functioning such as avolition, anhedonia, asociality, affective flattening, and poverty of speech (Barbato, 1996; Foussias, Agid, Fervaha, & Remington, 2014; Messinger et al., 2011). Positive symptoms refers to behaviours or experiences that are additional to, or not usually present in, typical experience. Examples include delusions, hallucinations, and disorganised speech and behaviour (Barbato, 1996; Huxley & Fonseca, 2014). Schizophrenia is also characterised by a wide range of cognitive deficits. These include impairments in perception, attention, working memory, cognitive control, and executive function (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Kelly et al., 2019).

Schizophrenia is ubiquitous (Barbato, 1996). It affects between four (McGrath, Saha, Chant, & Welham, 2008; Saha, Chant, Welham, & McGrath, 2005) and seven (Moreno-Küstner, Martín, & Pastor, 2018) people per thousand (lifetime prevalence), approximately 29 million people globally (Barbato, 1996). The estimated heritability of schizophrenia is around 80% (Hilker et al., 2017) and its prevalence tends to be higher among ethnic minority groups such as Māori (Kake, Arnold, & Ellis, 2008). Onset of positive symptoms is typically in late adolescence (Gogtay, Vyas, Testa, Wood, & Pantelis, 2011), although there are sex differences. Onset in males is higher during adolescence whereas onset in females is usually later (Eranti, MacCabe, Bundy, & Murray, 2013; Häfner, 2005; Rabinowitz, Levine, & Häfner, 2006).

Schizophrenia is associated with reduced life expectancy. Comorbid medical conditions (Laursen, 2014; Weber et al.), lifestyle factors (Laursen, 2014), and suicide (Palmer et al. 2005) contribute to the 20-year reduction in
life-span compared to the average population (Laursen, 2014). Risk of suicide is higher immediately following first diagnosis (Palmer et al. 2005; Simon et al. 2018).

Cognitive dysfunction is common in schizophrenia (Hofer et al., 2005). Common neurocognitive deficits include poor working memory and executive dysfunction (Millan, Fone, Steckler, & Horan, 2014; Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). Social cognition, or the cognitive processes that underlie social interaction and the ability to perceive, interpret, and respond to others, is also diminished in schizophrenia (Green et al., 2008). For example, theory of mind, the ability to infer mental states of others and self (Brüne, 2005), is impaired (Bora, Yucel, & Pantelis, 2009).

Schizophrenia has a social, emotional, and financial impact on individuals, their families, and the wider community. The consequences of schizophrenia include social disability, such as unemployment (Bouwmans, De Sonneville, Mulder, & Hakkaart-van Roijen, 2015) and reduced self-care (Montejo, 2010). Cognitive ability has been shown to predict employment and independent living outcomes in schizophrenia (Hofer et al., 2005). Conversely, employment predicted increased well-being (Priebe, Warner, Hubschmid, & Eckle, 1998). In young people, employment and social inclusion predicted recovery (Berry & Greenwood, 2018). Therefore, cognitive deficits associated with schizophrenia lead to reduced social integration that affects outcome. Social dysfunction is compounded by the negative effects of self- and social-stigma (Karidi et al., 2010; Koschorke et al., 2014; Lien et al., 2018). Family relationships can positively affect psychosocial functioning (Guada, Hoe, Floyd, Barbour, & Brekke, 2012). However, schizophrenia places a strain on families (Ahlem et al., 2017; Caqueo-Urízar et al., 2017; Shibire et al., 2003; Y. Yu et al., 2017), especially caregivers (Mitsonis et al., 2012). Thus, the support network required to facilitate positive outcomes is affected. Schizophrenia contributes to health care costs disproportionately to its prevalence (H. Y. Chong et al., 2016). The length of untreated psychosis was found to predict outcome (relapse and positive symptoms), such that the longer the delay to treatment, the poorer the outcome (Austin et al., 2015; Cechnicki, Hanuszkiewicz, Polczyk, & Bielańska, 2011; Marshall et al., 2005; McGorry, Nelson, Goldstone, & Yung, 2010; Veru,
Jordan, Joober, Malla, & Iyer, 2016). Therefore, early intervention has a positive individual, social, and financial impact but efficacy is hindered by diminished functioning.

### 1.1.2 Aberrant Salience

Factors that contribute to schizophrenia include genetic and biological (Fromer et al., 2014; Kavanagh, Tansey, O’Donovan, & Owen, 2015; Müller, Weidinger, Leitner, & Schwarz, 2015; Ripke et al., 2014), social and environmental (Blomström et al., 2016; Kirkbride et al., 2017). Whereas research has investigated associations between such factors, the link between neurobiology and phenomenology of psychosis is rarely addressed. Psychosis is associated with phenomenological factors such as sharpened senses, increased significance, impending understanding, and heightened emotionality and cognition (Cicero, Kerns, & McCarthy, 2010). These factors suggest an increased salience of internal and external stimuli.

Kapur (2003) proposed that the positive symptoms (or psychosis) occur as a direct or indirect result of aberrant salience. Aberrant salience is the assignment of importance to otherwise irrelevant internal and external stimuli. Aberrant salience can be attached to completely irrelevant stimuli, or it can exaggerate the importance of moderately relevant stimuli (henceforth referred to as irrelevant stimuli). For example, hallucinations represent a direct exaggeration of internal stimuli whereas delusions occur as the result of an implausible explanation for the aberrant salience of external stimuli, thus are indirect. Additionally, the presence of delusions and subthreshold hallucinations has been shown to predict onset of schizophrenia and may reflect the early effects of aberrant salience (Smeets et al., 2013).

Aberrant salience may explain the relationship between neurological disturbances in the dopaminergic system and the symptoms of psychosis. Dopaminergic dysregulation in schizophrenia is thought to cause, or create, stimulus salience (Kapur, 2003). Spontaneous dopamine neuron firing in the mesocorticolimbic pathways, in conjunction with the presentation (internal or external) of an irrelevant stimulus, leads to an erroneous association based on
the typical functions of dopamine. In other words, the brain interprets the stimulus as important because of dopaminergic firing. However, whereas erroneous triggering of the mesocorticolimbic system may cause irrelevant stimuli to be momentarily salient, this does not account for aberrant salience. Deficits in motivational salience, including the monitoring and updating of stimulus information, are required to support aberrant salience.

1.1.3 Motivational Salience

Motivational salience is the desire to obtain or avoid a stimulus. Motivational salience refers to the anticipatory pleasure that fluctuates based on state neurobiological factors, such as hunger (Berridge, 2013). Motivational salience affects approach and avoidance (motivated) behaviour and is affected by sensitivity to gain and loss (Gray, 1981; Gray & McNaughton, 2000). Furthermore, sensitization to environmental risk factors may result in an enduring amplified response to internal and external cues (Collip, Myin-Germeys, & van Os, 2008), affecting motivated behaviour and contributing to aberrant salience.

1.1.4 The Missing Link

Many factors contribute to the symptoms of schizophrenia. The aberrant salience framework links the neurobiological and phenomenological factors of psychosis. Evidence suggests that schizophrenia is associated with behaviour that reflects aberrant salience. However, specific measures of aberrant salience have yielded inconsistent results and comparison of aberrant salience measures is needed. Furthermore, the current body of evidence supporting aberrant salience lacks data about the relationship between aberrant salience and motivational salience. Thus, key aspects of the aberrant salience framework remain untested.

1.2 Research aims

The aim of the current research project was to investigate the relationships among measures of motivational salience and aberrant salience. Based on Kapur’s (2003) aberrant salience theory, measures of aberrant salience and
motivated behaviour should correlate, such that impairments in motivated behaviour should predict higher aberrant salience scores. Whereas a failure to find this relationship may challenge the aberrant salience hypothesis, the construct validity of measures of aberrant salience also need substantiating.

The objectives of the project were to determine whether aberrant salience measures are: (a) measuring the same construct; (b) correlated with measures of motivated behaviour, motivational salience, and reinforcer sensitivity; and (c) measuring a construct unique to schizophrenia or a characteristic of other psychopathologies.

At the time of project design, two standardised measures of aberrant salience were identified for use in the study: the Salience Attribution Test (SAT; Roiser et al., 2009) and the Aberrant Salience Inventory (ASI; Cicero et al., 2010). The SAT is a computerised cognitive behavioural task that utilises a reinforcement learning paradigm to assess speed of response to relevant and irrelevant stimuli. The ASI is a self-report, yes/no questionnaire that measures the phenomenological experience of aberrant salience. Motivational salience was measured using the Effort Expenditure for Rewards Task (EEfRT; Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009) and the Stimulus Chase Task (SCT; Hall, Chong, McNaughton, & Corr, 2011). The EEfRT provides a measure of the willingness to exert effort (motivated behaviour) based on reward value and probability of obtaining reward. The Stimulus Chase Task provides a ratio of gain relative to loss sensitivity and approach relative to avoidant behaviour. Use of these two measures of motivational salience, therefore, provided the opportunity to explore the relationship between factors affecting motivational salience and their relationship to aberrant salience.

1.3 Thesis Outline

In reviewing the aberrant salience hypothesis, it is important to look at each component of the hypothesis, whether evidence supports a difference in schizophrenia, compared to unaffected individuals, and how this relates to aberrant salience. Therefore, I review three issues.

In Chapter 2 I look at aberrant salience. I first review literature linking dopaminergic activation to aberrant salience then present evidence
investigating aberrant salience in schizophrenia. I then review evidence showing how the salience network and default mode network interact to support salience processing and how atypical neural activation in these networks may contribute to aberrant salience in schizophrenia. Finally, I present findings from studies using the SAT and the ASI before discussing limitations of the aberrant salience hypothesis.

In Chapter 3, I consider reward and motivation. First, I outline the function of dopaminergic activation along the mesocorticolimbic pathways and how this supports reward processing. I define motivational salience and highlight the link between dopamine and motivational salience. I present the reinforcement sensitivity theory, linking this theory to motivational salience, and outlining issues with the current, popular measure. Following this, I critically evaluate evidence suggesting that dopamine signals salience and reward. I review how disruptions to dopamine impact reward processing before turning attention to evidence of differential reward and motivation processing in schizophrenia.

In the final literature review, Chapter 4, I assess whether research supports the theoretical association between aberrant salience and motivational salience. I review neurological and behaviour evidence, comparing findings from unaffected individuals with those found in individuals with schizophrenia. I highlight the lack of evidence on the relationship between these two constructs. I propose a potential extension to the aberrant salience framework, derived from currently available literature, that could support an explanation for negative and positive symptoms.

Chapters 5 and 6 are manuscripts, submitted as journal articles, reporting on findings from this research. In the first study, I assessed the relationship among measures of aberrant salience, reward processing, and reinforcer sensitivity in university students. This study was run to obtain baseline data on relationships among the measures. This manuscript was published in the *International Journal of Methods in Psychiatric Research* (Neumann & Linscott, 2018). As Chapter 5, it was amended to fit with the thesis format. The second manuscript, appearing as Chapter 6, reports on the relationship between the same measures in individuals diagnosed with
schizophrenia, individuals experiencing anxiety, and individuals unaffected by mental disorder. This manuscript has been submitted for publication (Neumann, Linscott, & Glue, 2019) and has been amended to fit the thesis format and remove redundancy (e.g., if components of methods were already described in earlier chapters, these were not repeated). The co-authors on these manuscripts were supervisors of my doctoral research. They contributed to conceptualization of the research, provided oversight of its design and planning, assisted with aspects of assessment and analyses, and contributed to preparation of the written reports. These contributions reflect the standard level of assistance provided by doctoral supervisors.

In the final chapter I discuss the overall results in light of the aims. I compare the findings to previous research, discuss potential implications for future research and the limitations of current studies. I suggest future research directions.
Chapter Two

Is Aberrant Salience the Core of Schizophrenia?

In this chapter I review the evidence for aberrant salience as an explanation of the positive symptoms of schizophrenia. I first briefly note the role of the neurotransmitter dopamine in signalling stimulus salience. I compare typical functioning with functioning in schizophrenia, reviewing neurological, cognitive, and behavioural evidence for aberrant salience in schizophrenia. I then present evidence of neural network influence on salience before presenting evidence of aberrant salience in schizophrenia using two indices: the Salience Attribution Task (SAT) and Aberrant Salience Inventory (ASI). I discuss the limitations of the aberrant salience hypothesis and review gaps in current evidence. These provide the questions addressed in the current thesis.

2.1 Dopamine and Aberrant Salience

2.1.1 Dopamine and salience

Dopamine cells often fire in the context of stimuli that are rewarding (Bromberg-Martin, Matsumoto, & Hikosaka, 2011; Wise, 2004; L. Zhang, Doyon, Clark, Phillips, & Dani, 2009; Zweifel et al., 2009) or novel (Berridge, 2013; Hazy, Frank, & O’Reilly, 2010; Horvitz, 2000; Schultz, 2010). Berridge and Robinson (1998) suggest dopamine is associated with incentive salience, the wanting rather than liking component of rewards. Dopaminergic neurons project to neural regions associated with cost and effort computations (Salamone, Correa, Mingote, & Weber, 2005; Salamone, Cousins, & Snyder, 1997; Wardle, Treadway, Mayo, Zald, & de Wit, 2011), emotion and valence processing (Jackson & Moghaddam, 2001), evaluation and prediction of outcomes (Jahn, Nee, Alexander, & Brown, 2014), and motivated behaviour (Balconi & Crivelli, 2010; McNaughton, 2004; Salamone et al., 1997). Thus, dopamine is associated with value encoding, reward anticipation, learning, and goal-directed behaviour (Kim, 2013).
Aversive stimuli were thought to elicit an inhibitory dopaminergic response (Schultz, 2007; Ungless, 2004). This inhibitory response suppresses the projection of activation to regions implicated in value computations (M. Matsumoto & Hikosaka, 2009) and prevents an association between aversive stimuli and reward value. More recent evidence suggests a common excitatory dopaminergic response to both appetitive and aversive stimuli (Bromberg-Martin et al., 2011). This excitatory response projects to the medial prefrontal cortex (mPFC; Ventura, Morrone, & Puglisi-Allegra, 2007), a region associated with focusing attention and planning (Kim, 2003), and to the dorsal striatum (Matsumoto & Hikosaka, 2009), which is associated with action selection and initiation (Belleine, Delgado & Hikosaka, 2007). Based on the projections to regions associated with attentional focus, for both appetitive and aversive stimuli, dopaminergic activation facilitates salience.

### 2.1.2 Dopamine and aberrant salience

The relationship between dopamine and schizophrenia was discovered following evidence that antipsychotics, which reduce the experience of psychotic symptoms, were dopamine antagonists (Howes & Kapur, 2009; Seeman, 1987). Kapur (2003) proposed that dysregulated dopaminergic firing in schizophrenia contributes to associations between irrelevant stimuli and motivational salience; the degree to which a stimulus elicits goal-directed behaviour. Because they block dopamine receptors, dopamine antagonists attenuate motivational salience (Wise, 2004) thus lessen the experience of psychosis (Kapur & Mamo, 2003).

According to the aberrant salience hypothesis, when dopamine firing is dysregulated, irrelevant external and internal stimuli are selected and attended to (Kapur, 2003; Winton-Brown, Fusar-Poli, Ungless and Howes, 2014). In everyday life, experiences are incorporated into schemata (Plant & Stanton, 2013). A schema is the generic cognitive representation of a stimulus that facilitates the integration and categorisation of information (Plant & Stanton, 2013). Novel stimuli may be incorporated into an existing schema or dismissed as unimportant (Graziano & Webb, 2015). However, in schizophrenia, irrelevant stimuli appear relevant due to aberrant salience. Irrelevant stimuli are,
therefore, incorporated into existing schemata (Howes and Kapur, 2009; Winton-Brown et al., 2014), which explains the ethno-cultural specificity of delusions and hallucinations reported in psychosis (Howes & Kapur, 2009; Stompe et al., 2006; Winton-Brown, Fusar-Poli, Ungless, & Howes, 2014; Yamada, Barrio, Morrison, Sewell, &Jeste, 2006). For example, a review of historical case studies found a relationship between delusional beliefs and the individual’s religious and cultural beliefs (Krzystanek, Krysta, Klasik, & Krupka-Matuszczyk, 2012).

Although the mechanism by which dopaminergic dysregulation influences salience is unclear, neurobiological (electroencephalographic) and imaging studies have identified regions of interest. Specifically, key networks associated with salience processing, which are influenced by dopamine activation, exhibit differential processing, structure, and function in schizophrenia compared to unaffected individuals.

### 2.2 Evidence supporting Aberrant Salience in Schizophrenia

Neurological, cognitive, and self-report data show differences in perceptual experience and cognitive processing indicative of aberrant salience. Such differences are evident in those at risk of, and diagnosed with, schizophrenia. The aberrant salience hypothesis states that, whereas biophysical differences lead to cognitive processing differences, it is the interpretation of these differences that leads to the development of symptoms. In assessing the aberrant salience hypothesis, it is important to consider methods for assessing conscious and subconscious cognitive processing. For example, data from self-report ratings provide an explicit measure of cognitive processing, whereas behavioural and physiological assessments provide implicit measures (Underwood & Bright, 1995).

#### 2.2.1 Aberrant attentional processing in individuals at risk of schizophrenia

Individuals at risk of psychosis show altered semantic processing, characteristic of aberrant salience. Kerns and Berenbaum (2000) investigated the relationships among measures of psychosis proneness, semantic processing and affective valence (positive and negative) in undergraduates. Participants were
assigned to one of three groups based on three measures of psychosis proneness: high perceptual aberration and/or magical ideation (high psychosis prone group), high social anhedonia (low psychosis prone group), or low perceptual aberration, magical ideation and social anhedonia (comparison group). Semantic processing and affective valence were measured using a word-pair association task. Baseline average response latency to unrelated word pairs were subtracted from response latency to target word pairs. Word-pairs were either semantic (e.g., animals) or functional. The low psychosis prone group responded faster to positively valenced words than negatively valenced words. The high psychosis group responded faster than the comparison group to semantically primed words. Heightened semantic priming has also been found in schizophrenia (Lerner, Bentin, & Shriki, 2012).

Additionally, the high psychosis prone group responded faster to non-associated words than baseline, whereas the low psychosis group responded slower than baseline (Kerns & Berenbaum, 2000). The results suggest prodromal aberrant attentional processing, resulting in the over-inclusion and increased importance of irrelevant stimuli.

### 2.2.2 Increased aberrant salience and reduced adaptive salience in schizophrenia

Aberrant salience in schizophrenia is evident in atypical self-rated and physiological responses to neutral stimuli. Haralanova, Haralanova, Beraldi, Moller, and Hennig-Fast (2012) investigated self-rated emotional arousal to pictures of neutral and negative social scenes in paranoid schizophrenia. Compared to unaffected individuals, participants with paranoid schizophrenia had higher levels of emotional arousal to neutral stimuli. Similarly, negative non-social stimuli elicited higher ratings of emotional arousal in schizophrenia than negative social stimuli (Okruszek et al., 2016). Schizophrenia is also associated with increased ERP amplitudes to neutral compared to negative (WP Horan, Hajcak, Wynn, & Green, 2013) and non-social compared to social stimuli (Peterman, Bekele, Bian, Sarkar, & Park, 2015). The adaptive pattern of heightened arousal to negative and social stimuli in unaffected individuals is, therefore, absent in schizophrenia. Instead, neutral and non-social stimuli elicit
higher arousal, indicating an aberrant assignment of importance to stimuli not attended to in unaffected individuals.

Deficits in social cognition have frequently been reported in schizophrenia (Couture, Penn, & Roberts, 2006; Daros, Ruocco, Reilly, Harris, & Sweeney, 2014; Kohler, Walker, Martin, Healey, & Moberg, 2010; Yalcinsiedentopf et al., 2014). Symptoms of psychosis are linked to the aberrant salience of social cues. One such nonverbal form of social communication is a non-verbal gesture, such as a hand motion (Perkins, 2016). Bucci, Startup, Wynn, Baker, and Lewin (2008) investigated the relevance assigned to non-verbal gestures in schizophrenia. While correctly interpreting meaningful gestures, albeit less accurately than unaffected individuals, participants who experienced delusions of reference misinterpreted the relevance of non-meaningful, incidental gestures. Delusions of reference is the belief that irrelevant stimuli have personal meaning (Startup, Bucci, & Langdon, 2009). Startup et al. (2009) argued that the salience of neutral stimuli results in a personally significant explanation of their importance, leading to delusions of reference. A subsequent study found participants with schizophrenia were more likely to misinterpret the personal significance of ambiguous gestures and gestures directed away from them but not incidental gestures directed towards them (White, Borgan, Ralley, & Shergill, 2016). These findings support the argument that irrelevant stimuli can be incorporated into schema and influence symptoms.

Aberrant salience is also evident in the atypical threat superiority effect in schizophrenia. The threat superiority effect is the tendency for more effective detection and preferential processing to be assigned to potentially threatening stimuli (e.g., angry faces or snakes; Pinkham et al., 2014; Subra, Muller, Fourgassie, Chauvin, & Alexopoulos, 2017). However, in schizophrenia, threat superiority effect is intact for non-social (e.g., snakes) but not social threats (e.g., angry faces; Pinkham et al., 2014). Additionally, unaffected individuals find angry faces more distracting than individuals with schizophrenia, who are more distracted by happy then angry or neutral faces (Grave, Soares, Morais, Rodrigues, & Madeira, 2017).
However, not all social cognition deficits are neatly explained within the aberrant salience hypothesis. Impairments in the perception of emotion (Kohler et al., 2010), including recognition of facial expressions (Abram et al., 2014; Daros et al., 2014; Yalçın-siedentopf et al., 2014), appear to reflect reduced adaptive salience. When discriminating between neutral and angry faces, participants with schizophrenia required significantly more facial information, attended to regions around the nose and mouth more, and regions around the eyes less, than unaffected individuals (Clark, Gosselin, & Goghari, 2013). Furthermore, schizophrenia was associated with a reduction in the number and duration of visual fixations on faces compared to unaffected individuals (Loughland, Williams, & Gordon, 2002; Nikolaides et al., 2016). Accuracy in emotion identification was not affected. Such findings indicate reduced adaptive salience, or importance of relevant stimuli, rather than aberrant salience.

2.2.3 Summary

Schizophrenia is associated with aberrant attention processing leading to an over inclusion of stimuli (Kerns & Berenbaum, 2000). In turn, arousal (Haralanova et al., 2012) and neural activation (W P Horan et al., 2013) are heightened in response to neutral stimuli and processing of non-meaningful (Bucci et al., 2008; T. P. White, Borgan, et al., 2016) and non-threatening social cues impaired (Grave et al., 2017). Reduced adaptive salience is evident in impaired processing of social cues (Clark et al., 2013; Loughland et al., 2002), including threatening ones (Okruszek et al., 2016; Peterman et al., 2015; Pinkham et al., 2014). The idea that positive symptoms develop from aberrant salience is also supported. Individuals at risk of psychosis exhibit aberrant salience (Kerns & Berenbaum, 2000). Furthermore, aberrant salience can explain the variance in expression of symptoms (Bucci et al., 2008; Startup et al., 2009; White et al., 2016). The data from various methodologies provide a strong argument for the aberrant salience hypothesis.
2.3 Neural Functions and Networks that Contribute to Aberrant Salience

2.3.1 Sensory gating

Sensory gating, or attentional filtering, allows the brain to filter out unnecessary information (Postle, 2005). McGhie and Chapman (1961) first suggested that there are sensory gating deficits in schizophrenia. This has been confirmed by subsequent neurophysiology using an electroencephalograph (EEG) to assess auditory sensory gating (Judd, McAdams, Budnick, & Braff, 1992; Myles-Worsley, 2002; Williams, Nuechterlein, Subotnik, & Yee, 2011). The P50 is an event-related potential (ERP) with a peak positivity around 50ms following presentation of an auditory stimulus. In unaffected individuals, the amplitude of the P50 is usually significantly smaller on the second presentation of an auditory stimulus compared to the first (Judd et al., 1992; Micoulaud-Franchi et al., 2012). This difference is represented as a ratio. Low ratios indicate auditory gating, that is, the filtering out of auditory stimuli on second presentation, with the inhibition occurring at a very early stage of processing (Judd et al., 1992; Micoulaud-Franchi et al., 2012). Higher P50 amplitude ratios in schizophrenia indicate reduced auditory gating (Judd et al., 1992; Myles-Worsley, 2002). It follows that reduced sensory gating could result in attendance to irrelevant stimuli and contribute to aberrant salience.

Inefficient sensory gating in schizophrenia is associated with perceptual experience and symptom severity. Micoulaud-Franchi et al. (2012) assessed P50 amplitude ratios, using an auditory click, in schizophrenia and unaffected individuals. They then presented participants with environmental sounds, heard in everyday life, and digitally created abstract sounds. Participants were asked to rate the valence of each sound. Compared to unaffected individuals, participants with schizophrenia had a higher mean P50 amplitude ratio, rated abstract sounds as more familiar, and rated reassuring and environmental sounds as more invasive and frightening. The P50 amplitude ratio positively correlated with the invasive rating of environmental sounds and negatively correlated with the familiarity rating of abstract sounds. Furthermore, delusion severity negatively correlated with familiarity ratings of environmental sounds.
The results show reduced sensory gating for auditory stimuli in schizophrenia is associated with an aberrant perceptual experience of stimuli.

However, sensory gating variances are not unique to schizophrenia. A meta-analysis of 39 studies indicated that, although the overall mean P50 amplitude ratio was lower for unaffected individuals, variance in the unaffected group was such that 40% of unaffected individuals fell within the schizophrenia group range (Patterson et al., 2008). El-kaim, Aramaki, Ystad, Kronland-Martinet and Cermolacce (2015) investigated the relationship between P50 amplitude ratios and perceptual inundation, the self-rated measure of how overwhelmed or flooded an individual felt when presented with auditory stimuli. Individuals with schizophrenia had higher P50 amplitude ratios and perceptual inundation than unaffected individuals. However, the positive correlation between P50 amplitude ratios and perceptual inundation was only significant for the whole group, not each group separately. Similarly, the positive correlation between perceptual inundation and self-rated measures of distractibility and over-inclusion of stimuli were only significant for the whole group. Therefore, although sensory gating facilitates the availability of stimuli, it is unlikely that sensory gating variance can explain aberrant salience.

2.3.2 Salience Network

The salience network (SN) co-ordinates the activation and deactivation of regions required for task-relevant processing. The SN includes the anterior insula, anterior cingulate cortex (ACC), amygdala, ventral tegmental area and hypothalamus (Menon, 2015; Uddin, 2017a). These regions show increased blood oxygen dependent (BOLD) signal, indicating increased activation, in response to internal (Jones, Ward, & Critchley, 2010) and external (Sridharan, Levitin, & Menon, 2008) stimuli. The SN integrates sensory information and facilitates the selection and initiation of behavioural responses (Chand & Dhamala, 2016b; Lamichhane & Dhamala, 2015; Uddin, 2017d, 2017b). Importantly, the SN co-ordinates the concomitant activation and deactivation of the central executive network (CEN) and default mode network (DMN; Chand & Dhamala, 2016a; Goulden et al., 2014; Sridharan et al., 2008; Uddin, 2017c). The CEN, comprising the dorsolateral prefrontal cortex (dLPFC) and lateral parietal
regions, shows increased activation during tasks requiring attention and
decision-making (Goulden et al., 2014; Sridharan et al., 2008). The DMN
(discussed in next section) is involved in self-referential processing and shows
decreased activation during task-related activities (Buckner, Andrews-Hanna, &
Schacter, 2008).

Structural and functional deficits in the SN in schizophrenia are related
to symptom severity. Schizophrenia has been associated with volume reduction
in the insula (Kim et al., 2003; Makris et al., 2006; Saze et al., 2007; Takahashi et
al., 2005) and ACC (Baiano et al., 2007), and reduced functional connectivity
between the insula and ACC (White, Gilleen, & Shergill, 2013; White, Joseph,
Francis, & Liddle, 2010). Reduced grey matter volume of the anterior insula and
ACC correlated with reality distortions (Palaniyappan, Mallikarjun, Joseph,
White, & Liddle, 2011). Dysrupted functional connectivity within the SN
positively correlated with intensity of delusions (Orliac et al., 2013).

Increased cognitive load affects the efficiency of the SN. Luo et al. (2014)
investigated the impact of aversive stimuli on working memory in unaffected
individuals. During functional magnetic resonance imaging (fMRI), participants
completed a working memory task, the N-back task, involving neutral or fearful
faces. Participants indicated, via button press, whether the current face was the
same or different to the face presented immediately prior (low load) or 2 items
previously (high load). Response times were faster, with fewer errors, for the
low compared to high working memory load. However, during the low load
task, more errors occurred for fearful faces than neutral faces. This pattern was
reversed during the high load task, with more errors for neutral faces. During
the low load task, activation in the SN was higher for fearful than neutral faces.
This pattern was reversed during the high-load task, with increased SN
activation for neutral faces. Thus, the stimulus dependent number of errors
during the N-back task was associated with increased activation in the SN.

Interestingly, for fearful faces during the high load task, Luo et al. (2014)
found increased activation in emotion processing regions not the SN. One
explanation for the apparent anomaly in findings is the temporal limitation of
fMRI. fMRI research indicates more regions of the SN are activated during
increased cognitive load (Chand & Dhamala, 2016a), whereas EEG data suggest
that activation in the SN precedes that of the CEN (Chand & Dhamala, 2016b). On first presentation of highly salient stimuli, such as fearful faces, the SN triggers activation of other regions. When the same fearful face is presented two pictures later, it is already being processed as a salient stimulus thus no additional activation of the SN is required. In contrast, neutral faces have not resulted in activation of additional regions therefore the SN activates. The efficiency of the SN is therefore reduced by cognitive load not just concurrent salient stimuli. Further research is needed to determine the feasibility of this explanation.

Diminished functional connectivity in schizophrenia impairs the function of the SN. During the resting-state in unaffected individuals, the SN has an excitatory influence on the dlPFC (Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013). In turn, the dlPFC has an inhibitory influence on the SN (Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013). In schizophrenia, this reciprocal pattern of activation is significantly reduced (Palaniyappan et al., 2013). Additionally, compared to unaffected individuals, resting-state functional connectivity in the right anterior insula is reduced in schizophrenia and correlates with severity of hallucinations (Manoliu et al., 2014). The right anterior insula plays a key role in the interconnection between neural regions (Bonnelle et al., 2012).

The SN, in unaffected individuals, co-ordinates the activation of key regions involved in task-related activities. However, the efficacy of the SN is impaired under increased cognitive load. In schizophrenia, reduced connectivity and volume in the SN is associated with symptom severity. Furthermore, the resting-state functional connectivity between the salience and central executive networks is impaired in schizophrenia. Given the association between increased SN activation and reduced efficacy during task-related activities in unaffected individuals, increased resting-state SN activation in schizophrenia may contribute to errors in self-referential processing.

### 2.3.3 Default Mode Network

The default mode network is implicated in self-referential processing. The DMN includes the mPFC, ventromedial prefrontal cortex (vmPFC), posterior cingulate
cortex (PCC), precuneus and inferior parietal lobule (Buckner et al., 2008; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009). The PCC influences activation in the mPFC, via the inferior parietal lobule (Davey, Pujol, & Harrison, 2016). In turn, the mPFC inhibits activation in the PCC (Davey, Pujol, & Harrison, 2016). Activation in the DMN increases during active self-referential tasks, such as autobiographical memory, moral decision making (Buckner et al., 2008), and the attribution of others’ mental states (Mars et al., 2012). Increased DMN activation is also associated with mind wandering (Scheibner, Bogler, Gleich, Haynes, & Bermpohl, 2017) and lapses in attention to external stimuli (Buckner et al., 2008). Conversely, DMN activation is attenuated during task-related activities that show increased activation in regions associated with active cognitive functions (Buckner et al., 2008; Crone et al., 2011; Scheibner et al., 2017).

Schizophrenia is associated with atypical DMN activation. Compared to unaffected individuals, individuals with schizophrenia showed increased activation in the DMN during resting-state (Kim et al., 2014; Whitfield-Gabrieli et al., 2009) and task-related activities (Anticevic et al., 2015; Chai et al., 2011; Garrity et al., 2007; Hoptman et al., 2010; Landin-Romero, Mckenna, Sarró, Aguirre, & Sarri, 2015; Littow et al., 2015; Pankow, Deserno, et al., 2015; Whitfield-Gabrieli et al., 2009). The increased task-related DMN activation is likely the result of reduced de-activation, which may be linked to increased dopamine synthesis (Carbonell et al., 2014). Concomitant to increased DMN activation, the CEN (Landin-Romero et al., 2015) and other task-related regions (Chai et al., 2011) show attenuated task-related activation in schizophrenia. The DMN therefore appears hyperactive in schizophrenia, resulting in atypical functional connectivity with the CEN.

There is impaired functional connectivity between the PCC and other DMN regions in schizophrenia, although evidence indicating the direction of impairment is conflicting. For example, increased (Skudlarski et al., 2010; Whitfield-Gabrieli et al., 2009) and decreased (Alonso-Solís et al., 2015; Orliac et al., 2013; Rotarska-Jagiela et al., 2010) resting-state functional connectivity with the PCC has been reported in schizophrenia compared to unaffected individuals. The conflicting findings may be due to methodological differences
in the assessment of functional connectivity (Whitfield-Gabrieli & Ford, 2012), namely seed-based methods, which assess the correlation of BOLD activation in pre-selected regions of interest, and independent component analysis, which is a mathematical procedure to spatially identify components without prior selection of regions of interest (Lee, Smyser, & Shimony, 2013). Although this would be a tidy explanation, findings supporting methodological differences are inconclusive (Alonso-Solís et al., 2015; Skudlarski et al., 2010; Whitfield-Gabrieli et al., 2009).

Atypical mPFC activation may account for the conflicting findings regarding PCC functional connectivity in schizophrenia. The mPFC is critical for self-referential processing (Benoit, Gilbert, Volle, & Burgess, 2010; Mitchell, Banaji, & Macrae, 2005; Turner, Simons, Gilbert, Frith, & Burgess, 2008). Despite directional disparities, there is consistent evidence of atypical functional connectivity between the mPFC and PCC in schizophrenia (Alonso-Solís et al., 2015; Bluhm et al., 2007; Jang et al., 2011; Larivière et al., 2017; Whitfield-Gabrieli et al., 2009). Given the reciprocal modulatory effect between the PCC and mPFC (Davey, Pujol, & Harrison, 2016), irregularities in mPFC activation may influence the functional connectivity between the two regions.

Activation in the mPFC is associated with symptoms of schizophrenia. Increased task-related mPFC activation in schizophrenia predicted positive and negative symptoms (Whitfield-Gabrieli et al., 2009). Conversely, mPFC activation during self-referential processing was reduced in schizophrenia compared to unaffected individuals (Vinogradov, Luks, Schulman, & Simpson, 2008). Attenuated mPFC activation during self-referential processing was related to poor insight (Raij, Riekki, & Hari, 2012), the level of awareness and attribution of symptoms (Mintz, Dobson, & Romney, 2003), and aberrant salience (Pankow et al., 2015). Interestingly, delusions were associated with increased activation in the mPFC during self-referential processing, whereas increased PCC activation was found in non-delusional schizophrenia compared to unaffected individuals (Larivière et al., 2017). The divergent mPFC activation in schizophrenia may lead to stimuli outside the self being explained as self-relevant and self-relevant stimuli being explained within external contexts.
Although much is yet to be learned about the DMN, evidence suggests it is linked with self-referential processing and shows decreased activation during task-related activities. In schizophrenia, there is a dysregulated pattern of DMN activation and functional connectivity that correlates with symptoms. The atypical DMN activation in schizophrenia may create erroneous associations between internal and external stimuli and the self-action or association, resulting in an over-attribution of importance to stimuli, or aberrant salience. Thus, the DMN is implicated as a key network underlying the aberrant salience hypothesis.

2.3.4 The potential contribution of the salience and default mode networks to aberrant salience

The DMN and SN are activated by dopaminergic firing. Using dopamine agonists and antagonists, Cole et al. (2013) investigated the role of dopamine on neural network functional connectivity. Ingestion of a dopamine agonist increased the functional connectivity between the SN and ventral striatum, a key neural region involved in reward processing. A significant decrease was seen after ingestion of a dopamine antagonist. Likewise, the dopamine agonist increased (and antagonist decreased) the functional connectivity between the DMN and the SN and other cortical regions (Cole et al., 2013). The hyperdopaminergic activation associated with schizophrenia, therefore, may facilitate increased resting-state functional connectivity between the DMN and SN.

Failure of the SN to deactivate DMN during task-related processing affects the processing of salient stimuli. A key function of the SN is the deactivation of the DMN during task-related activities (Goulden et al., 2014; Jilka et al., 2014; Sridharan et al., 2008; Uddin, 2017c). Reduced task-related deactivation of the DMN (Bonnelle et al., 2012; Jilka et al., 2014), which correlated with reduced behavioural inhibition (Bonnelle et al., 2012; Jilka et al., 2014), was found in traumatic brain injury affecting the SN. These findings were linked to weakened right anterior insula activation (Jilka et al., 2014). Furthermore, in unaffected individuals, increased resting-state functional connectivity between the SN and DMN predicted the distractibility of salient and non-salient visual stimuli during an auditory task (Götting et al., 2017).
Combined, these findings suggest DMN deactivation, by the SN, is necessary for attending and responding to salient stimuli.

Research into the effect of psychedelics suggests reduced resting-state activation in the DMN and SN contributes to aberrant salience. Carhart-Harris et al. (2012) administered the psychedelic psilocybin, and a placebo, to participants with no history of mental health issues. For both placebo and psilocybin conditions, participants underwent MRI scans, ascertaining either cerebral blood flow or BOLD activation. Following the scans, participants rated statements regarding the intensity of their psychedelic experience. These included characteristics similar to those associated with aberrant salience. For example, “Everything seemed ‘alive,’” “I experienced a loss of separation from my surroundings,” “The experience had a spiritual or mystical quality,” and “I felt unusual bodily sensations” (Carhart-Harris et al., 2012 page 4, Supporting Information). Psilocybin was associated with decreased cerebral blood flow and BOLD activation in the SN (ACC) and DMN (mPFC and PCC) and reduced functional connectivity between the mPFC and PCC. Cerebral blood flow in the ACC and PCC negatively correlated with self-rated intensity of the experience. Furthermore, functional connectivity between the DMN and task-related networks increased following psilocybin (Carhart-Harris et al., 2013). Aberrant salience, therefore, appears to be linked to atypical functional connectivity between the DMN, SN, and task-related regions.

Dysfunction of the SN facilitates aberrant associations between self-referential and task-related processing that contributes to the symptoms of schizophrenia. Compared to unaffected individuals, individuals with schizophrenia showed reduced functional connectivity between the ACC and mPFC (Yan et al., 2012). Conversely, activation in the DMN (Manoliu et al., 2014) and CEN (Chai et al., 2011; Manoliu et al., 2014) was augmented and correlated with reduced right anterior insula activation (Manoliu et al., 2014). The frequency and intensity of hallucinations correlated with the atypical resting-state activation in these three networks (Manoliu et al., 2014).

Increased functional connectivity between the SN and DMN, which is linked to hyperdopaminergic activation, is associated with symptoms of schizophrenia. The failure of the SN to deactivate the DMN during task-related
activities, leads to disruptions in the processing of salient stimuli. Thus, the dysregulated connectivity between the DMN and salience network may be a key mechanism underlying aberrant salience.

### 2.3.5 Summary

Schizophrenia is associated with decreased sensory gating (Judd et al., 1992; Myles-Worsley, 2002; Williams et al., 2011) and a dysregulated pattern of neural activity in regions associated with self-referential processing (J. S. Kim et al., 2014; Micoulaud-Franchi et al., 2012) and task-related activities (e.g. Anticevic et al., 2015; Chai et al., 2011; Littow et al., 2015). Underlying this is an impairment in the functioning of the SN (Baiano et al., 2007; Saze et al., 2007; T. White et al., 2013), which co-ordinates the activation of these neural regions. Furthermore, sensory gating deficits lead to increased processing of irrelevant stimuli, resulting in higher cognitive load that further impacts SN efficiency (Luo et al., 2014). The subsequent erroneous associations of the importance of internal and external stimuli facilitates the development of positive symptoms of psychosis (Manoliu et al., 2014; Orliac et al., 2013; L Palaniyappan et al., 2011). These findings implicate the SN and DMN as the neural mechanisms underlying aberrant salience.

### 2.4 Measures of Aberrant Salience

The aberrant salience hypothesis links neural, cognitive, phenomenological, and behavioural factors. Different methodologies are used to test each of these factors but comparing different methodologies is problematic. For example, self-report and behavioural measures of constructs, such as impulsivity, have a weak relationship but each moderately correlate with a third factor, real-life behaviour (Sharma, Markon, & Clark, 2014). However, Karcher et al. (Karcher, Cicero, & Kerns, 2015) found a relationship between behavioural and self-report measures of magical thinking and reversal learning. Therefore, if the aberrant salience hypothesis is true, the interdependence between some of the factors should be evident, despite differing methodologies. The purpose of the current project was to investigate the relationships among some of these factors, namely aberrant salience and motivational salience. This is important
given Kapur (2003) proposed that aberrant salience was mediated by motivational salience. The SAT and ASI assess two different factors within the aberrant salience hypothesis: behavioural and phenomenological.

Two measures were identified as having been developed to assess aberrant salience: the SAT (Roiser et al., 2009) and the Aberrant Salience Inventory (Cicero et al., 2010). At the time of writing, these were the only available standardised measures of aberrant salience. In the following sections, I discuss each measure in turn, including a description, review of research, and discussion of the limitations.

2.4.1 Salience Attribution Task

The Salience Attribution Task (SAT; Roiser et al., 2009) is a computerised learning paradigm that uses stimulus reinforcement to assess implicit and explicit aberrant and adaptive salience. Stimulus reinforcement facilitates associative learning by rewarding responses to conditioned stimuli, which are stimuli without an innate rewarding value (Anselme & James, 2015). During the SAT, participants respond as quickly as possible to a stimulus (a black box which appears centre screen) presented with task relevant or task irrelevant stimuli (Roiser et al., 2009). Participants are assigned one of four possible scenarios that vary in the weighted relevance of the dimension of colour (red or blue) or shape (household object or animal). For the task-relevant dimension, one level (e.g., household object) has a high probability (87.5%) of being reinforced while the other (e.g., animal) has a low probability (12.5%). For the task-irrelevant dimension, both levels (e.g., blue and red) have a 50% probability of being reinforced. Response latency to the presentation of the black box determines the amount of money that can be earned. However, the probability of reward is determined by the stimulus type. Participants are instructed to identify which of the four stimulus types yields the highest probability of reward.

During the SAT, the explicit task is self-report, assessing the ability to identify the likelihood of reward associated with each stimulus dimension, while the implicit task is behavioural. Implicit salience is measured using response latency (ms) while explicit salience is measured using visual analogue
scale (VAS) rating (mm). The task consists of two trial blocks, with a VAS rating at the end of each. Implicit adaptive salience is calculated as the difference between mean response latency for low (10%; e.g., household object) versus high (90%; e.g., animal) reinforcement probability trials. Implicit aberrant salience is calculated as the absolute difference in response latency between the two task-irrelevant dimensions (e.g., blue and red; Roiser et al., 2009). Explicit measures are calculated as the difference in probability rating between the low- and high-probability relevant stimuli (adaptive) and between the two irrelevant stimuli (aberrant). Salience is therefore defined as the difference between probabilistic learning for relevant (adaptive) and irrelevant (aberrant) stimuli in self-report (explicit) and behavioural (implicit) measures.

Individuals with no history of psychotic disorder show increased adaptive salience relative to aberrant salience. Roiser, Stephan, den Ouden, Friston, and Joyce (2010) found unaffected individuals responded faster to high- versus low-probability stimuli (implicit adaptive salience). Furthermore, the ability to distinguish high- from low-probability relevant stimuli (explicit adaptive salience), increased across the trial blocks. Implicit and explicit adaptive salience measures were positively correlated. There was also a small difference in reward probability ratings for task irrelevant stimuli (explicit aberrant salience), that was constant between task blocks. Implicit aberrant salience was also present, with participants responding more quickly to the irrelevant dimension they perceived as having a higher reward probability. There was no relationship between adaptive and aberrant salience measures nor between aberrant salience indices. As discussed in Chapter 4, if the aberrant salience hypothesis is correct, SAT aberrant salience indices should negatively correlate with adaptive salience indices, which measure motivational salience. Furthermore, if antipsychotics reduce adaptive salience, adaptive salience should not be impaired in medication naïve individuals with schizophrenia.

The SAT measure of adaptive salience denotes reward processing, whereas SAT aberrant salience inversely relates to engagement of task-related regions. Roiser et al. (2010) used fMRI to investigate correlates between neural activation and the SAT indices in unaffected individuals. High-probability relevant stimuli correlated with BOLD activation in two reward processing
regions, the ventral tegmental area and ventral striatum. Presentation of irrelevant stimuli rated as having a high probability of reward (explicit aberrant salience) correlated with decreased activation in the dIPFC (involved in task processing) and increased activation in the middle temporal gyrus. The middle temporal gyrus shows increased activation when orienting attention between internal (self-referential) and external (task-related) cues (Davey et al., 2016; Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015). Although not implicating the DMN directly (Roiser et al., 2010), the findings support the idea that aberrant salience involves atypical self-referential processing of external stimuli. There was no correlation between implicit aberrant salience and BOLD activation.

The SAT shows good discriminant validity in unaffected individuals. Schmidt and Roiser (2009) compared the SAT indices with measures of: learned irrelevance; reversal of probabilistic learning; reinforcement sensitivity; working memory; and a continuous performance test (which assesses sustained attention and the ability to maintain context of relevant information when presented with irrelevant information). Participants who reported no history of psychiatric disorder were assessed for schizotypy. Factor analysis revealed that SAT implicit aberrant salience was independent of the other measures and was negatively related to social anhedonia. Explicit adaptive salience loaded positively, and explicit aberrant salience negatively, onto one factor that the authors labelled operant/explicit learning. There was no evidence of a relationship between explicit aberrant salience and schizotypy.

Although the findings offer some support for the construct validity of the SAT implicit aberrant salience, the SAT did not support predictions based on the aberrant salience hypothesis. Additionally, whereas aberrant salience may be present in unaffected individuals, one assumption of the hypothesis is that this does not have the robust effect that the incorporation of irrelevant stimuli into schemata has in schizophrenia. Therefore, aberrant salience is not just perception but also the cognitive explanation. Aberrant salience should, therefore, be minimal or even absent in unaffected individuals. And even though schizotypy predicts symptom onset, participants were below the mean scores
for the general population (Mason & Claridge, 2006). Thus, a key constraint of the study was the exclusion criterion of a history of psychiatric disorders.

In contrast, individuals with sub-clinical symptoms show evidence of aberrant salience that is associated with atypical neural activation. Roiser, Howes, Chaddock, Joyce and McGuire (2013) investigated aberrant salience in individuals who exhibited abnormal beliefs, which the authors classified as ultra-high risk of psychosis (UHR). Participants completed the SAT during fMRI followed by positron emission topography, which was used to ascertain dopamine synthesis capacity. The UHR participants scored higher than unaffected individuals on explicit aberrant salience but not implicit aberrant salience. The UHR group’s tendency to attribute salience to irrelevant stimuli was related to the severity of their abnormal beliefs. The explicit aberrant salience index is measured as the relative difference between the perceived value of stimulus types rewarded at chance. A greater difference reflects greater value, therefore importance, of one irrelevant stimulus. Furthermore, striatal dopaminergic synthesis capacity in UHR correlated negatively with neural activation in the hippocampal region during irrelevant stimulus presentation (Roiser et al., 2013). This correlation was positive in unaffected individuals. Aberrant salience in the prodromal phase, therefore, includes both the perception of, and assignment of importance to, irrelevant stimuli.

In the first study assessing SAT indices in schizophrenia, investigators found limited support for the utility of the SAT in identifying aberrant salience. Roiser et al. (2009) examined differences in adaptive and aberrant salience in participants with schizophrenia (all on antipsychotic medication) and unaffected individuals. There was decreased implicit adaptive salience in the schizophrenia group but not explicit adaptive salience nor explicit or implicit aberrant salience. Participants with treatment resistant schizophrenia (TRS), defined as individuals on antipsychotics who still experienced delusions, had higher explicit aberrant salience scores than those who were treatment responsive. There was also evidence of relationships between SAT aberrant salience and symptoms. Explicit aberrant salience predicted delusions and negative symptoms, although the latter relationship was weak. Conversely, schizophrenia participants who reported an absence of negative symptoms had
lower explicit aberrant salience scores than unaffected individuals. These results suggest an impaired capacity to differentiate probabilistic outcomes for task relevant, but not irrelevant, stimuli in schizophrenia that is associated with positive and negative symptoms of schizophrenia.

Recent studies have been more successful in finding a relationship between the SAT aberrant salience and schizophrenia. Pankow et al. (2015) found individuals with schizophrenia exhibited significantly increased implicit aberrant salience compared to unaffected individuals. Interestingly, the mean implicit aberrant salience scores for individuals with subclinical delusions fell between, but not significantly different from, that of unaffected individuals and those with schizophrenia.

Katthagen et al. (2016) investigated the construct validity of SAT implicit aberrant salience in schizophrenia and unaffected individuals. They employed the SAT and an implicit salience paradigm, which was similar to the SAT implicit indices. However, participants were not advised there was a relationship between stimulus types and reward. This was done to reduce increased attention, therefore salience, for all stimuli. The SAT explicit and implicit adaptive salience scores were higher for unaffected individuals, whereas implicit aberrant salience scores for both the SAT and implicit salience paradigm were higher for individuals with schizophrenia. Furthermore, the measures of implicit aberrant salience correlated positively with each other and negatively with reversal learning. No correlations between implicit and explicit aberrant salience measures nor between aberrant and adaptive salience measures were indicated. The results suggest explicit knowledge of a reward contingency does not affect outcome. However, there are limitations to the authors’ claim that the results validate the SAT as a measure of aberrant salience. The implicit salience paradigm measured implicit aberrant salience in the same way as the SAT, thus is subject to the same methodological issues. Additionally, the failure to find an effect of reward contingency may reflect a failure to attend to instructions (reduced adaptive salience).

Abboud et al. (2016) investigated the impact of antipsychotics on SAT indices. They argued that individuals with TRS would exhibit differences in aberrant salience compared to unaffected individuals but that antipsychotics
would reduce adaptive salience. There were no group differences in explicit aberrant or implicit adaptive salience. The TRS group had lower explicit adaptive salience scores and were more likely to underestimate the likelihood of high, but not low, probability reinforced stimuli than unaffected individuals. Higher implicit aberrant salience in TRS was related to impaired working memory. Given previous findings of explicit aberrant salience in the prodromal phase (Roiser et al, 2013), the authors suggest that persistent delusions in TRS may be due to an inability to unlearn early dopaminergic related aberrant salience (Abboud et al., 2016).

Alternative explanations for inconsistent findings using the SAT have been identified and discounted by subsequent research. One such explanation is that the conscious awareness of aberrant stimuli is more prominent during the prodromal stage (Roiser et al., 2013). However, Smieskova et al. (2015) found no difference in the SAT measures of aberrant salience between unaffected individuals, those at risk of psychosis and those with first episode psychosis. They suggested one of the issues with the SAT is that common cognitive processing deficits seen in schizophrenia, such as attention and executive function, may confound results. Subsequent data support this argument (Abboud et al., 2016). Smieskova et al. (2015) suggested impaired neural responsivity in the anterior cingulate cortex and insula, associated with antipsychotics, may interfere with salience attribution. A more recent article casts doubt on this suggestion. In assessing the BOLD response during the SAT, Walter et al. (2016) found no association between SAT aberrant salience and insula activation or symptom severity. Conversely, there was an association between severity of positive symptoms and increased insula activation. The evidence therefore suggests atypical SN function in schizophrenia that is related to symptoms but not the SAT indices of aberrant salience.

The SAT was developed as a measure of aberrant and adaptive salience, however subsequent research has yielded conflicting results. Although there is some indication of increased aberrant salience in schizophrenia (Katthagen et al., 2016; Pankow et al., 2015) this finding is inconsistent (Roiser et al., 2009; Smieskova et al., 2015). Increased explicit aberrant salience has been identified in TRS individuals compared to those for whom antipsychotics are effective.
Support for the construct validity of the SAT is also limited (Katthagen et al., 2016; Roiser et al., 2010; K. Schmidt & Roiser, 2009). Furthermore, speculative explanations for differential findings (Roiser et al., 2013; Smieskova et al., 2015) are not supported by subsequent evidence (Walter et al., 2016). It has also been suggested that aberrant salience is involved in the early development of symptoms, with other factors contributing to the severity of symptoms (Smeets et al., 2013). Inconsistent findings for SAT indices in schizophrenia may, therefore, reflect variances in the integration of irrelevant stimuli into a schema. Combined with the effect of antipsychotics, this may serve to reduce sustained attention to stimuli that do not adhere to the believed explanation.

### 2.4.2 Aberrant Salience Inventory

The ASI is a 29-item questionnaire designed to ascertain the key experiential factors associated with aberrant salience (Cicero et al., 2010). Specifically, the ASI assesses experiences such as heightened perception, understanding, emotionality, and significance of internal and external stimuli that otherwise would not be attended to (Cicero et al., 2010). The ASI was developed from factor analysis of undergraduate (n = 233) responses to an initial list of yes/no items (Cicero et al., 2010). Five factors were identified: increased significance, senses sharpening, impending understanding, heightened emotionality, and heightened cognition. Removal of items that were highly endorsed (>80%) or had high loadings (> .30) on more than one factor left the resultant 29-item questionnaire. The ASI was then administered to another undergraduate group (n = 348) along with measures of dissociation, social anhedonia, absorption and psychosis-proneness. Psychosis-proneness was defined as increased magical ideation, perceptual aberration, and referential thinking. The ASI correlated weakly with social anhedonia and highly with psychosis-proneness measures, although not as highly as the psychotic-proneness measures correlated to each other. Similar findings were obtained in an Italian version of the ASI administered to undergraduates (Raballo et al., 2017).

The ASI also shows discriminant validity in those at risk of psychosis compared to unaffected individuals, but inconsistent evidence in individuals.
with psychosis. Cicero et al. (2010) compared ASI scores for: participants with high psychosis proneness (1.96 SD above mean on either magical ideation or perceptual aberration scales); participants with high social anhedonia (2 SD above mean); a comparison group (who scored less than 0.5 SD above mean on magical ideation, perceptual aberration, and anhedonia scales); individuals diagnosed with schizophrenia or schizoaffective disorder; and individuals diagnosed with a nonpsychotic disorder. The psychosis proneness group had higher ASI scores than the comparison group and social anhedonia group, who also scored higher than the comparison group. Furthermore, ASI scores were higher in individuals with a primary diagnosis of schizophrenia or schizoaffective disorder than individuals diagnosed with a non-psychotic disorder (Cicero et al., 2010). Ratings on the ASI have also been associated with lifetime psychotic symptoms (Godini et al., 2015; Lelli et al., 2013) and do not appear to be affected by pharmacological treatment (Tofani et al., 2016). Conversely, a subsequent study found higher ASI scores in schizophrenia failed to reach significance (Ceaser & Barch, 2016). Further research into the discriminant validity of the ASI is needed.

The relationship between ASI and self-identity predicts the severity of positive symptoms of psychosis. Cicero, Becker, Martin, Docherty, and Kerns (2013) investigated the interaction between aberrant salience and self-concept clarity; the stability, consistency and cognitive availability of one’s beliefs about oneself. Psychotic-like experiences were defined as magical ideation and perceptual aberration, with individuals scoring 2 SD above the mean included in the high schizotypy group. Mean ASI and self-concept clarity scores were obtained, with ± 1 SD from group means used to determine high and low scores for each measure. In individuals with high schizotypy scores, the interaction between high (but not low) ASI scores and low-self-concept predicted psychotic-like experiences, including delusions. A subsequent study revealed an interaction between the ASI and both self-concept clarity and low ethnic identity that predicted psychotic-like symptoms in undergraduates (Cicero & Cohn, 2018). There was no significant interaction between ASI and self-concept clarity in predicting anhedonia or paranoia (Cicero et al., 2013). ASI and self-concept clarity predicted paranoia individually. The authors suggest that
individuals with an unclear self-concept are more prone to a psychotic-like interpretation of the experience of aberrant salience. A subsequent study revealed a positive relationship between self-concept clarity and psychotic-like experiences in undergraduates.

Published research using the ASI is scarce and more research is required to determine the discriminant validity of the ASI. One strength of the questionnaire is the focus on the perceived importance, rather than just the identification, of stimuli that previously went unnoticed. According to the aberrant salience hypothesis, the positive symptoms of schizophrenia develop from the explanation given to the importance of irrelevant stimuli, not from simply noticing stimuli. Furthermore, the interaction between the ASI and self-concept clarity, in the prediction of symptom severity, supports the idea that atypical self-referential processing contributes to aberrant salience. However, whereas the ASI measures a trait that is found in schizophrenia, it is not clear whether this trait is unique to schizophrenia or indeed measuring aberrant salience.

2.4.3 Summary of Evidence

Research indicates sensory gating deficits in schizophrenia lead to increased availability of irrelevant stimuli (Judd et al., 1992; McGhie & Chapman, 1961; Micoulaud-Franchi et al., 2012). Impaired functioning in the SN (Manoliu et al., 2014; Lena Palaniyappan et al., 2013) facilitates the aberrant cognitive processing of available stimuli. Specifically, an aberrant connectivity between the DMN and task-related neural regions (Landin-Romero et al., 2015; Manoliu et al., 2014; Skudlarski et al., 2010; Woodward, Rogers, & Heckers, 2011) leads to increased importance being assigned to irrelevant stimuli, or aberrant salience.

Evidence supports the idea of aberrant salience in schizophrenia (Grave et al., 2017; Haralanova et al., 2012; W P Horan et al., 2013; Kerns & Berenbaum, 2000). Supporting data include that from two specific measures of aberrant salience, the SAT and ASI. The SAT is based on stimulus reinforcement and associative learning. Inconsistent findings from the SAT may reflect a difference between the awareness of irrelevant stimuli and the incorporation of
that awareness into an explanation. Thus, the aberrant salience of stimuli is determined by stimulus pairing with dopaminergic firing and fit with the internal explanation or schema. The ASI offers a phenomenological measure of aberrant salience but published research on the ASI is limited. Furthermore, it is unclear whether the trait that the ASI measures is aberrant salience or unique to schizophrenia.

2.5 AS Limitations

The dopaminergic theory of schizophrenia, on which the aberrant salience hypothesis is based, suggests hyperactive dysregulation of the dopaminergic system underlies the positive symptoms of schizophrenia (Kapur, 2003). Evidence for this is founded on the effect of antipsychotics in reducing dopamine activation and symptoms. One of the limitations surrounding a purely dopaminergic explanation is, however, the limited and inconsistent effect of antipsychotics. For example, some patients report a reduction in the importance of symptoms, not the absence of symptoms (Sarin & Wallin, 2014). Others report experiencing little or no effect of antipsychotics (Suzuki et al., 2012; White et al., 2016). There is also insufficient evidence supporting the effect of antipsychotics on negative or cognitive symptoms (Lau, Wang, Hsu, & Liu, 2013).

Glutamate plays an important role in the development and expression of psychotic symptoms. The hypo-glutamate hypothesis suggests decreased function of a key glutamate receptor, N-methyl-D-aspartate (NMDA), offers a partial explanation for the positive, negative and cognitive symptoms of schizophrenia (Farber et al., 1995; Jentsch & Roth, 1999). For example, certain antipsychotics (e.g. clozapine and haloperidol) prevent or reverse schizophrenia-like symptoms in animals exposed to NMDA antagonists (Jentsch & Roth, 1999). Antipsychotic add-on treatments that enhance NMDA function improve positive and negative symptoms, general psychopathology scores, and cognitive function in TRS (Kantrowitz et al., 2010; Lane et al., 2013). A hypo-glutamate hypothesis may better explain the negative symptoms and cognitive deficits seen in schizophrenia.
However, neurotransmitters interact to affect cognitive function (Laruelle, Kegeles, & Abi-Dargham, 2003). For example, the inactivation of NMDA glutamate receptors in dopamine neurons results in the absence of dopaminergic firing, impairing cue-dependent learning (Zweifel et al., 2009).

Whereas research fuels the debate on which hypothesis best explains schizophrenia, there are limitations in any singular explanation (Jentsch & Roth, 1999). A combination of hypo-glutamatergic and hyper-dopaminergic activation may provide a more comprehensive explanation of symptoms (Olney & Farber, 1995) and antipsychotic treatment resistance.

Another criticism of the aberrant salience hypothesis is that aberrant salience may not be specific to schizophrenia. Poletti and Sambataro (2013) suggest aberrant salience may be extended to explain delusions in other disorders, neurological damage, or disease. Research is therefore needed to ascertain whether aberrant salience is unique to schizophrenia.

### 2.6 Conclusion

Aberrant salience in schizophrenia is indicated in semantic processing (Kerns & Berenbaum, 2000), subjective arousal ratings to visual scenes (Haralanova et al., 2012), subjective ratings of auditory stimuli (Micoulaud-Franchi et al., 2012), facial cues in emotional recognition (Goghi, Sponheim, & MacDonald 3rd, 2010), and interpretation of gestures (Bucci et al., 2008; White et al., 2016). Furthermore, individuals with schizophrenia exhibit atypical neural activation in regions associated with salience (Anticevic et al., 2015; Cole et al., 2013; Kim et al., 2014; White, Gilleen, & Shergill, 2013), task filtering (e.g. Judd et al., 1992; McGhie & Chapman, 1961; Micoulaud-Franchi et al., 2012), and self-referential processing (Pankow et al., 2015). Specific measures (Cicero et al., 2010; Roiser et al., 2009) have been developed to assess aberrant salience. However, further research is required to assess the validity of these measures.

Numerous explanations have been offered regarding the inconsistent findings supporting aberrant salience measures, including stage of the disorder (Roiser et al., 2013) and medication (Smieskova et al., 2015). However, the aberrant salience hypothesis includes a cognitive explanation of aberrant
salience that pre-empts the development of positive symptoms. Negative symptoms are often present prior to first episode psychosis (Foussias et al., 2014) and are retrospectively identified as an indicator. If aberrant salience pre-empts, and contributes to, positive symptoms, initial negative symptoms may reflect a period of reconstruction of the individual’s position of self within the world. Whether an underlying mechanism, or reflective of a subsequent effect, aberrant salience is strengthened by reduced functional connectivity within and between key neural networks involved in salience and self.

Continued aberrant salience may lead to an explanation whereby the rationale for aberrant salience becomes embedded in an individual’s view of the world and themselves. This in turn may lead to positive symptoms such as delusions, paranoia and hallucinations. Whereas antipsychotics reduce the salience of new, irrelevant stimuli, they dampen rather than reverse existing aberrant salience associations.

Understanding the mechanisms underlying the development of symptoms is important for early intervention. A key prerequisite to achieving this goal is that issues in the definition of aberrant salience are addressed and evidence sought to ascertain whether aberrant salience is unique to schizophrenia. The current research project was designed to elucidate the relationship between aberrant salience measures and their specificity in identifying aberrant salience in schizophrenia.
Chapter Three

Reward and Motivation

Kapur (2003) argued that dopamine's role as a mediator of motivational salience underlies the connection between dopaminergic dysregulation and aberrant salience in schizophrenia. As outlined in chapter's 1 and 2, the aberrant salience hypothesis links the relationship between dopamine and schizophrenia to symptom development and maintenance. Aberrant salience itself is mediated by disrupted motivational salience, which is influenced by dopaminergic function. This chapter summarizes theories and research linking reward processing and motivated behaviour. I review literature to evaluate the links between dopamine, reward processing, and motivational salience. I first provide an overview of dopamine's role in signalling reward and salience of appetitive and aversive cues. I then briefly explore the current understanding and definition of motivational salience and the influence of reinforcer sensitivity on motivated behaviour. Next, I examine the role of dopamine in motivational salience, using neurological and cognitive behavioural evidence from unaffected individuals. I conclude with a review of the evidence for disrupted reward processing and motivational salience in schizophrenia.

3.1 Dopamine and Reward Processing

Evidence that dopamine depletion in rats reduced instrumental behaviour for obtaining food led to the idea that dopamine and reward processing are linked (Wise, 2004). Reward processing involves the perception and assessment of stimuli, events, or behaviour that have a beneficial, or rewarding, outcome. Theories of reward processing have developed from animal and human studies where the availability of dopamine is altered, either pharmacologically or through disease. The prominent theory was that dopamine cell firing signalled rewarding stimuli and, by strengthening the connection between a stimulus and response outcome, dopamine release produced reinforcement learning. However, reinforcement learning is also linked to motivational salience, i.e., the
cognitive process involved in directing attention and behaviour towards (approach) or away from (withdrawal) stimuli.

It should be noted that dopamine is not the only neurotransmitter involved in reward processing – although it appears to be the final common path. For example, glutamate activation in the nucleus accumbens mediates dopaminergic activation in the ventral tegmental area (Floresco, Todd, & Grace, 2001). Gamma-aminobutyric acid inhibits dopaminergic activation (Barrot et al., 2012) and modulates existing reward-related behaviours (Seo et al., 2016). However, a comprehensive review of all neurotransmitters involved in reward and motivation processing is beyond the scope of this thesis.

The following subsections present a specific focus on dopamine function as it impacts on motivational salience. There is a large literature that also links dopamine to addiction (Bosker, Neuner, & Shah, 2017), flexible and persistent processing that contributes to creative cognition (Boot, Baas, van Gaal, Cools, & De Dreu, 2017), depression (Bonhomme & Esposito, 1998), and motor function (Mishra, Singh, & Shukla, 2018), and the impact of stress during adolescence on adult aggression (Tielbeek et al., 2018). But the current project did not include pharmacological or neural imaging methods, so an in-depth review of the complex role of dopamine and associated neural circuitry in these other brain processes is beyond the scope of the chapter. There are a number of detailed reviews on the relationship of dopamine to reward processing structures and connectivity (Haber, 2017; Ikemoto, Yang, & Tan, 2015; Malvaez, Shieh, Murphy, Greenfield, & Wassum, 2019; Yang et al., 2018) and their effect on motivated behaviour (Gentry, Schuweiler, & Roesch, 2019) and cognitive function (Malvaez et al., 2019; Martinez-Rubio, Paulk, McDonald, Widge, & Eskandar, 2018; Miendlarzewska, Bavelier, & Schwartz, 2016).

### 3.1.1 Tonic versus phasic firing

Rapid (phasic) and slow (tonic) firing of dopamine neurons have different functions. Phasic dopamine firing is associated with processing of rewarding stimuli (Bromberg-Martin, Matsumoto, & Hikosaka, 2011; Zhang, Doyon, Clark, Phillips, & Dani, 2009; Zweifel et al., 2009), facilitating associative learning
3: Reward and Motivation

(Zweifel et al., 2009) and motivated behaviour (Phillips, Stuber, Helen, Wightman, & Carelli, 2003; Wassum, Ostlund, & Maidment, 2012). Reward magnitude and probability also influence phasic firing (Phillips, Walton, & Jhou, 2007). Although phasic firing has predominantly been related to rewarding stimuli, it also occurs in response to aversive and novel stimuli (Bromberg-Martin et al., 2011; Matsumoto & Hikosaka, 2009; Schultz, 2010).

Tonic firing is independent of phasic firing (Parkinson et al., 2002) and is thought to provide the necessary dopamine levels to support learned (Parkinson et al., 2002) and non-reward related behaviour (Zweifel et al., 2009). Increased tonic firing reduces reward-related behaviours (Bass et al., 2013; Mikhailova et al., 2016), suggesting tonic firing may function to moderate the intensity of phasic firing (Hage & Khaliq, 2015; Parkinson et al., 2002; L. Zhang et al., 2009). Therefore, whereas phasic firing is associated with learning stimulus-outcome associations, tonic firing is associated with maintaining homeostasis.

3.1.2 Dopaminergic pathways

Reward-associated stimuli activate two key dopaminergic reward pathways: the mesolimbic and mesocortical systems. These dopamine pathways arise in the ventral tegmental area and act on D1-like and D2-like receptors. The roles and functions of D1 and D2 receptors, which include motor, cognitive, and automatic processes, depend critically on which type of neurons they are expressed on (Ikemoto et al., 2015; Jiang et al., 2014; Keeler, Pretsell, & Robbins, 2014; Kellendonk et al., 2006; Locke et al., 2018; Stopper & Floresco, 2015; Wei et al., 2018). For example, D1 receptor inhibition in the lateral cerebellar nucleus impaired spatial navigation memory, response inhibition, and working memory in rodents (Locke et al., 2018). D1 receptors in the medial prefrontal cortex and nucleus accumbens are involved in risk taking and decision making whereas D2 receptors in the PFC are involved in exploration of options in line with changing probabilities (Stopper & Floresco, 2015). The mesolimbic and mesocortical systems project to different neural regions, and so have different functions.
The mesolimbic system comprises dopaminergic projections from the ventral tegmental area to key reward-related regions. Such regions include the nucleus accumbens (Horvitz, 2000; Wise, 2004), which forms part of the ventral striatum (VS). The nucleus accumbens is associated with, fear (S. S. Y. Li & McNally, 2015; Lopes et al., 2012), aversion (Al-Hasani et al., 2015; Bergamini et al., 2016), sleep (Oishi et al., 2017; Valencia Garcia & Fort, 2018), pain (Sardi, Tobaldini, Morais, & Fischer, 2018; Seminowicz et al., 2019), impulsivity (Caprioli et al., 2014; Donnelly et al., 2014; Wu et al., 2018) and reward. It is this last that is the focus of this chapter. For example, activation in the nucleus accumbens is associated with salience (Zaehle et al., 2013), reward-predicting cues (Weiland et al., 2014; Zweynert et al., 2011), and reward-related behaviour (Mikhailova et al., 2016; Parkinson et al., 2002; Stuber et al., 2011). The orbitofrontal cortex (OFC) and mPFC moderate the reward seeking drives resulting from nucleus accumbens activation (Stopper & Floresco, 2015).

Dopamine depletion in the nucleus accumbens impairs acquisition of reward-stimulus associations and task performance based on previously learned pairing (Dalley et al., 2002; Parkinson et al., 2002). However, the nucleus accumbens is also associated with motivated behaviour (Balconi & Crivelli, 2010; McNaughton & Corr, 2004; Pascucci, Hickey, Jovanovic, & Turatto, 2017; Salamone et al., 1997) and motivational salience (Berridge, 2012). Therefore, rather than being a reward or pleasure centre, the nucleus accumbens is thought to be involved in cost and effort computations (Salamone & Correa, 2002).

The amygdala also interacts with the mesolimbic pathway, facilitating the evaluation of decisions (Chudasama et al., 2013; Rogers et al., 2004; Yu, R, Zhou, & Zhou, 2011) and processing of emotions and motivationally relevant stimuli (Cunningham & Brosch, 2012). The amygdala is involved in the control of virtually all responses that involve increased arousal, such as fear (Duvarci, Popa, & Paré, 2011; J. H. Lee, Lee, & Kim, 2017; H. Li et al., 2013; Penzo et al., 2015), anxiety (Babaev, Pilette Chatain, & Krueger-Burg, 2018; Gray & McNaughton, 2000; Sah, 2017), and stress (Lakshminarasimhan & Chattarji, 2012; Motoike et al., 2016), and memory (Beyeler et al., 2016; Inman et al., 2018). Cunningham et al. (2012) argue that the amygdala guides processing and
responding after a stimulus is deemed relevant, ascertaining the relevance of stimuli in relation to the organism’s motivational state.

The mesocortical pathway comprises dopaminergic projections to prefrontal cortical regions responsible for executive functioning, including the medial prefrontal cortex and anterior cingulate cortex (Kim, 2013). The prefrontal cortex is primarily associated with higher cognitive functions such as planning (Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2011), attention (Katsuki & Constantinidis, 2012), and working memory (Katsuki & Constantinidis, 2012; Markowitz, Curtis, & Pesaran, 2015), social, emotional and executive function (Schultz, 2017b), and decision-making (Domenech et al., 2015). Of note, in the context of the aberrant salience hypothesis, the prefrontal cortex is associated with motivated behaviour. The medial prefrontal cortex is involved in goal-directed behaviour (Laskowski et al., 2016; Pinto & Dan, 2015), signalling unexpected omission of an outcome (Alexander & Brown, 2011). The anterior cingulate cortex is also involved in goal-directed behaviour (Laskowski et al., 2016), as well as learning, evaluation, and prediction of outcomes (Alexander & Brown, 2011; Jahn et al., 2014).

The mesolimbic and mesocortical systems interact. Reduced D2/D3 receptor availability in the nucleus accumbens, indicating increased dopamine neurotransmission, is associated with increased activation in the medial prefrontal cortex during reward anticipation (Weiland et al., 2014). However, whereas the mesolimbic system appears to support the initial evaluation of stimuli, the mesocortical system supports the higher cognitive functioning required for goal-directed behaviour.

3.1.3 Dopamine does not only signal reward

Dopamine neurons fire in response to aversive stimuli. Aversive stimuli inhibit dopamine neurons in the dorsal ventral tegmental area and excite those in the ventral region of the ventral tegmental area (Brischoux, Chakraborty, Brierley, & Ungless, 2009). Excitatory responses to aversive stimuli activate regions involved in orienting behaviour and motivational salience (Matsumoto & Hikosaka, 2009). Inhibitory responses to aversive stimuli suppress the usual reward-associated activation to regions implicated in value computations.
Aversive stimuli elicit an activation-suppression-activation response (Fiorillo, Song, & Yun, 2013). The sequence is thought to reflect: an initial sensory intensity (or salience); motivational value (decreased for aversive where activation is increased for appetitive); then a second rebound activation, that mirrors the suppression seen at the same time following a reward (Fiorillo et al., 2013). Dopamine neurons, therefore, function to direct attention to an aversive stimulus while suppressing reward associated value.

Dopamine neurons fire to signal salience. Novelty (Horvitz, 2000; Schultz, 2010; Wittmann, Bunzeck, Dolan, & Düzel, 2007) and stimulus intensity (Fiorillo et al., 2013; Salamone et al., 2005) elicit an increased dopaminergic response. Horvitz (2000) argued that dopamine neurons respond to salient and arousing novel stimuli but are not involved in reward value. Subsequent findings show that, as an outcome becomes more predictable, neuronal responses to appetitive and aversive stimuli attenuate in a similar manner (Matsumoto & Hikosaka, 2009). The attenuated neural response indicates reduced salience. However, repeated presentation of a reward was not found to reduce reward consumption (Berridge, 1996; Berridge & Robinson, 1998). The disparity between attenuated neuronal activation and sustained behaviour somewhat supports Horvitz’s argument. However, it may also be that continued consumption of a reward, or successful avoidance of an aversive stimulus, also reduces its value.

Stimulus value influences the activation of dopamine neurons; with appetitive and aversive stimuli represented on a continuum that is differentially weighted at the neuronal level. The attenuation in dopaminergic response due to repetition is such that there is less activation for appetitive and less inhibition for aversive stimuli (Matsumoto & Hikosaka, 2009). In contrast, Fiorillo (2013) found that dopamine neuron activation in the midbrain of monkeys was no different for predicted versus unpredicted aversive stimuli. Furthermore, dopamine neurons did not activate in response to the omission of an aversive outcome, which should be signalled as a more positive outcome. Fiorillo (2013) argued these findings suggest appetitive and aversive stimuli are represented as two different dimensions. In response, Matsumoto, Tian, Uchida
and Watabe-Uchida (2016) specifically investigated the way in which dopamine neurons in mice responded to appetitive and aversive stimulus value. Most dopamine neurons were inhibited by aversive cues and excited by appetitive cues. Furthermore, in addition to a prediction-related reduction in dopamine neuron firing to appetitive cues, aversive cues elicited a prediction-related increase in dopamine neuron firing. However, some neurons did show variability. The degree to which these neurons were affected by repetition for appetitive stimuli (reduced excitation) and aversive stimuli (reduced inhibition) was directly related to the degree of activation or inhibition of a neuron to unexpected appetitive and aversive stimuli respectively. The findings support and extend the continuum theory, highlighting an additional mechanism by which value is weighted.

3.1.4 Summary

Animal studies indicate dopaminergic pathways support the processing of stimuli to inform goal-directed behaviour (e.g., Bromberg-Martin et al., 2011; Laskowski et al., 2016; Zweifel et al., 2009). Excitatory dopaminergic responses to appetitive stimuli mediate attention and value processing. In response to aversive stimuli, excitation supports attentional processing, whereas inhibition suppresses reward-related value processing (Matsumoto & Hikosaka, 2009). As such, the negative value of aversive stimuli is supported by the inhibition of dopamine neurons. Dopamine is, therefore, integral to the salience and value of appetitive and aversive stimuli.

3.2 Motivational Salience

3.2.1 What is motivational salience?

Motivation has been defined a number of ways: as activation of an instinctive drive; as incentive salience resulting from conditioned associations between a stimulus and outcome; and as a conscious process (Anselme & James, 2015). Berridge (1996) challenged these views, arguing there is a difference between wanting (anticipatory pleasure) and liking (consummatory pleasure) that is independent of subjective experience. Whereas dopamine influences wanting, it is not required for liking (Berridge & Robinson, 1998). Wanting is also evident
in addiction, with prolonged drug use creating increased sensitisation to wanting, but not liking (Robinson & Berridge, 2000). According to Berridge (2013), motivation is a component of incentive salience that fluctuates based on state factors, such as hunger and stress. The other component of incentive salience is the knowledge acquired from previously learned associations. However, given that incentive is often associated with reward, motivational salience is a more accurate term for the construct thought to mediate aberrant salience.

The motivational salience of a stimulus is relative to the context-specific information it provides. Le Pelley, Beesley, and Griffiths (2014) investigated whether there was a comparative influence of semantic and perceptual salience on cue competition. Le Pelley et al. (2014) used blocking, where conditioning of one element (B) of a stimulus (AB) is reduced when another element of the same stimulus (A) has already been conditioned. Competing cues (A) were looked at more frequently than target cues (B). However, unusual high-salience target cues (e.g., caterpillars as food) were blocked more than relevant low-salience target cues (e.g., rice). Motivational salience is, therefore, the level of desire generated by the context-relevance of a stimulus to engage in approach or avoidance behaviour.

### 3.2.2 Neurobiology of motivational salience

Motivational salience depends on dopaminergic activation. Berridge and Robinson (1998) suggested that the dopamine system is important for motivational salience but not for hedonic pleasure. Rats with surgically depleted dopamine exhibited as many hedonic and aversive reactions to appetitive and aversive stimuli as healthy control rats. The authors also suggested dopamine is not necessary to mediate reward predictions. Specifically, studies investigating reinforcement learning often use prior deprivation (Berridge, 2012) – for example, asking participants to fast before a task involving food as a reward. Increased dopaminergic activation may, therefore, reflect an increased value of the food reward due to hunger, or increased motivational salience (Berridge, 2012). This is supported by evidence that dopamine depletion can reduce motivated behaviour, even following
deprivation. Hebart and Gläscher (2015) temporarily depleted dopamine in healthy participants who had fasted. They found that dopamine depletion reduced the motivated behaviour for food-related rewards.

Bromberg-Martin et al. (2011) argued that different dopamine neurons are related to distinct neural networks and so distinct roles in motivation. One type of dopamine neuron is inhibited by aversive stimuli and is excited by appetitive stimuli; and sends the resultant signals to neural regions involved in seeking, evaluation, and value learning. Thus, this type of dopamine neuron signals motivational value. The other type is excited by both aversive and appetitive stimuli and projects to neural regions involved in orienting, cognition, and motivation. This second type of dopamine neuron therefore signals motivational salience. Both neuron types form parts of both the mesolimbic and the mesocortical systems associated with reward processing.

As with reward, motivational salience is mediated by neurotransmitters that affect dopamine. Rodent studies suggest that presentation of aversive or appetitive stimuli produces an increase in norepinephrine in the medial prefrontal cortex, which is required to stimulate dopamine flow in the nucleus accumbens. Following presentation of rewarding stimuli, mice with norepinephrine depletion in the medial prefrontal cortex had reduced dopamine in the nucleus accumbens and reduced norepinephrine in the prefrontal cortex (PFC) compared to sham mice (Ventura et al., 2007). Furthermore, the norepinephrine depleted mice showed no behavioural preference for rewarding stimuli nor aversion to aversive stimuli. Another rodent study found a positive relationship between norepinephrine release in the medial prefrontal cortex and reward value (Puglisi-Allegra & Ventura, 2012).

3.2.3 The Reinforcer Sensitivity Explanation of Motivated Behaviour

According to the reinforcement sensitivity theory (RST; Gray, 1970, 1981; Gray & McNaughton, 2000), motivated behaviour (approach or withdrawal) is affected by approach sensitivity (which can be produced by gain or omission of loss) and withdrawal sensitivity (loss and omission of gain). Approach sensitivity leads to positive goal seeking behaviour, whereas withdrawal
sensitivity leads to negative goal withdrawal and can be viewed as a higher susceptibility to fear (Gray, 1970). In this context, reinforcers are best labelled appetitive and aversive, rather than rewarding or punishing, to ensure inclusion of reward and the absence of punishment (appetitive) or punishment and the absence of reward (aversive; Corr, 2001). At the core of RST are three motivational systems: the behavioural activation system (BAS), the fight-flight-freeze system (FFFS), and the behavioural inhibition system (BIS). The nature of these systems can be summarised as follows:

- BAS produces approach behaviour, facilitating responses to appetitive stimuli, including omission of punishers.
- FFFS is associated with fear and produces active avoidance behaviour, such as removing oneself from a perceived threat or avoiding omission of rewards.
- BIS is associated with anxiety, is sensitive to stimuli, and mediates behaviour in instances of approach-avoidance conflict, where both positive and negative reinforcers exist.

Therefore, whereas BAS is activated by gain and produces approach behaviour and FFFS is activated by loss and produces avoidant behaviour, BIS is activated by conflict between competing levels of FFFS and BAS systems and perceived threat. BIS activation inhibits the avoidant behaviour initiated by FFFS and the approach behaviour initiated by BAS. BIS activation also initiates cognitive functions, such as risk assessment and memory scanning, in order to evaluate conflict and determine appropriate behaviour.

A number of factors affect the subsequent functional behaviour (approach or avoidance) during conflict. The size of the reward in relation to the threat and reinforcer sensitivity (trait sensitivity to gain and loss) interact to determine the decision to approach or avoid (McNaughton, Deyoung, & Corr, 2016). However, behaviour during conflict is also determined by the perceived threat proximity or intensity (defensive distance; McNaughton & Corr, 2004; McNaughton et al., 2016). Whereas a small defensive distance results in freeze behaviour and an intermediate defensive distance in withdrawal, a large defensive distance may result in approach behaviour.
The psychological response to approach and avoidance, and so conflict, is affected by motivational distance and also by the behavioural options available (McNaughton & Corr, 2004). A close and substantive threat will result in panic, producing undirected escape when this is possible and attack when it is not. Less proximal threat will result in fear and avoidance; or if threat is chronic and avoidance impossible, it will result in depression. Arguably, all these (including depression) are adaptive responses to danger. When both approach and avoidance are activated, and in conflict, the BIS is activated. This increases attention and arousal, while decreasing defensive distance (i.e. increasing perceived threat). Recently it has been suggested that BIS activation also reduces the impact of appetitive stimuli (McNaughton & Corr, 2014); that is, both the FFFS and BAS are subject to negative bias, which increases activity in the one and decreases activity in the other. So, differences in sensitivity of all three systems will affect the processing of conflicts with the FFFS (directly) and the BIS (indirectly) affecting the defensive distance and the BAS affecting appetitive distance (McNaughton & Corr, 2004). Thus, abnormally high FFFS or BIS sensitivity coupled with a distal threat, or even an imagined one, can result in a maladaptive psychological response. As such, psychopathology is the expression of abnormally high or abnormally low reinforcer sensitivity.

RST explains motivated behaviour as the interaction between approach (BAS), withdrawal (FFFS), and conflict (BIS). When not in close balance BAS and FFFS interact to inform motivated behaviour. FFFS activation increases avoidant behaviour and decreases concurrent approach behaviour. BAS activation increases approach behaviour and decreases concurrent avoidance behaviour. During approach-avoidance conflict (equal activation of BAS and FFFS), BIS blocks output from both FFFS and BAS and increases attention and arousal. Critically, BIS activation also means that aversive stimuli are perceived as more aversive and appetitive stimuli are less appetitive.

### 3.2.4 The BIS/BAS Scale

The Carver and White (1994) BIS/BAS scale is a 20-item questionnaire that uses a 4-point Likert-scale, with 7 items providing a unidimensional measure of BIS (CWBIS). The remaining items provide measures of three BAS (CWBAS)
subscales. The items focus on emotional reactions to stimuli. CWBIS is intended to be a measure of anxiety in response to aversive stimuli whereas the CWBAS subscales measure the author’s perceived manifestation of distinct CWBAS sensitivities: goal pursuit (drive); response to reward (reward responsiveness); and tendency to seek novel and rewarding experiences and act quickly to attain goals (fun-seeking). Given issues with the BIS/BAS Scale, outlined in section 3.2.5, the scale was not used in the current project. However, for completeness and because the scale has been a predominant measure for reinforcer sensitivity over the last 30 years, I include here a brief summary of the BIS/BAS scale findings.

CWBIS reflects sensitivities in neural signalling of loss. Boksem et al. (2006) found higher CWBIS scores predicted larger error related negativity amplitude. Error related negativity occurs after an erroneous response. A follow up study revealed higher CWBIS scores were related to larger error related negativity amplitude following punishment but not reward (Boksem, Tops, Kostermans, & De Cremer, 2008). Lower CWBIS scores predicted larger error signalling following gain compared to loss. This is in line with evidence that the CWBIS score predicts level of attenuated VS activation following gain (Simon et al., 2010). The self-report CWBIS measure appears, therefore, to reflect increased signalling of loss, thus loss sensitivity.

CWBIS also reflects conflict monitoring. Amodio, Master, Yee, and Taylor (2008) used a Go/No-Go task to investigate the relationship between event-related negativity and N2 and CWBIS/CWBAS scale scores. The N2 is an event-related potential located within the anterior cingulate cortex and is thought to reflect conflict monitoring and top-down inhibition (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003). Higher N2 amplitudes are indicated during anticipation of a No-Go (inhibited) response to infrequent stimuli compared to an anticipated Go response (Nieuwenhuis et al., 2003). Amodio et al. (2008) found N2 amplitudes were larger for incorrect responses, with CWBIS score predicting N2 amplitudes following response inhibition and error related negativity amplitude. CWBIS has subsequently also been associated with larger feedback-related negativity amplitude during false feedback (Balconi & Crivelli,
Thus, CWBIS reflects sensitivities in neural activation during conflict monitoring.

CWBAS provides an overall score and, as noted above, three subscale scores for reward responsiveness, drive, and fun-seeking. CWBAS reflects sensitivities in neural signalling of gain. Boksem et al. (2006) found higher CWBAS was associated with larger error positivity amplitude. Error positivity signals salience and error awareness (Boksem et al., 2008). Higher CWBAS was associated with larger ERN amplitude following reward omission than punishment (Boksem et al., 2008). This increased sensitivity to reward omission over loss was also indicated in CWBAS subscales. Namely, CWBAS-drive predicted increased error positivity and CWBAS-reward responsiveness predicted increased error related negativity amplitude following reward omission compared to loss (Boksem et al., 2008). Overall CWBAS score also predicted increased VS and medial orbitofrontal cortex (mOFC) activation following gain, and less deactivation of the mOFC following gain omission. Activation in both the VS (Gradin et al., 2011; Schlagenhauf et al., 2014; White, Kraguljac, Reid, & Lahti, 2015) and the OFC (Bunzeck, Doeller, Dolan, & Duzel, 2012; Jimmy Jensen & Walter, 2014; Kahnt, Park, Haynes, & Tobler, 2014; S E Morris & Salzman, 2011) are associated with tracking motivational salience. Combined the findings suggest CWBAS predicts increased salience of reward and reduced sensitivity to negative outcomes.

CWBAS also reflects neural signalling related to the assessment and instigation of approach behaviour. CWBAS score was positively correlated with left-sided frontal cortical asymmetry, indicating greater approach motivation (Amodio et al., 2008). CWBAS score also predicts P3 latency (De Pascalis et al., 2010) and amplitude, especially when presented with false feedback (Balconi & Crivelli, 2010). Increased P3 amplitude is thought to reflect proactive assessment and modification of behaviour to facilitate better outcomes (Balconi & Crivelli, 2010; Broyd et al., 2012). Interestingly, neural activity did not always manifest in motivated behaviour (Amodio et al., 2008).
3.2.5 Construct validity of the BIS/BAS scales

The Carver and White (1994) scales are frequently used as measures of BIS and BAS. However, the scales are not anchored in the biology of, and do not accurately reflect, RST. First, there is no scale for FFFS. Secondly, the theoretical validity of the CWBAS items is questionable and provides three subscale measures that do not correspond with BAS. Third, the scales fail to provide appropriate measures for approach and avoidant behaviours. RST is modelled on rodent behaviour (and particularly the effects of anxiolytic drugs on such behaviour), whereas the BIS/BAS scale measures are self-report. Furthermore, the BIS/BAS scale was developed on the basis of the initial RST outline and has not been amended to reflect updates to the theory. For example, the scale does not account for goal conflict, nor the interactive effect of FFFS and BAS on BIS. Thus, while initially a reasonable start for a tool to measure the emotion systems of RST, the BIS/BAS scales should be interpreted with caution. Therefore, more robust measures of BIS and BAS are needed.

3.2.6 The Stimulus Chase Task

The Stimulus Chase Task (Hall et al., 2011) was designed to offer a valid, simple, measure of FFFS and BAS. The SCT is a computerised task that uses response latency to calculate approach and avoidance behaviour and the value of gain and loss. Using the SCT, Hall et al. (2011) reported a stronger approach than avoidance tendency when averaging over the effects of gain and loss. Conversely, when averaging across approach and avoidance, they found evidence of loss aversion. Normative aversion to loss, such that loss is valued more than gain of equivalent magnitude, has been demonstrated by studies within the field of neuroeconomics (Lee, 2013). The findings denote a complex set of cognitive processes underlying behavioural output in humans that could not be measured by questionnaires or even standard go-no go tasks.

Whereas a description of the SCT is provided later (see section 5.3.2), it is worth highlighting here that analysis of SCT data is only undertaken for individuals whose pattern of behaviour adhered to the matching law. The matching law is the interaction between rates of behavioural response and reinforcement within a reinforcement schedule (C. W. Chong, 2013). Of note,
individuals whose behaviour is chaotic would be excluded from analysis (section 5.3.2). The implications of such loss of such data needs to be considered, especially in schizophrenia, where impairments in reward processing and motivational salience may result in chaotic behaviour (see sections 3.4, 7.1.3, and 7.4).

3.2.7 Summary

Motivational salience incorporates innate responses, desire, and previous experience (Berridge, 2013; Le Pelley et al., 2014). Motivational salience is mediated by dopaminergic firing in regions associated with reward processing and is affected by neurobiological factors, such as stress and deprivation (Berridge & Robinson, 1998; Bromberg-Martin et al., 2011; Hebart & Gläscher, 2015). Motivational salience can be measured by changes in neural activation and motivated behaviour. According to the RST, conflicting desires to approach and withdraw result in increased arousal and attention concomitant with inhibition of both behavioural tendencies (McNaughton & Corr, 2004, 2014). The subsequent decision to approach or avoid is determined by defensive distance (McNaughton & Corr, 2004; McNaughton et al., 2016). Motivational salience, therefore, is the level of desire to engage in motivated behaviour, to obtain or avoid a stimulus or event outcome that is affected by state factors and reinforcer sensitivity.

3.3 Reward processing and motivational salience

Activation in dopaminergic pathways occurs in response to stimuli that grab attention due to external stimulus properties, internal states, and previous experience. However, whether the mesolimbic and mesocortical pathways support reward value or motivational salience remains a matter of debate. In this section, I will briefly outline two separate functions of dopaminergic firing: reward value processing and motivational salience. I will review evidence from imaging and behavioural studies in healthy participants and from single neuron and behavioural studies in animals. I will then review evidence from disruptions to dopamine via pharmacological manipulation, disease, and
lesions. I will use the evidence to argue that dopamine can act as a signal both of reward value and of motivational salience.

3.3.1 Argument 1: Dopamine is a reward signal

One argument is that dopamine signals reward and risk, not motivational salience. Schultz (2015) argued that reward is composed of external (i.e. physical sensory) components, salience, and reward value. Reward value is a subjective component that leads to motivational salience and can then be estimated by a behavioural response. Reward is generally operationalised as a standard measure of magnitude across participants. For example, money is often used due to the common understanding of incremental changes in monetary value. According to Schultz (2015), the behavioural response (approach) functions as a measure of reward value. Specifically, midbrain dopamine neurons encode the difference between the current reward and previous experience of that reward outcome, even in the absence of associated reward seeking behaviour (Bayer & Glimcher, 2005). Additionally, reward-related VS activation appears relative to other available rewards (Cromwell, Hassani, & Schultz, 2005) and anticipated reward magnitude (Roiser et al., 2010). Schultz (2017a) argued that reward value is analogous to economic utility, or the usefulness of a stimulus, with reward-prediction errors serving as a measure of utility. Thus, dopaminergic activation facilitates reinforcement learning based on utility, which in turn informs reward value.

The mesolimbic system also supports reinforcement learning. Increased midbrain activation is associated with higher reward probability during reward-predicting cue presentation (Dreher, Kohn, & Berman, 2006) and lower reward probability at outcome (unexpected reward; Dreher et al., 2006; Fiorillo, Tobler, & Schultz, 2003). Uncertain rewards elicit sustained VS activation during the delay between reward-cue and outcome (Dreher et al., 2006; Fiorillo et al., 2003). The level of VS activation is positively associated with the degree of uncertainty rather than expected reward value (Dreher et al., 2006). Such sustained dopaminergic activation may facilitate reinforcement learning. Compared to neutral cues, reward cues elicit higher repetition-related functional connectivity in the right anterior hippocampus, posterior
parahippocampal cortex, and mOFC (Zweynert et al., 2011). These findings suggest dopamine mediates reinforcement learning, signalling expected reward value and better reward outcome, supporting the idea that dopamine primarily signals reward.

Schultz (2013) defined motivational salience as the capacity for stimuli to elicit attention that amplifies neuronal responses and is evidenced in motivated behaviour. He proposed three forms of salience: physical, novel, and motivational. Physical salience refers to the physical intensity, such as a bright colour or large object. Novel salience refers to novel or surprising stimuli that elicit attention. Although influenced by learning and memory, both physical and novel salience are stimulus driven (Schultz, 2015). Schultz (2013) suggested that only the motivational aspect of motivational salience applies to reward and wanting. However, he argued that motivational salience itself has a limited effect on reward-based dopaminergic systems. He based this on evidence that more dopamine neurons fire to reward prediction errors (RPE) than to salience of appetitive and aversive events.

However, reinforcement learning, and associated increases in dopaminergic activation, are also shown in response to aversive stimuli (e.g. Jensen et al., 2007; Matsumoto & Hikosaka, 2009). Schultz (2015) argued that dopaminergic responses to aversive or neutral stimuli are due to physical intensity, novelty, or presentation within a rewarding context. However, such dopaminergic activation pertains to the potential reward association, not salience itself (Schultz, 2017a).

### 3.3.2 Argument 2: Dopamine signals salience and reward

A second argument is that the mesolimbic dopamine system is a motivational system that signals salience not reward value (Horvitz, 2000; Jimmy Jensen & Walter, 2014). Esslinger et al. (2013) found a comparable increase in VS activation to rewarded and unrewarded stimuli during decision-making. Furthermore, regardless of whether reward cues were being attended to, increased reward-cue activation in the VS and ventral tegmental area has been shown (Rothkirch, Schmack, Deserno, Darmohray, & Sterzer, 2014). Conversely, repeated rewards resulted in attenuated activation in the hippocampus,
amygdala (Zweynert et al., 2011), and ventral tegmental area (Matsumoto & Hikosaka, 2009) without affecting motivated behaviour (Berridge, 1996; Berridge & Robinson, 1998). The continuation of motivated behaviour suggests that the reward still had consummatory value (i.e., it was still rewarding); but that reward certainty reduced the salience of the stimulus. These findings support the role of the dopaminergic system in signalling salience, which is affected by the context-specific value of a stimulus. In contrast to Schultz’s (2013) argument that salience is predominantly stimulus driven, these findings suggest that salience is not just the ability of a stimulus to grab attention.

The arguments about the function of the dopaminergic system may appear academic; but the distinction being made here is important in the context of aberrant salience. If, as argued by Schultz (2015), dopamine neurons primarily function to signal reward value, how does this fit with the aberrant salience hypothesis? For example, dopaminergic hyperactivation in schizophrenia would more likely result in a stimulus that should be neutral being signalled as rewarding rather than, given its limited effect, motivationally salient. However, a neutral stimulus is not rewarding, therefore has no reward value. Additionally, the lack of reward would not support associative or reinforcement learning. Dopaminergic hyperactivation could not, therefore, cause a neutral stimulus to become important based on value. Conversely, the argument that dopaminergic activation signals salience (Horvitz, 2000; Jimmy Jensen & Walter, 2014) fits within the aberrant salience framework.

There is evidence to support dopaminergic function as either reward value or salience. Each is supported by mostly behavioural or fMRI data with human participants; and by single unit recording with animals. However, electroencephalograph evidence suggests dopaminergic activation in reward pathways signals salience and value. An electroencephalograph is used to record event related potentials or rhythms, which are specific temporo-spatial forms of activity generated by neural responses to stimuli (Ventouras, Asvestas, Karanasiou, & Matsopoulos, 2011). Event related potentials associated with reward-based feedback are thought to reflect activation of reinforcement learning systems (Cohen, Elger, & Ranganath, 2007), via different
aspects of error processing (De Pascalis et al., 2010), that direct motivated behaviour to best facilitate goal-attainment (Walsh & Anderson, 2012).

Feedback event-related potentials signal reward value and stimulus salience. The P300, or P3, occurs in the centro-parietal region during anticipation (cue-P3) and feedback (FB-P3). Cue-P3 and FB-P3 amplitudes increase as a function of reinforcement magnitude (Pornpattananangkul & Nusslock, 2015; Y. Zheng et al., 2017), with larger amplitudes for gain compared to loss cues and feedback respectively (Y. Zheng et al., 2017). The P3 is thought to respond to motivationally salient cues (Broyd et al., 2012), tracking the process of stimuli identification (Twomey, Murphy, Kelly, & O’Connell, 2015). The P3 therefore represents an end-to-end evaluation process of stimulus salience and value.

The amplitudes of reward-based feedback ERPs are associated with unexpected outcomes and reward magnitude. Feedback related negativity is associated with unexpected outcomes, and reflects phasic dopaminergic firing generated in the anterior cingulate cortex (Walsh & Anderson, 2012). Feedback-related negativity amplitude is higher when the outcome is unexpected (Cooper, Duke, Pickering, & Smillie, 2014; Sambrook & Goslin, 2015; Talmi, Atkinson, & El-Deredy, 2013), for unexpected omission compared to unexpected delivery (Talmi et al., 2013), and for high compared to low magnitude outcomes (Hird, El-Deredy, Jones, & Talmi, 2018; Sambrook & Goslin, 2015; Talmi et al., 2013). The data indicate the feedback-related negativity is sensitive to salience and value.

Reward-related feedback ERPs excite and inhibit dopaminergic firing. Feedback-related negativity is also associated with the generation of RPEs (Cooper et al., 2014; Hird et al., 2018; Sambrook & Goslin, 2015). RPE can be positive or negative and reflect differences between expected and actual outcome values (Schultz, 2017c). Positive RPE is thought to generate increases in phasic dopamine firing whereas negative RPE generates decreases (Walsh & Anderson, 2012). The feedback-related negativity, therefore, also reflects feedback monitoring.

Reward-related feedback ERPs signal errors in motivated behaviour. An event-related negativity, sometimes referred to as error negativity, occurs at
fronto-central sites (Boksem et al., 2006). The event-related negativity follows an erroneous response (Ventouras et al., 2011). Event-related negativity amplitude is larger for errors resulting in monetary loss compared to failure to gain (Potts, 2011) and unexpected negative outcomes compared to expected negative outcomes (Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003; Yasuda, Sato, Miyawaki, Kumano, & Kuboki, 2004). The proposed function of the event-related negativity is to inform future goal-directed responses to facilitate more adaptive, or advantageous, behaviour (Boksem et al., 2006; Holroyd & Coles, 2002). That event-related negative signals the value of loss is evident in the form of the variation in its amplitude.

Schultz’s argument that dopamine neurons signal reward conflicts with the aberrant salience hypothesis. Conversely, the aberrant salience theory aligns with the argument that dopamine signals salience. However, reward ERP’s activate in response to both appetitive and aversive value and salience. Rather than signalling either value or salience, the so-called reward system, therefore, appears to monitor salience and value.

3.3.3 Other neural regions involved in reward and salience

As discussed in Chapter 2 (section 2.2), the processing of salience involves regions within and outside the reward pathways. For example, the anterior cingulate cortex (part of the mesocortical pathway and salience network) and anterior insula (part of the salience network) are associated with motivated behaviour. Medford and Critchley (2010) suggested that the anterior insular cortex highlights motivationally salient information whereas the anterior cingulate cortex integrates the information for selection and preparation of responses. The anterior cingulate cortex is involved in monitoring and evaluating actual outcomes against predicted outcomes (Alexander & Brown, 2011; Jahn et al., 2014; Laskowski et al., 2016). The anterior insula, which is part of the salience network, integrates sensory information (Lamichhane & Dhamala, 2015). Pharmacological silencing of insula neurons in rats reduced approach behaviour towards food (Kusumoto-Yoshida, Liu, Chen, Fontanini, & Bonci, 2015). In humans, increased activation in the right anterior insula was associated with attention to reward-related cues (Rothkirch et al., 2014).
Lamichhan and Dhamala (2015) used dynamic causal modelling to assess the relationship between anterior cingulate cortex and anterior insula during decision-making. Dynamic causal modelling is used to predict and infer the neuronal interaction between cortical regions (Friston, Harrison, & Penny, 2003). Lamichhan and Dhamala (2015) found activation in the insula drove ACC activation, thus the two regions interacted to inform goal-directed behaviour. These findings support a crucial role of the insula in signalling motivational salience to inform motivated behaviour initiated by the anterior cingulate cortex.

Another key region involved in motivational salience is the OFC, which plays a role in motivational salience, incorporating previous experience or learning. Early evidence, from individuals with frontal lesions, suggested OFC damage caused perseveration indicative of reversal learning and extinction issues (Rolls, Hornak, Wade, & McGrath, 1994). Subsequent research has shown increased activation in the OFC in response to novel (Bunzeck et al., 2012), rewarding (Bunzeck et al., 2012; S E Morris & Salzmann, 2011), and aversive stimuli (S E Morris & Salzman, 2011). Additionally, the OFC appears to encode value for appetitive and aversive stimuli comparably (Kahnt et al., 2014). However, the OFC neuron firing rates in OFC-lesioned rats was not attenuated by continued reward-omission, whereas in sham rats it was (Takahashi et al., 2011). There was no difference in behaviour between sham and lesioned rats. Thus, the motivated behaviour in OFC-lesioned rats reduced, in line with reduced reward value, but neural activation signalling salience did not. This finding suggests that the OFC plays a crucial role in updating the motivational salience of a stimulus. Whereas the OFC is not the only region associated with motivational behaviour, as discussed in the following sections (3.3.5 and 3.3.7), disruption to OFC function directly influence motivated behaviour.

3.3.4 Reward, salience, or both?

The evidence that I have summarised suggests that, rather than signalling reward or salience, dopaminergic pathways signal both value and salience. Reinforcement learning, associated with the dopaminergic pathways, occurs in
response to appetitive (Dreher et al., 2006; Fiorillo et al., 2003) and aversive stimuli (Jensen et al., 2007; Matsumoto & Hikosaka, 2009). Dopaminergic activation is moderated by reward value relative to magnitude (Roiser et al., 2010), prior outcome (Bayer & Glimcher, 2005) and current alternative rewards (Cromwell et al., 2005). However, consummatory behaviour does not reduce in response to repeated rewards (Berridge, 1996; Berridge & Robinson, 1998) but neural activation does (Matsumoto & Hikosaka, 2009; Zwynert et al., 2011). Whereas uncertain reward elicits sustained activation in the mesolimbic system, this attenuates for certain rewards (Dreher et al., 2006; Fiorillo et al., 2003). As the reward is still being consumed, the attenuated neural activation suggests processing of salience rather than just value. This argument is supported by evidence that OFC-lesioned rats cease motivated behaviour following continuous reward-omission, despite no change in OFC neuron firing rates (Takahashi et al., 2011). EEG evidence also suggests ERPs associated with reward processing signal value and salience (Lamichhane & Dhamala, 2015; Potts, 2011; Rothkirch et al., 2014; Sambrook & Goslin, 2015; Talmi et al., 2013; Y. Zheng et al., 2017), tracking the progress of stimulus identification (Twomey et al., 2015) and outcome (Boksem et al., 2006; Cooper et al., 2014; Hird et al., 2018) that directs future motivated behaviour.

The evidence of the previous sections also challenges Schultz’s (2010) definition of motivational salience as applying only to reward and wanting. Aversive stimuli elicit dopaminergic activation and reinforcement learning (Jensen et al., 2007; Matsumoto & Hikosaka, 2009). The occurrence and value of aversive outcome are signalled in reward-related ERPs (Holroyd et al., 2003; Potts, 2011; Yasuda et al., 2004). Additionally, processing in regions such as the anterior insula (Kusumoto-Yoshida et al., 2015; Lamichhane & Dhamala, 2015) and OFC (Bunzeck et al., 2012; Kahnt et al., 2014) are required to initiate motivated behaviour. Therefore, the dopaminergic systems appears crucial in the initial detection and on-going signalling of stimulus salience.

Evidence from ostensibly health individuals, therefore, supports the role of dopaminergic pathways in processing motivational salience and value. This fits with Berridge’s (2012) definition of motivational salience incorporating previously learned value associations and current neurobiological and
environmental factors. However, without value (positive or negative), there is no motivation. Conversely, motivation is usually needed to obtain valued outcomes. Behaviour is affected by both reward value and salience (Kahnt et al., 2014), which have a strong interactive effect. It is, therefore, not surprising that research employing healthy participants has revealed activation in regions associated with reward value and salience.

3.3.5 Influence of dopamine disruptions on reward processing and motivated behaviour in rodents

Human studies provide important information about motivated behaviour and associated neural activation. However, they are unable to provide the level of temporo-spatial information needed to determine differences in neuron firing rates in response to reward and motivation. Animal studies that combine behavioural measures with single-unit recording, pharmacological, or surgical manipulation offer additional insight.

The argument that dopamine signals value is confounded by the different functions of presynaptic and postsynaptic D2 receptors. Bratcher, Farmer-Dougan Dougan, Heidenreich, and Garris (2005) investigated the impact of D2 and D1 like receptor agonists on reward responding in rats. The D2 agonist produced a dose-related increase in lever press for reward. This finding suggests D2 receptors support signalling of reward value, as measured by motivated behaviour. Conversely, the D1 receptor agonist reduced response rates at higher doses, which the authors argued reflects reduced reward sensitivity, but rats continued to explore their surroundings. The authors suggested D2 receptors regulate learned response whereas D1 regulate general search and respond to novel stimuli. This explanation fits with Schultz’s (2015) argument that the dopaminergic system relates to reward. However, postsynaptic D2 receptors stimulate locomotor activity whereas presynaptic D2 receptors inhibit locomotor activity (Beaulieu & Gainetdinov, 2011). Thus, D2 receptor agonists can induce a dose related effect whereby low doses affect presynaptic D2 receptors, inhibiting locomotor activity, whereas higher doses affect postsynaptic D2 receptors and increase activity (Beaulieu & Gainetdinov, 2011). Thus, the increased response behaviour observed by Bratcher et al.
(2005) may be due to this biphasic effect rather than reflecting a reward value response.

The influence of dopaminergic firing on working memory may account for impairments in reinforcement learning and reversal learning. Overexpression of striatal D2 receptors in mice resulted in an increase in the number of stimulus-reward pairings before learned associations were evidenced in behaviour (Kellendonk et al., 2006). Additionally, upregulation of striatal D2 receptors was associated with perseveration of previously reinforced responses (Bach et al., 2008) and increased latency of response during reversal trials, without impacting accuracy (Kellendonk et al., 2006). These findings implicate hyperdopaminergic activation in reward pathways in behavioural inflexibility and slower reinforcement learning. Interestingly, overexpression of postsynaptic striatal D2 receptors has been shown to impair dopaminergic firing in the ventral tegmental area (Krabbe et al., 2015), which in turn impairs working memory (Duvarci et al., 2018), evident in behaviour (Bach et al., 2008). Rather than reward value or motivational salience, the effect of overexpression on working memory may account for deficits in reward-based learning and behavioural flexibility.

Overexpression of striatal D2 receptors influences motivated behaviour but not reward value. Rodents can be genetically modified (transgenic) to reflect the increased striatal D2 receptors in schizophrenia (overexpression). Overexpression of postsynaptic D2 receptors in the nucleus accumbens (part of the striatum) resulted in increased willingness to expend effort for reward without altering consummatory behaviour or reward value (Trifilieff et al., 2013). This finding is in line with evidence that elevated dopamine enhances anticipatory but not consummatory pleasure (Smith, Berridge, & Aldridge, 2011) and supports the argument that dopaminergic pathways signal motivational salience.

Rodent studies suggest disruptions to dopamine availability affects motivational salience but not reward value (Smith et al., 2011; Trifilieff et al., 2013). This supports the argument that motivational salience and value are separate factors.
### 3.3.6 Influence of dopamine disruptions on reward processing and motivated behaviour in humans

Whereas rodent studies provide useful information, there are limitations in translation to human cognition, which is less easily observed in behaviour. Another means to investigate reward processing and motivational salience in humans, is to utilise combined behavioural and neuroimaging techniques. These allow better insight into spatial (fMRI) and temporal (EEG) neural activity during task performance, with behavioural measures providing insight into factors that contribute to motivation. Manipulation of these factors facilitates the use of subtraction method to identify associations between behaviour and neural activation.

Increased dopamine availability reduces the negative value of aversive stimuli. Shiner et al. (2014) used a dopamine agonist (L-dopa) to investigate reversal shifting during a probabilistic learning task. The probabilistic learning task allows the evaluation of response (behaviour) to shifting reward probabilities. In a probabilistic learning task, contingencies of reward-associated stimuli are learnt through a pattern of reinforcement for correct responses (Waltz & Gold, 2007). The contingency is then changed, requiring the participant to discern such a change has occurred and alter response strategies accordingly (Waltz & Gold, 2007). Such reversal learning is dependent on the ventromedial prefrontal cortex and dopaminergic systems (Waltz & Gold, 2007). Shiner et al. (2014) used cues signalling two outcome contingencies for incorrect responses, gain omission or monetary loss. Results indicated that, in the placebo condition, accuracy on the first trial following the reversal shift was significantly better in the monetary loss compared to gain omission trials. This finding suggests a stronger negative value of loss compared to gain omission. In the L-Dopa condition, performance in reversal shifting for monetary loss cues was significantly reduced, resulting in similar behavioural responses to gain omission and monetary loss cues. According to Corr and McNaughton (2012), reduction in negative value would be associated with increased motivated behaviour. The results, therefore, suggest increased dopamine reduces the negative value of more aversive outcomes. This pattern was reflected in neural activation. Administration of L-Dopa was associated with reduced activation in
the ventromedial prefrontal cortex in response to reversal cues. Furthermore, compared to placebo, ventromedial prefrontal cortex activation following L-Dopa was attenuated for reversal learning signalled by monetary loss, but increased for reversals signalled by gain omission. Therefore, increased dopamine resulted in reduced sensitivity to higher losses.

Reduced dopamine availability affects motivated behaviour. Parkinson’s disease is characterised by dopamine loss that causes inflexible motor and cognitive function (Aarts et al., 2012). Parkinson’s disease is associated with impairments in reward processing. For example, elevated delay discounting (Szamosi, Nagy, & Kéri, 2012), whereby smaller immediate rewards are valued over larger future rewards, and impaired implicit learning (Moody, Chang, Vanek, & Knowlton, 2010). Furthermore, changes in behaviour during the task to incorporate performance feedback, exhibited in unaffected individuals, was not seen in medicated individuals with Parkinson’s disease (Di Rosa, Schiff, Cagnolati, & Mapelli, 2015). This finding is comparable to the reduced valuation of aversive stimuli shown in unaffected individuals administered with L-Dopa (Shiner et al., 2014), therefore an effect of L-Dopa cannot be ruled out. Additionally, differences in neuronal response to reward in Parkinson’s disease (unmedicated) are not always reflected in motivated behaviour (Goerendt, Lawrence, & Brooks, 2004). This is thought to be driven by compensatory neural mechanisms, as regions of the cerebellum showed increases in activation comparable to the OFC in unaffected individuals (Goerendt et al., 2004).

Unmedicated Parkinson’s disease has been associated with aberrant reward processing, namely a reduced effect of anticipated reward on motivated behaviour (Aarts et al., 2012). This contrasts with increased motivated behaviour exhibited in transgenic D2 receptor mice (Trifilieff et al., 2013). Interestingly, medicated Parkinson’s disease patients appeared to learn better from positive feedback compared to unmedicated patients, who learnt better from negative feedback (Frank, Seeberger, & O’Reilly, 2004). Therefore, the effects of dopamine depletion contrast and compare with the effects of upregulating striatal D2 receptors.

Human data suggest attenuated dopaminergic firing is associated with numerous reward processing impairments (Di Rosa et al., 2015; Moody et al.,
2010; Szamosi et al., 2012), although these are not always reflected in motivated behaviour (Goerendt et al., 2004). Additionally, increasing dopamine availability dampens the negative value of aversive stimuli, by disrupting underlying neural activation (Shiner et al., 2014). Differences in rodent (Beaulieu & Gainetdinov, 2011; Bratcher et al., 2005) and human data (Di Rosa et al., 2015) may explain the inconsistent evidence of dopamine's role in signalling salience. The conflicting findings also highlight the limitation of generalising rodent behaviour to explain human cognition. Overall, the evidence suggests a relationship between reward value and motivational salience that is mediated by dopamine.

3.3.7 Summary

Reward processing and motivational salience engage key dopaminergic pathways. The two key pathways, mesolimbic and mesocortical, facilitate initial stimulus evaluation and goal-directed behaviour (e.g. Alexander & Brown, 2011; Chudasama et al., 2013; Laskowski et al., 2016; Salamone & Correa, 2002; Weiland et al., 2014; Zweynert et al., 2011). However, dopaminergic activation also occurs in response to aversive stimuli indicating dopamine modulates motivational salience (Berridge, 2012; Matsumoto & Hikosaka, 2009).

Behavioural evidence suggests dopamine modulates motivational salience and value of outcome. The two arguments about the function of dopamine, signalling reward value (Schultz, 2013) or motivational salience (Horvitz, 2000; Jimmy Jensen & Walter, 2014), were reviewed. Overall, the evidence supports the argument that the mesolimbic and mesocortical pathways process both motivational salience and value. These findings could be interpreted as evidence that motivational salience and value are the same thing. However, the relationship between motivational salience and value is illustrated in studies where disrupted dopamine availability affects motivated behaviour to obtain a reward but not consummatory behaviour. Motivational salience and value appear, therefore, to be separate, interacting factors.

Context and physiological state also affect dopaminergic activation. Wise (2004) argued dopamine contributes to motivational arousal, conditioned reinforcement, and motivational salience. He suggested reward-predicting
conditioning can act to direct and modulate subsequent behaviour and stamp-in memories for associations that precede reward. This fits with evidence of behavioural differences using electroencephalograph and disruptions to normal dopaminergic functioning. However, this is just part of the picture. Internal states and alternative options and outcomes also affect firing in mesocorticolimbic regions. Much as the study of Parkinson’s disease has provided insight into attenuated dopamine, key insights can be obtained by investigating populations where dopamine functioning is increased organically rather than artificially. In the next section, I review evidence of impairments in reward processing and motivational salience in schizophrenia, which is associated with ongoing hyperdopaminergic activation.

### 3.4 Reward and Motivation in Schizophrenia

Schizophrenia is associated with deficits in reward processing and motivation. These deficits are expressed in atypical reward-related behaviour and co-occurrent neurological differences.

#### 3.4.1 Disrupted reward processing and motivational salience in schizophrenia

Schizophrenia is associated with impaired reinforcement learning for rewarding outcomes (Dowd, Frank, Collins, Gold, & Barch, 2016; Serra, Jones, Toone, & Gray, 2001). Compared with unaffected individuals, participants with schizophrenia, and individuals who met the criteria for schizotypal personality disorder (both first-degree relatives and unrelated) were slower to learn from reward reinforcement (Serra et al., 2001). During reinforcement learning paradigms, higher reward probability stimuli are less frequently selected by individuals with schizophrenia than unaffected individuals (Dowd et al., 2016). Whereas these findings could be explained as the impact of negative symptoms, the link between negative symptoms and deficits in reward-driven learning is inconsistent (Dowd et al., 2016; Gold, Waltz, & Matveeva, 2012). Additionally, gradual learning appears intact, albeit slower, in schizophrenia (Gold, Waltz, Prentice, Morris, & Heerey, 2008). Reinforcement learning impairments in schizophrenia may, therefore, be limited to rapid learning (Gold et al., 2008).
Conversely, reinforcement learning from aversive outcomes appears intact, irrespective of the severity of negative symptoms (Gold et al., 2012). Studies using a Go/NoGo paradigm have found individuals with schizophrenia did not learn to speed up responses to obtain reward, however the ability to stop behaviour to avoid the aversive outcome was intact (Strauss et al., 2011; Waltz, Frank, Robinson, & Gold, 2007; Waltz, Frank, Wiecki, & Gold, 2011). Faster response times to aversive stimuli in schizophrenia (Andersen et al., 2016) contrasts with evidence that increasing dopamine availability in unaffected individuals reduces the value of aversive stimuli (Shiner et al., 2014).

Reduced reward value and poor adaptation to change affect reward-related behaviour in schizophrenia. Individuals with schizophrenia have shown enhanced delay discounting (Ahn et al., 2011; Brown, Hart, Snapper, Roffman, & Perlis, 2018; Heerey, Robinson, McMahon, & Gold, 2007; Weller et al., 2014), choosing smaller, immediate rewards over larger, delayed rewards. Inconsistency in responding enhanced delay discounting in schizophrenia (Weller et al., 2014). However, even consistent responders with schizophrenia chose the smaller, more immediate reward more frequently than unaffected individuals (Weller et al., 2014). These findings suggest enhanced delay discounting predominantly reflects reduced reward value rather than impairments in strategizing, attention to task, or even motivation. Reversal learning, which indicates the ability to adapt to changing contingencies, is also impaired in schizophrenia (Schlagenhauf et al., 2014; Waltz & Gold, 2007). Thus, individuals with schizophrenia are less able to adjust their behaviour to maximise reward.

Impaired working memory in schizophrenia (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Lee & Park, 2005) may account for poor performance in reward paradigms. Gold, Waltz, Prentice, Morris, and Heerey (2008) argued that reinforcement learning deficits in schizophrenia are due to the effect of impaired working memory on reward value during rapid learning. Collins, Brown, Gold, Waltz, and Frank (2014) investigated the effect of working memory on reinforcement learning by manipulating task difficulty (number of items to remember). In unaffected individuals, reinforcement reduced the speed of response, whereas difficulty increased the speed of
response. In schizophrenia, reinforcement learning was diminished over time and for higher task difficulty, with a larger effect of task difficulty in later trials. Furthermore, difficulty had less effect on speed of response. There is also evidence that working memory impairments in schizophrenia are associated with enhanced delay discounting (Heerey et al., 2007) and impaired reversal learning (Schlagenhauf et al., 2014; Waltz & Gold, 2007). Such findings suggest impaired working memory contributes to anomalous reward-related behaviour in schizophrenia.

Schizophrenia is associated with reduced motivated behaviour. Tasks such as the Effort Expenditure for Rewards Task (EEfRT; Treadway et al., 2009) provide an index of motivated behaviour (button press) for rewards of differing magnitude and probability of winning. Evidence from EEfRT and similar tasks suggest that, despite comparable subjective monetary value, individuals with schizophrenia are less willing to expend effort for reward (Green, Horan, Barch, & Gold, 2015; Reddy et al., 2015), especially when reward value and likelihood are higher (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013). This contrasts with unaffected individuals, who show increased effort for higher rewards and probability (Fervaha, Graff-Guerrero, et al., 2013; Treadway et al., 2009). Evidence of an effect of the interaction between probability and reward on effort is inconsistent in unaffected and schizophrenia populations (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013), but has been associated with reduced self-report motivation and pleasure (William P. Horan et al., 2015).

Differences in motivated behaviour may be due to impaired decision-making rather than reinforcement learning. Cognitive performance in schizophrenia and unaffected individuals has been shown to predict increased effort for higher reward (Gold et al., 2013). However, schizophrenia has been associated with a reduced ability (no reduction in response time) to learn stimulus contingencies from high probability rewards, but not uncertain (50%) rewards (Koch et al., 2010). Fervaha, Foussias, Agid, and Remington (2013) argued such findings reflect impaired cost and effort computation, in schizophrenia, that is due to either value discounting or overestimating costs. This argument fits with evidence suggesting impairments in value representations during decision-making (S E Morris, Holroyd, Mann-Wrobel, &
Gold, 2011) and issues with updating value during reversal learning in schizophrenia (Gold et al., 2008). However, working memory also correlates with differences in optimal decision making in schizophrenia (Gold et al., 2008; Premkumar et al., 2008), thus may underlie maladaptive decision-making.

Negative symptoms of schizophrenia also impact motivated behaviour (Gold et al., 2013), if not consummatory pleasure (Gard, Kring, Gard, Horan, & Green, 2007). High negative symptoms were associated with reduced reinforcement learning in response to rewarding outcomes (Gold et al., 2012). These findings are accordant with reduced responsivity to feedback in medicated Parkinson’s disease (Di Rosa et al., 2015). Individuals with schizophrenia who scored high on negative symptoms showed no preference for learning from outcome value or probability (Strauss et al., 2011). This contrasted with an increased bias for probability over reward value learning in unaffected individuals and individuals with schizophrenia who scored low on negative symptoms (Strauss et al., 2011). However, not all studies compared positive and negative symptoms (Gold et al., 2012) and those that did still found low negative symptom scores were associated with elevated differences compared to unaffected individuals (Strauss et al., 2011). Therefore, the findings demonstrate an association between reduced reward value and schizophrenia that is amplified by negative symptoms.

Schizotypy research suggests impairments in motivational salience change in line with symptom severity. Higher reality distortion has been shown to predict increased responsivity to neutral outcome cues (Balog, Somlai, & Kéri, 2013). Higher reported unusual experiences and introverted anhedonia have been associated with slower responses to cues predicting aversive outcomes (Balog et al., 2013). Anhedonia has been associated with reduced effort for high uncertain rewards (50%; Treadway et al., 2009) and increased effort for uncertain low and medium value rewards (McCarthy, Treadway, & Blanchard, 2015). Reduced anticipatory pleasure was associated with prodromal negative (Engel, Fritzschke, & Lincoln, 2013) and positive (Schlosser et al., 2014) symptoms of schizophrenia. However, reduced anticipatory pleasure was not reported in individuals with recent onset (< 5 years) or chronic (> 5 years) schizophrenia (Schlosser et al., 2014). Additionally,
depression only predicted reduced anticipatory pleasure in at risk (exhibiting prodromal symptoms) individuals, not schizophrenia (Schlosser et al., 2014). The findings suggest the directional relationship between motivational salience and symptom severity vary, although the effect of antipsychotics should be considered.

Schizophrenia is associated with anomalous reward-related behaviour (Ahn et al., 2011; Brown et al., 2018; Heerey et al., 2007; Schlagenhauf et al., 2014; Waltz & Gold, 2007; Weller et al., 2014). Reinforcement learning is impaired for appetitive (Dowd et al., 2016; Serra et al., 2001) but not aversive stimuli (Gold et al., 2012; Strauss et al., 2011; Waltz et al., 2007, 2011). Poor working memory contributes to deficits in reinforcement learning (Collins et al., 2014), adaptation to changing contingencies (Schlagenhauf et al., 2014; Waltz & Gold, 2007), and reward value (Heerey et al., 2007) and is associated with maladaptive decision-making (Gold et al., 2008; Premkumar et al., 2008). Atypical reward-related behaviour is exacerbated by negative symptoms (Gold et al., 2012; Strauss et al., 2011) and likely precedes onset (Balog et al., 2013; Engel et al., 2013; Schlosser et al., 2014). However, reinforcement learning for aversive stimuli appears intact. Thus, dysregulated dopamine in schizophrenia affects reward processing and motivational salience for appetitive but not aversive outcomes.

### 3.4.2 Reinforcer sensitivity in schizophrenia

Reduced loss aversion is indicated in schizophrenia. Currie et al. (2017) amended the prisoner's dilemma to assess loss aversion in schizophrenia. During the standard prisoner's dilemma, participants choose to stay silent (co-operate) or betray each other based on known potential outcomes (Flood and Dresher, 1950). Mutual co-operation and mutual betrayal result in both participants receiving a less aversive or medium aversive outcome respectively. However, if one participant betrays and one co-operates, the co-operating participant will receive the most aversive outcome. In the amended version, all outcomes yielded gains in the gain frame, losses in the loss frame, and equal value outcomes in the neutral frame for co-operate and betray (Currie et al., 2017). Unaffected individuals exhibited loss aversion, with a reduced number of
co-operate choices in the loss compared to gain frame. This difference was not seen in the schizophrenia group, who exhibited comparable co-operate choices for loss and gain frames, suggesting reduced loss aversion. However, schizophrenia has been associated with impaired value representation during decision-making (S E Morris et al., 2011) and issues with updating value during reversal learning (Schlagenhauf et al., 2014; Waltz & Gold, 2007) for appetitive but not aversive stimuli. It is therefore unclear whether the findings were due to reduced loss sensitivity, or cognitive or social impairment.

Understanding sensitivity to loss and gain may explain differences in motivated behaviour in schizophrenia. For example, there is a comparable effect of gain and loss on task choice during social co-operation (Currie et al., 2017) and speed of response during reinforcement learning (Collins et al., 2014). Some findings indicate reduced reward value (Weller et al., 2014), however increased loss aversion has also been found (Currie et al., 2017). Combined with evidence of impaired reinforcement learning for appetitive but not aversive stimuli (Strauss et al., 2011; Waltz et al., 2007, 2011), behavioural findings point to a lessening difference in the effect of gain and loss on motivated behaviour in schizophrenia.

3.4.3 Neurological Differences in Reward and Motivation in Schizophrenia

Schizophrenia is associated with atypical VS activation during reward processing, although findings are inconsistent (Table 3.1). For example, VS activation for gain relative to loss outcomes has been reported as comparable and dissimilar to unaffected individuals. Reported differences in VS activation during reward anticipation and stimulus valence are also inconclusive. Attenuated VS activation in schizophrenia is frequently reported, and predicts impairments in learning, symptom severity, and motivated behaviour. However, there is evidence of enhanced VS activation in schizophrenia during reward processing and no difference in comparison to unaffected individuals during reward processing.

Neural regions involved in higher cognitive functions also show atypical activation during reward processing in schizophrenia. Activation in task-related (amygdala, hippocampus, midbrain), but not default mode network (insula,
ACC), regions is attenuated in response to gain but not loss (Table 3.1). The amygdala and hippocampus support the identification of salient stimuli (J. Zheng et al., 2017). The amygdala appears activated during reward (appetitive) processing, and is thought to signal reward intensity and value (Bissonnette, Gentry, Padmala, Pessoa, & Roesch, 2014), ascertaining stimulus relevance relative to current motivational state (Cunningham & Brosch, 2012). The midbrain contributes to the coordination of motor (Bear, Connors, & Paradiso, 2007) and cognitive performance (Andreasen et al., 1996; Stoodley, Valera, & Schmahmann, 2012). The insula is involved in signalling motivationally salient stimuli (Medford & Critchley, 2010), whereas the anterior cingulate cortex is thought to signal changes in reinforcement contingencies (Alexander & Brown, 2011; Jahn et al., 2014) and initiate motivated behaviour (Laskowski et al., 2016; Medford & Critchley, 2010). A meta-analysis of seven studies revealed, among other things, reduced anterior cingulate cortex volume in schizophrenia compared to healthy controls (Baiano et al., 2007).

Overall, the picture is one of atypical activation during reward-processing that impacts the end-to-end assessment and tracking of salient stimuli in schizophrenia. Atypical VS activation contributes to decreased anticipation of reward, reduced value of positive outcomes, and failure to engage key regions associated with decision-making. Diminished activation in regions that interpret and update information and facilitate adaptation to contingencies further impacts motivational salience and behaviour. Atypical activation in individuals with a higher risk of developing psychosis suggests anomalous reward processing precedes clinical symptom onset. Understanding the directional interaction between atypical reward-related activation and symptoms, is an important step in understanding the development of psychosis.
### Table 3.1

Neural activation in schizophrenia compared to unaffected individuals during reward processing

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Participants</th>
<th>Group differences</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS activation during reward processing</td>
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<td></td>
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</tr>
<tr>
<td>MID</td>
<td>10 SC</td>
<td>Attenuated VS activation in SC in response to reward- and loss-cue stimuli</td>
<td>Juckel et al. (2006)</td>
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<td></td>
<td>10 UI</td>
<td></td>
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<tr>
<td>Modified MID with certain gain and certain loss</td>
<td>17 SC</td>
<td>No group differences. Greater VS activation in response to anticipated gains than losses and for larger than smaller gains in both groups.</td>
<td>Waltz et al. (2010)</td>
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<tr>
<td></td>
<td>17 UI</td>
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<tr>
<td>Progressive ratio task - measure of effort for reward.</td>
<td>41 SC</td>
<td>VS activation enhanced for wins compared to losses in both groups.</td>
<td>Wolf et al. (2014)</td>
</tr>
<tr>
<td></td>
<td>37 UI</td>
<td>However, correlation between reduced VS activation and reduced effort only found in SC.</td>
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<td></td>
<td>fMRI</td>
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<tr>
<td>Reinforcement learning</td>
<td>15 SC</td>
<td>Enhanced VS activation during encoding of expected reward value in SC.</td>
<td>Gradin et al. (2011)</td>
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<td></td>
<td>20 UI</td>
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<td></td>
<td>15 MDD</td>
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<td></td>
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<tr>
<td>Probabilistic learning task (gain/gain omission)</td>
<td>14 SC</td>
<td>Reduced VS responses during reward compared to no-reward outcomes in SC, which predicted negative symptom severity and diminished associative learning.</td>
<td>Gradin et al. (2013)</td>
</tr>
<tr>
<td></td>
<td>18 UI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MID</td>
<td>44 SC</td>
<td>Attenuated VS activation during reward anticipation in SC, MDD and AD.</td>
<td>Hägele et al. (2014)</td>
</tr>
<tr>
<td></td>
<td>54 UI</td>
<td>Depressive symptoms predicted attenuated VS activation during reward anticipation, regardless of diagnosis</td>
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<td></td>
<td>24 MDD</td>
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<td></td>
<td>26 AD</td>
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<tr>
<td>MID</td>
<td>54 FDR</td>
<td>Hypoactivation in VS during reward anticipation in FDR.</td>
<td>Grimm et al. (2014)</td>
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<tr>
<td></td>
<td>80 UI</td>
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<td>fMRI</td>
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<td>Paradigm</td>
<td>Participants</td>
<td>Group differences</td>
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<tr>
<td>MID</td>
<td>27 SC*</td>
<td>Shorter RT for gain than loss omission tasks. Hypoactivation in the VS during reward (gain and loss omission) anticipation in SC, which correlated with increased salience attribution to neutral cues and positive symptoms.</td>
<td>Esslinger et al. (2012)</td>
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<tr>
<td></td>
<td>27 UI</td>
<td></td>
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<tr>
<td>Pavlovian learning of CS with aversive or neutral UCS</td>
<td>18 SC</td>
<td>Enhanced VS activation to neutral CS. Neural finding consistent with: a) SC inability to distinguish between conditioned neutral and aversive stimuli in self-report; and b) higher galvanic skin responses (arousal) for neutral UCS, with levels similar to those of aversive UCS.</td>
<td>Jensen et al. (2008)</td>
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<td></td>
<td>18 UI</td>
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<tr>
<td>Modified MID, where outcome (gain, loss, neutral) was either certain (outcome not affected by behaviour) or uncertain (outcome dependent on behaviour)</td>
<td>31 SC*</td>
<td>Speed of response slowest for neutral cues in UI but for certain gain and loss cues in SC. Attenuated VS activation in SC for all cues, but most pronounced for uncertain gain and loss cues.</td>
<td>Nielsen et al. (2012)</td>
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<td></td>
<td>31 UI</td>
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<tr>
<td>Reversal Learning (positive and negative feedback)</td>
<td>24 SC^</td>
<td>Attenuated VS activation related to impaired reversal learning</td>
<td>Schlagenhauf et al. (2014)</td>
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<td></td>
<td>24 UI</td>
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<tr>
<td>Probabilistic monetary reward task (gain)</td>
<td>22 SC</td>
<td>Attenuated VS activation during prediction errors in SC</td>
<td>White et al. (2015)</td>
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<td></td>
<td>19 UI</td>
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<tr>
<td>Reward processing</td>
<td>Meta-analysis</td>
<td>SC and UI from 40 Studies: anticipation (23), feedback (9), and prediction error (8) suggests attenuated VS activation during reward (gain) anticipation in SC.</td>
<td>Radua et al. (2015)</td>
</tr>
<tr>
<td>MID task</td>
<td>15 SC^</td>
<td>The valence of unexpected feedback affected response in SC. During loss omission (gain), activation in the VS was attenuated. During gain omission (loss), activation in the medial prefrontal cortex was enhanced. Functional connectivity between the VS and prefrontal cortex was also diminished in SC.</td>
<td>Schlagenhauf et al. (2009)</td>
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<td>Paradigm</td>
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<td>Atypical activation in other neural regions during reward processing</td>
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<td>Probabilistic reinforcement learning task</td>
<td>26 SC</td>
<td>Reduced event-related negativity to negative feedback associated with impaired probabilistic learning, but only when certainty of winning was high</td>
<td>Morris, Heerey, Gold, and Holroyd (2008)</td>
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<td>task (monetary gain)</td>
<td>27 UI</td>
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<tr>
<td>Classical conditioning; temporal difference error</td>
<td>18 SC</td>
<td>Attenuated activation in the midbrain, insula, putamen, and cerebellum to unexpected reward but not aversive (omission) outcomes in SC compared to UI.</td>
<td>Waltz et al. (2009)</td>
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<td></td>
<td>18 UI</td>
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<tr>
<td>Modified MID with certain gain and certain loss</td>
<td>17 SC</td>
<td>Attenuated activation found in regions involved in the interpretation of VS signals and updating of information, including the PFC and amygdala</td>
<td>Waltz et al. (2010)</td>
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<tr>
<td></td>
<td>17 UI</td>
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<tr>
<td>Modified gambling paradigm</td>
<td>19 SC</td>
<td>Impaired learning of stimulus-reward contingencies. The inverse correlation between reward predictability and right dorsolateral PFC activation in UI was absent in SC.</td>
<td>Koch et al. (2010)</td>
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<td>fMRI</td>
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<tr>
<td>Reinforcement learning</td>
<td>15 SC</td>
<td>Attenuated expected reward value activation in the amygdala-hippocampal complex and parahippocampal gyrus in SC.</td>
<td>Gradin et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>20 UI</td>
<td>Prediction error encoding activation attenuated in caudate, thalamus, insula, and amygdala-hippocampal complex in SC.</td>
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<tr>
<td></td>
<td>15 MDD</td>
<td>Severity of psychotic symptoms correlated with the degree of attenuated activation during encoding of expected reward value and prediction error at outcome</td>
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<tr>
<td>Probabilistic learning task (gain/gain omission)</td>
<td>14 SC</td>
<td>Weaker functional connectivity between regions, including the midbrain and right insula, in SC. In response to rewards, task-related regions (midbrain, striatum, amygdala/hippocampus) did not significantly activate but salience network regions (insula, anterior insular cortex) did. Both regions activated in UI.</td>
<td>Gradin et al. (2013)</td>
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<td>18 HC</td>
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<tr>
<td></td>
<td>57UI</td>
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<td>fMRI</td>
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<tr>
<td>Paradigm</td>
<td>Participants</td>
<td>Group differences</td>
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<tr>
<td>MID</td>
<td>21 SCRisk</td>
<td>Increased activation in prefrontal cortical regions and the posterior cingulate cortex during reward anticipation in SCRisk. Positive symptoms correlated with VS and anterior insula activation during reward anticipation. There was an inverse correlation between VS activation during outcome and negative symptoms.</td>
<td>Wotruba et al. (2014)</td>
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<td></td>
<td>24 UI</td>
<td></td>
<td></td>
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<tr>
<td>Classic conditioning to aversive stimuli</td>
<td>100 UI SC</td>
<td>Reality distortion and introvertive anhedonia inversely related to skin conductance response (arousal) during presentation of aversive conditioned stimuli. Introvertive anhedonia also correlated with response time for conditioned stimuli</td>
<td>Balog et al. (2013)</td>
</tr>
</tbody>
</table>

Note. MID = Monetary Incentive Delay task where motivated behaviour for gain (reward or avoid loss); CS = conditioned stimulus; UCS = unconditioned stimulus; SC = individuals with schizophrenia; SC* = antipsychotic naïve SC; SC^ unmedicated SC; UI = unaffected individual; MDD = major depressive disorder; AD = alcohol dependence; FDR = first degree relative of individual with schizophrenia; USib = unaffected sibling of individual with schizophrenia; SCRisk = medication free individuals who scored high on measures of psychosis risk and proneness; VS = ventral striatum; PFC = prefrontal cortex.
3.4.4 How much do antipsychotics affect motivated behaviour?

It is worth considering the effect of medication, given that antipsychotics are dopamine antagonists (Seeman, 1987). However, the findings regarding antipsychotic dose and behaviour are inconclusive. Gold et al. (2013) found no relationship between antipsychotic dose and performance during a reinforcement learning task. Insel et al. (2014) found higher atypical antipsychotic doses were associated with increased reinforcement learning, increased sensitivity to negative feedback (changed behaviour faster), and reduced prediction error responses in the striatum and medial prefrontal cortex. Antipsychotics have also been shown to reduce avoidance behaviour (Feng, Sui, & Li, 2013; Zhang, Fang, & Li, 2011).

The effect of antipsychotics on neural activation is similarly unknown. During reward anticipation, typical antipsychotics attenuated bilateral VS activation, whereas only left VS activation was attenuated in individuals on atypical antipsychotics (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006). However, there is also evidence of attenuated VS activation in unmedicated schizophrenia. In drug naïve, first-episode psychosis, activation was attenuated in response to value and motivational salience in the ventral tegmental area, VS and anterior cingulate cortex compared to matched controls (Nielsen et al., 2012). Attenuated reward-cue activation in the VS positively correlated with positive symptom severity (Nielsen et al., 2012). The level of prediction-error VS attenuation between drug naïve and previously medicated individuals with schizophrenia was comparable (Schlagenhauf et al., 2014). The findings suggest dampened activation in the VS in both medicated and unmedicated individuals.

This brief review shows that effects of antipsychotic medication on reward processing and motivational salience are inconsistent. In response to value and motivational salience, similar attenuated activation in key mesocorticolimbic regions has been indicated in drug naïve, first-episode psychosis and medicated schizophrenia. One of the issues with using dose as a covariate is the individual variance in dose efficacy. In other words, two individuals who present with similar symptoms, including severity, may show variance in symptom reduction on the same antipsychotic and dose. Findings
indicating an association with reward processing deficits and dose may, therefore, be due to factors that contribute to dose efficacy.

### 3.4.5 Summary

Dopamine could signal reward (Schultz, 2010) or control motivational salience (Horvitz, 2000; Jimmy Jensen & Walter, 2014); but appears to do both (e.g. Boksem et al., 2006; Cooper et al., 2014; Dreher et al., 2006; Hird et al., 2018; Twomey et al., 2015) Indeed, dopamine appears to mediate the interaction between reward value and motivational salience.

Impairments in motivated behaviour and reward processing in schizophrenia are not comparable to findings which rely on pharmacologically induced dopamine changes. In unaffected individuals, dopamine agonists dampen the value of negative outcome (Shiner et al., 2014) whereas overexpression of D2 receptors in adult rodents increases the effort for reward (Trifilieff et al., 2013). In schizophrenia, reinforcement learning is impaired for appetitive but not aversive stimuli (Strauss et al., 2011; Waltz et al., 2007, 2011) and participants exhibit reduced effort for reward (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013; Green et al., 2015; Reddy et al., 2015; Treadway et al., 2009).

Positive and negative symptoms of schizophrenia are associated with different impairments that affect motivational salience. Specifically, negative symptoms are associated with reduced anticipation (Gold et al., 2012; Strauss et al., 2011; Wolf et al., 2014) whereas positive symptoms affect salience (Gradin et al., 2011). Neural (Radua et al., 2015; Schlagenauf et al., 2014, 2009; D. M. White et al., 2015) and cognitive (Duvarci et al., 2018; Gold et al., 2013, 2008; Gradin et al., 2011; Koch et al., 2010; Krabbe et al., 2015; Premkumar et al., 2008; Waltz et al., 2009) differences in schizophrenia may account for the conflicting findings and highlight the limitations of research in non-clinical populations. Reinforcer sensitivity, which affects motivated behaviour (Gomez, Cooper, McOrmond, & Tatlow, 2004) and associated neural activation (e.g. Amodio et al., 2008; Balconi & Crivelli, 2010; De Pascalis et al., 2010; Simon et al., 2010), differs in schizophrenia (Currie et al., 2017). However, the construct
validity of popular measures calls into questions assumptions made from the outcome of such measures.

Finally, data on antipsychotic medication and behavioural and neural indicators are mixed. This may be due to variables that affect dose efficacy. The effect of antipsychotic medication, therefore, requires further research that incorporates factors beyond merely dose.

Overall, dopamine appears to signal both salience and reward value, and may control their interaction. In unaffected individuals, the two processes are so intrinsically related that it can be difficult to disentangle effects from underlying neural mechanisms. Disruptions to normal dopaminergic functioning suggest the interaction between value and motivational salience is reliant on dopamine. The crucial role of dopamine is evident in behavioural and neural disruptions during reward processing and motivational salience in schizophrenia. Importantly, the interaction between motivational salience and value is disrupted in schizophrenia and reflected in dysregulated patterns of neural activation. The evidence therefore suggests dopamine does not signal value or salience, but both.

3.5 Conclusions

Mesocorticolimbic pathways are associated with the processing of both appetitive and aversive stimuli (Bromberg-Martin et al., 2011; Hage & Khaliq, 2015; Schultz, 2010), with registering outcome value, and with motivational salience (e.g. Boksem et al., 2006; Cooper et al., 2014; Dreher et al., 2006; Hird et al., 2018; Twomey et al., 2015). Deficits in reward processing in schizophrenia can be linked to factors contributing to motivational salience. Impaired decision-making in schizophrenia affects motivated behaviour (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013; Green et al., 2015; Reddy et al., 2015). Specifically, the reduced ability to update stimulus-value is diminished (Schlagenhauf et al., 2014; Waltz & Gold, 2007), leading to impaired value representations during decision-making (S E Morris et al., 2011). Atypical neural activation can account for some differences in reward and motivation in schizophrenia (e.g. Sarah E. Morris et al., 2008; Schlagenhauf et al., 2009), but not all. However, dopamine signals both motivational salience and value, which
interact in unaffected individuals. The dysregulated pattern of behaviour and neural activation in schizophrenia may, therefore, reflect a dissociation between value and motivational salience.
Chapter Four
Does dysfunctional motivational salience mediate the development of aberrant salience?

4.1 Introduction

Kapur (2003) proposed that dopaminergic dysregulation in schizophrenia alters motivational salience and so results in the aberrant assignment of importance to irrelevant stimuli. Typically, salient stimuli trigger firing in dopamine neurons (Fiorillo et al., 2013; Horvitz, 2000; Salamone et al., 2005; Schultz, 2010; Wittmann et al., 2007). This facilitates the assessment of the stimulus in regard to value (threat or reward) and motivational salience. As defined in the previous chapter, motivational salience is the desire to approach or avoid a stimulus and incorporates current neurobiological factors, previous outcome, situational context, and stimulus value. According to Kapur (2003), hyperdopaminergic activation in schizophrenia results in dopamine neurons firing outside the usual context. Given the typical function of dopaminergic firing, irrelevant stimuli that are present during dysregulated firing may be assigned value. In this circumstance, motivational salience is based purely on spontaneous neuronal firing and not on attributes of the current external stimulus, such as its utility. The assignment of importance to irrelevant stimuli is, according to Kapur, aberrant salience.

As demonstrated in Chapter 2, there is evidence of increased aberrant salience in schizophrenia. There is also evidence, outlined in Chapter 3, that schizophrenia is associated with impaired reward processing that affects motivated behaviour. Reported findings linking atypical activation in reward-related regions and impaired reward processing in schizophrenia are inconsistent. However, dysregulated dopaminergic activation appears to affect salience tracking and cognitive functions (e.g. decision-making) that, in turn, affect motivational salience. In this chapter, I explore whether there is evidence to support Kapur’s (2003) proposed relationship between motivational salience and aberrant salience.
Extending the behavioural evidence presented in section 2.4.1, I first review behavioural evidence from paradigms not specifically measuring aberrant salience. I review behavioural evidence indicating schizophrenia is associated with a tendency to focus on irrelevant stimuli during reward processing. This is followed by a review of neuroimaging evidence of atypical activation in regions associated with reward processing, salience, and the self. Next, I explore the disruptions to higher cognitive processing and how these disruptions may contribute to aberrant salience. Finally, I highlight gaps in the published research that I aim to address.

4.2 Behavioural evidence

To understand why such a hypothetical craving would be directed toward one food in particular, it is important to note that the incentive salience attributed by an activated dopaminergic system is not simply projected indiscriminately toward every stimulus in sight. Attributions of incentive salience are always guided by systems of associative learning. (Berridge, 1996, p. 17)

The salience of a stimulus is determined by many variables, such as the individual’s current neurobiological state, prior experience, and other available stimuli. In schizophrenia, there appears to be a reduced ability to discount irrelevant stimuli and a dampened effect of relevant stimuli. Together, these changes lead to increased distractibility, aberrant associative learning, and reduced sensitivity to loss.

Schizophrenia is associated with increased interference from task-irrelevant cues with high salience. During a modified Stroop task, smokers with schizophrenia were slower than unaffected smokers to identify the colour of smoking-related words than neutral words (Freeman et al., 2013). All participants were asked to refrain from smoking 15 minutes prior to giving consent. Reported wanting for, and enjoyment of, smoking a cigarette increased with time, with no difference between groups. Therefore, the findings suggest a reduced ability to ignore motivationally salient cues in schizophrenia.
Schizophrenia is also associated with increased interference from neutral cues. Anticevic et al. (2011) investigated the effect of distractor stimuli on working memory. During a visual working memory task using geometric shapes, distractor stimuli were either task-relevant (a geometric shape), task-irrelevant (aversive or neutral pictures), or not present (no distractor). Participants with schizophrenia rated all distractor type stimuli as more arousing than unaffected individuals, but both groups rated aversive stimuli as more arousing than neutral stimuli. Unaffected individuals exhibited reduced accuracy following aversive distractors compared to neutral and task-relevant distractors. In contrast, schizophrenia was associated with reduced accuracy for all distractor types, with more interference from neutral and task-relevant stimuli than unaffected individuals. There was no effect of distractor type on response time and group accuracy was comparable during no distraction. The effect of neutral stimuli on accuracy in schizophrenia, despite lower arousal ratings and no impact on motivated behaviour, suggests an inability to ignore irrelevant stimuli.

Irrelevant cues appear more salient in schizophrenia. Morris, Griffiths, Le Pelley, and Weickert (2013) investigated learned irrelevance in schizophrenia. Learned irrelevance occurs when exposure to a stimulus with no predictive value results in it being deemed irrelevant. Learned irrelevance can interfere with later associative learning for that stimulus (Dess & Overmier, 1989). Morris et al. (2013) found learned irrelevance was diminished in schizophrenia when cognitive load was high (higher number of cues), but evident when cognitive load reduced. Thus, when attentional resources were limited, irrelevant stimuli were more salient. Individuals with schizophrenia also learnt more about nonpredictive cues than unaffected individuals and did not exhibit the bias towards predictive cues seen in unaffected individuals. The difference between groups was not accounted for by associative learning ability. Furthermore, the ability to ignore irrelevant stimuli was inversely related to positive symptom severity. Diminished learned irrelevance has also been reported in individuals who score high on introverted anhedonia (Haselgrove et al., 2016), one attribute of schizotypy.
Relevant cues appear less salient in schizophrenia. For example, Currie et al. (2017) used a novel version of the prisoners’ dilemma paradigm, where participants played against a computer that followed pre-programmed strategies: loss, gain, or neutral (neither co-operation nor betrayal would outperform the other). Unaffected individuals were more likely to co-operate in gain than loss trials. However, no differences were indicated in co-operation choices between loss and gain trials in schizophrenia. Schizophrenia has also been associated with reduced susceptibility to confirmation bias (Doll et al., 2014) and reduced learning from positive (but not negative) feedback (Dowd et al., 2016). These findings cannot simply be attributed to deficits in reinforcement learning, which appears intact in schizophrenia (Bansal et al., 2018; Collins, Albrecht, Waltz, Gold, & Frank, 2017). Similarly, the argument that deficits in working memory can account for impaired reinforcement learning (Collins et al., 2017) fails to explain valence differences seen in schizophrenia.

Aberrant salience is evident in the increased salience of irrelevant stimuli in schizophrenia (Anticevic et al., 2011; R. Morris et al., 2013). However, reduced adaptive salience also appears to occur in schizophrenia (Currie et al., 2017; Doll et al., 2014; Dowd et al., 2016). The argument that reduced adaptive salience is due to the effect of antipsychotics in dampening dopaminergic activation (Roiser et al., 2009) is challenged by evidence of reduced adaptive salience in both medicated and unmedicated first-episode psychosis (Smieskova et al., 2015) and attenuated reward-related neural activation was also found in drug naive schizophrenia (Nielsen et al., 2012; Schlagenhauf et al., 2014). Conversely, increased aberrant and reduced adaptive salience supports the argument of a dissociation between value and motivational salience in schizophrenia. In other words, the salience of relevant and irrelevant stimuli appears to converge in schizophrenia.

4.3 Neuroimaging evidence

There are a number of neural regions associated with reward processing and motivational salience that show atypical activation in schizophrenia. Typical phasic firing of dopamine neurons triggers activation or inhibition in these
regions. Dysregulated dopaminergic firing can, therefore, lead to atypical behaviour. For example, the artificial stimulation of ventral tegmental dopamine neurons in rats led to reward-related behavioural responses to neutral stimuli that had no predictive or sensory reward cues (Saunders, Richard, Margolis, & Janak, 2018). This is consistent with Kapur’s (2003) idea that aberrant dopaminergic firing can instigate or create aberrant conditioned responses to irrelevant stimuli.

4.3.1 Atypical activation during reward processing: value or salience?

One of the key regions involved in reward processing, the VS, shows disordered activation in schizophrenia. Compared to unaffected individuals, schizophrenia is associated with reduced activation in the VS in response to reward cues, whether these relate to gain or omission of loss (Nielsen et al., 2012; Radua et al., 2015). This has been shown in unmedicated patients (Juckel, Schlagenhauf, Koslowski, Wüstenberg, et al., 2006; Schlagenhauf et al., 2009) and those on typical, but not atypical, antipsychotics (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006). Attenuated VS activation during reward anticipation has also been found in first-episode psychosis (Esslinger et al., 2012) and individuals with a first-degree relative with schizophrenia (Grimm et al., 2014). However, the pattern of attenuated VS activation in schizophrenia is inconsistent. For example, compared to unaffected individuals, individuals with schizophrenia have shown no difference in VS activation to gain and loss outcomes (Waltz et al., 2010; Wolf et al., 2014), attenuated VS activation to gain only (Hägele et al., 2014; Schlagenhauf et al., 2009) and enhanced VS activation during reward encoding (Gradin et al., 2011). A similar inconsistent pattern has been found in response to neutral (non-salient) cues, with VS activation attenuated (Jimmy Jensen & Walter, 2014) or comparable to gain and loss cues (Nielsen et al., 2012). Activation of the VS in schizophrenia, therefore, appears inconsistently dysregulated.

Atypical VS activation during reward processing varies with symptom severity. Papanastasiou et al. (2018) investigated differences, in striatal and PFC neural activation during reward processing, between individuals scoring low or high on the psychotic-like experience (PLE) scale at two time points: 14 and 19
years of age. Compared to the low PLE group, high PLE was associated with decreased striatal activation and increased PFC activation at 19 compared to 14 years. Positive symptoms have been associated with increased VS activation in individuals considered UHR (Wotruba et al., 2014) but attenuated activation in unmedicated individuals diagnosed with schizophrenia (Nielsen et al., 2012). During reward anticipation, activation in the VS and right anterior insula positively correlated with positive symptoms in UHR individuals (Wotruba et al., 2014). However, activity in the left VS and medial orbitofrontal cortex inversely related to negative symptoms (Wotruba et al., 2014). Attenuated VS activation correlated with the severity of negative symptoms in schizophrenia, both unmedicated (Juckel, Schlagenhauf, Koslowski, Wüstenberg, et al., 2006) and those on typical antipsychotics (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006). Attenuated VS activation in response to salient stimuli predicted positive symptom severity in unmedicated individuals with schizophrenia (Nielsen et al., 2012). Hence, whereas VS activation in response to reward cues was associated with positive symptoms in UHR, attenuated VS activation was related to positive and negative symptoms in individuals with schizophrenia, with some indication of this in individuals with sub-clinical symptoms.

As reviewed in Chapter 3, VS activation signals salience. In unaffected individuals, VS activation was enhanced for cues with high context salience rather than unusual cues with high novel salience (e.g. rice versus a caterpillar as food; Le Pelley et al., 2014), for reward-cues even when unattended (Le Pelley et al., 2014), and during decision-making (Esslinger et al., 2013). VS activation attenuates with repetition (H. Matsumoto et al., 2016) but motivated behaviour does not (Berridge, 1996; Berridge & Robinson, 1998). Greater implicit aberrant salience (as assessed by the SAT) predicted attenuated reward-prediction error activation, in the VS and orbitofrontal cortex, and higher ventral striatal presynaptic dopamine capacity (Boehme et al., 2015). Thus, as well as reward value, enhanced VS activation signals adaptive and aberrant salience.

Atypical VS activation affects aberrant salience. Administration of an NMDA receptor antagonist to mice, inducing schizophrenia-like responses, resulted in altered neural responses suggestive of increased aberrant salience.
and reduced adaptive salience (Moessnang, Habel, Schneider, & Siegel, 2012). In schizophrenia, incorrect identification of a distractor stimulus as salient was associated with increased prefrontal and striatal activation (Ceaser & Barch, 2016). The degree of striatal activation positively correlated with self-reported aberrant salience (Ceaser & Barch, 2016). Reduced adaptive behaviour in schizophrenia predicted attenuated activation in the globus pallidus, which is innervated by the VS (Ceaser & Barch, 2016).

EEG findings suggest aberrant attention is given to irrelevant stimuli in schizophrenia. Anderson et al. (2016) investigated neural activation to target and distractor (novel, neutral, and aversive) stimuli in schizophrenia, first-degree relatives, and unaffected individuals. ERPs of interest included: P3a, which is associated with novelty detection; P3b, associated with task-relevant cues; and the late positive potential (LPP), which is typically larger for emotional stimuli. First-degree relatives and individuals with schizophrenia had smaller P3b amplitudes in response to target stimuli, indicating reduced attentional processing. In response to aversive stimuli, they found attenuated early-LPP's in first-degree relatives and individuals with schizophrenia, indicating deficits in attention. First-degree relatives also exhibited increased sustained attention (larger late-LPP) for aversive stimuli that was not found in schizophrenia. There were no group differences in P3a amplitude, thus novelty detection appeared intact in schizophrenia. However, despite having ERP amplitudes that are comparable to those seen in first-degree relatives, individuals with schizophrenia behaved differently. Schizophrenia was associated with slower response times for neutral and quicker response times for aversive stimuli.

Conversely, larger LPP amplitudes (both early and late) to negative stimuli have been identified in schizophrenia. Horan, Hajcak, Wynn, and Green (2013) used neutral and unpleasant pictures, with the latter preceded by negative or neutral descriptions, during EEG. Unaffected individuals had larger LPP in response to negative pictures preceded by negative descriptions than those preceded by neutral descriptions or the neutral pictures. In schizophrenia, compared to neutral conditions, a larger early LPP (indicating increased attention or motivational salience) occurred in response to negative
pictures, regardless of the description that preceded it. The late-LPP in schizophrenia was larger for negative stimuli preceded by a neutral description than when preceded by a negative one. Thus, neutral information appeared to elicit sustained attention to negative stimuli.

In schizophrenia, increased VS activation predicted aberrant salience whereas attenuated activation in a region innervated by the VS predicted reduced adaptive behaviour (Ceaser and Barch, 2016). EEG evidence suggests reduced attention to negative stimuli in schizophrenia and first-degree relatives (Andersen et al., 2016). Negative cues elicited sustained attention in first-degree relatives, but not schizophrenia, and increased motivated behaviour schizophrenia (Andersen et al., 2016). Conversely, increased initial and sustained attention in schizophrenia was reported in response to negative stimuli (W P Horan et al., 2013). Sustained attention was enhanced when the negative cue followed an irrelevant stimulus. The overall picture is one where atypical VS activation predicts increased aberrant and decreased adaptive salience in schizophrenia.

The relationship between VS activation and salience differs in first-episode psychosis (FEP). Compared to unaffected individuals, VS activation to reinforcer stimuli was attenuated in antipsychotic naïve FEP participants (Esslinger et al., 2012). The difference between neutral and gain trial VS activation was significantly smaller than in unaffected individuals, although there was no difference in response time to reward tasks. Given the continued motivated behaviour, the findings suggest atypical VS activation decreased adaptive salience rather than affecting reward value. However, salience signalling appeared intact. Antipsychotic naïve FEP rated unknown faces as more familiar. In contrast, VS activation negatively correlated with number of non-famous faces rated as familiar (aberrant salience) and positively with correct identification of famous faces as familiar (adaptive salience). In FEP, therefore, VS activation is attenuated in line with reduced adaptive salience but is not enhanced for increased aberrant salience.

The pattern of striatal activation in individuals at risk of psychosis is similar to that in FEP. Schmidt, Antoniades et al. (2016) used the SAT to assess the neural correlates of aberrant and adaptive salience over time (mean interval
17 months), in individuals who were considered UHR (assessed using the Comprehensive Assessment of At-Risk Mental States) compared to individuals not at risk. The UHR scored higher on explicit aberrant salience at baseline and higher on implicit aberrant salience at follow-up. There was no evidence supporting a relationship between altered neural activation and aberrant salience scores. Explicit and implicit adaptive salience were also impaired in UHR. At baseline, impaired adaptive salience was related to attenuated VS activation during reward prediction. At follow-up no differences between groups were shown. Furthermore, an improvement over time in abnormal beliefs in UHR was associated with increased VS activation related to adaptive salience.

The lack of evidence supporting a relationship between VS activation and aberrant salience in FEP and UHR suggests aberrant salience precedes striatal dysfunction. In contrast, attenuated striatal activation appears to coincide with reduced adaptive salience. Furthermore, improved striatal activation during adaptive salience predicted symptom reduction. Combined with evidence from schizophrenia, the findings appear to support an effect of VS activation on adaptive but not aberrant salience.

Overall, schizophrenia is associated with disordered VS activation during reward processing paradigms. However, inconsistent finding suggest a poor fit between VS activation and reward value or valence processing. The findings may, instead, reflect the effect of VS activation on salience. Prodromal and FEP findings indicate that self-reported aberrant salience precedes the onset of changes in striatal activation. Thus, aberrant salience may affect striatal function. A mechanism by which this may occur is the impact of cognitive functions that affect salience tracking in schizophrenia.

4.3.2 The central executive network contributes to aberrant salience in schizophrenia

Atypical activation in the central executive network (CEN) sustains the aberrant processing of stimulus salience. CEN activation is enhanced during task-related activities such as attention and decision-making (Goulden et al., 2014; Sridharan et al., 2008). A key node of the CEN is the dorsolateral prefrontal
cortex (dIPFC; Goulden et al., 2014; Sridharan et al., 2008). Activation in the dIPFC signals working memory and attentional processing, including the filtering out of distractor stimuli (Anticevic et al., 2011; Katsuki & Constantinidis, 2012).

Anticevic et al. (2011) investigated the effect of neutral and aversive distractors on working memory maintenance. In unaffected individuals, dIPFC activation predicted better working memory and, during distractor stimuli, task performance. The relationship between better performance and dIPFC activation was absent in schizophrenia. In unaffected individuals, dIPFC activation was enhanced in response to aversive, compared to neutral, distractor stimuli. This pattern was reversed in schizophrenia, with higher dIPFC activation in response to neutral distractor stimuli. Given the role of the dIPFC in filtering distractors (Anticevic et al., 2011; Katsuki & Constantinidis, 2012), these findings suggest attenuated dIPFC activation decreases filtering of irrelevant stimuli, increasing attention to neutral stimuli yet diminishing attention to aversive stimuli. This pattern of diminished difference between aversive and neutral task-related dIPFC activation is similar to that found between reinforcer (gain/loss) and irrelevant (neutral) stimuli in reward-related regions (Esslinger et al., 2012; Gradin et al., 2013; Grimm et al., 2014)

The emerging pattern is one where neural activation in response to stimuli that could be deemed relevant, on the basis of rewarding or aversive outcomes, is diminished in schizophrenia but activation to irrelevant, neutral stimuli is enhanced.

The neural correlates of aberrant salience in the CEN differ between unaffected individuals and individuals with schizophrenia. In unaffected individuals, attenuated dIPFC activation was associated with explicit aberrant salience, as measured by the SAT (Roiser et al., 2010). This finding contrasts with the association between enhanced dIPFC activation and aberrant salience in schizophrenia (Anticevic et al., 2011). Differences in methodologies may have contributed to the conflicting findings. Anticevic et al. (2011) measured implicit aberrant salience in schizophrenia, with increased dIPFC activation indicating aberrant attentional processing. Roiser et al. (2010) assessed the correlation between aberrant reinforcement learning and neural activation during
presentation of low versus high reward probability cues in unaffected individuals. Irrelevant stimuli that were erroneously associated with higher probability of reward elicited a smaller dLPFC response. This effect was greater in unaffected individuals who scored higher in explicit aberrant salience. Given Anticevic et al.’s (2011) findings, the attenuated activation in the dLPFC in the Roiser et al. (2010) study may reflect reduced working memory. However, a more likely explanation lies with the issue of generalising findings from unaffected individuals to individuals with schizophrenia. Aberrant salience is evident in unaffected individuals, but higher in schizophrenia (e.g. Cicero et al., 2010; Haralanova et al., 2012; Katthagen et al., 2016; Roiser et al., 2010). According to Kapur (2003), hyperdopaminergic activation in schizophrenia creates salience of irrelevant stimuli. However, ostensibly healthy participants would not be expected to have hyperdopaminergic activation. Furthermore, neural activation in response to neutral, appetitive, and aversive stimuli differs between unaffected individuals and those with schizophrenia (Esslinger et al., 2012; W P Horan et al., 2013; J Jensen et al., 2008; Koch et al., 2010). Therefore, underlying neural differences between the groups likely explain the difference in the degree of aberrant salience.

4.3.3 The default mode network contributes to aberrant salience in schizophrenia

Atypical activation in the default mode network (DMN) precedes symptom onset, is associated with symptoms of schizophrenia, and impairs task-related performance. The DMN, which includes the posterior cingulate cortex and medial prefrontal cortex (mPFC; Buckner et al., 2008; Uddin et al., 2009), is usually more active during self-referential tasks and less active during task performance (Buckner et al., 2008; Crone et al., 2011; Scheibner et al., 2017). Reduced resting-state functional connectivity within the DMN has been reported in both individuals with schizophrenia (Bluhm et al., 2007; Mannell et al., 2010; Whitfield-Gabrieli et al., 2009) and first degree relatives (Jang et al., 2011). Reduced prefrontal resting-state DMN functional connectivity correlated with increased psychopathology scores in first degree relatives (Jang et al., 2011). In early psychosis, resting state hyperactivation in the mPFC has been
associated with positive, but not negative, symptoms (Anticevic et al., 2015). In schizophrenia, reduced resting-state right anterior PFC activation was associated with negative symptoms (Mingoia et al., 2012). Additionally, impaired working memory performance in schizophrenia was predicted by DMN hypoactivation during resting-state (Whitfield-Gabrieli et al., 2009). In treatment-resistant schizophrenia, increased resting-state functional connectivity between the dorsal striatum and DMN regions correlated with positive symptom severity (T. P. White, Wigton, et al., 2016). During task-related activity, first-degree relatives and individuals with schizophrenia exhibited increased activation in the mPFC and the dIPFC, with performance negatively correlating with mPFC activation (Whitfield-Gabrieli et al., 2009). Finally, compared to unaffected individuals, increased activation in the DMN during reward anticipation has been reported in individuals with subclinical symptoms of psychosis (Wotruba et al., 2014) and first-degree relatives (Hanssen et al., 2015). Combined, the evidence suggests resting-state DMN hypoactivation is associated with symptoms of schizophrenia, with DMN hyperactivation during task-related activities impairing performance.

The lack of DMN suppression during task-related activation is associated with increased salience of irrelevant stimuli and reduced adaptive salience. Mice given an NMDA receptor antagonist, to induce schizophrenia-like behaviour, exhibited altered, salience-specific neural responses (Moessnang et al., 2012). In mice conditioned to a stimulus pair (tone + shock), mPFC activation in response to motivationally salient stimuli (tone) was reduced following administration of the NMDA receptor antagonist. Conversely, mice not conditioned to a stimulus pair exhibited an increased neural response to motivationally salient stimuli. In schizophrenia, increased activation in DMN regions in response to neutral distractors was also seen on trials where the behavioural response to a task was incorrect (Anticevic et al., 2011).

4.3.4 The salience network: the key to aberrant salience?

The SN acts as a switch between the CEN and DMN (Chand & Dhamala, 2016a; Goulden et al., 2014; Sridharan et al., 2008; Uddin, 2017c). The anterior cingulate cortex (ACC) and insula (specifically the anterior) are two nodes of the
SN (Menon, 2015; Uddin, 2017a). Inactivation of the ACC reduced rodent anticipatory behaviour to rewarding stimuli and increased behaviour to irrelevant stimuli (J. Kim, Wasserman, Castro, & Freeman, 2016). As anticipatory behaviour was related to task choice, the authors argued the ACC is necessary to reduce the distraction from irrelevant stimuli and direct attention.

Atypical SN activation in schizophrenia contributes to aberrant salience. Reduced activation in the SN, including the insula, was found during prediction error at outcome (Gradin et al., 2011). Schmidt, Palaniyappan et al. (2016) found reduced right insula-ACC connectivity during reward prediction in unmedicated (but not medicated) first episode psychosis compared to unaffected individuals. The authors argued that the predictive strength of a salient stimulus triggers insula activation, which functions to identify whether additional processing (motor action or cessation, acquisition of knowledge) is required to update the predictive model. Their argument is supported by evidence of reduced activation in the insula and right precentral gyrus (motor region) during adaptive salience in first episode psychosis (Smieskova et al., 2015). Thus, attenuated activation in the SN may be a key factor in the difference between aberrant salience in unaffected individuals and individuals with schizophrenia.

4.3.5 The effect of antipsychotics on networks associated with aberrant salience

Antipsychotics decrease activation in the DMN and SN during the resting state. Wang et al. (2017) looked at the effect of antipsychotics on DMN and SN functional connectivity. Compared to unaffected individuals, unmedicated schizophrenia was associated with increased activation during resting-state in many DMN regions, including right posterior cingulate/precuneus, and increased functional connectivity in the left medial frontal gyrus, left precuneus, and left superior frontal gyrus. Increased activation was also found in most SN regions, with only the left superior temporal gyrus showing increased functional connectivity. The alterations in functional connectivity were associated with symptom scores. Activation in the right posterior cingulate inversely correlated with negative symptoms and positively with positive symptom such as delusions, hallucinations and reality distortions. Following 6-
8 weeks of treatment with antipsychotics, the abnormal pattern of functional connectivity in the DMN was no longer evident. Similarly, functional connectivity in regions of the SN decreased. The difference in right posterior cingulate/precuneus activation pre- and post-treatment negatively correlated with clinical global impressions score change. In other words, reduced symptoms were associated with reduced hyperactivation in DMN and SN. In conjunction with evidence suggesting these regions contribute to salience processing, these findings implicate the DMN and SN in aberrant salience.

4.3.6 Summary

The aberrant salience hypothesis is that positive symptoms of schizophrenia arise from the inappropriate attachment of motivational salience to functionally neutral stimuli and a maladaptive reduction in the motivational salience of reinforcers (Kapur, 2003). Schizophrenia is associated with atypical activation in the VS that: is linked to symptoms (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Nielsen et al., 2012; Papanastasiou et al., 2018; Wotruba et al., 2014); is associated with salience during reward processing (Ceaser & Barch, 2016; Esslinger et al., 2012; Nielsen et al., 2012); and contributes to aberrant salience (Ceaser & Barch, 2016; W P Horan et al., 2013). Whereas research into motivational and aberrant salience has focused on neural regions associated with reward processing, other neural networks are also implicated. The CEN, DMN, and SN play roles in salience processing. Sustained attention to irrelevant stimuli is indicated in LPP amplitudes (Andersen et al., 2016; W P Horan et al., 2013) and CEN activation (Anticevic et al., 2011). Atypical activation in the DMN in schizophrenia is associated with aberrant processing of salience, impaired task performance, and is indicated in first-degree relatives (Hanssen et al., 2015; Whitfield-Gabrieli et al., 2009). Furthermore, atypical DMN and CEN activation correlates with symptoms, with antipsychotics reducing both atypical activation and symptoms (Wang et al., 2017). The SN contributes to aberrant salience by failing to modulate activation in the DMN and CEN (Gradin et al., 2011; A. Schmidt, Palaniyappan, et al., 2016; Smieskova et al., 2015). Therefore, atypical activation in the SN in schizophrenia impacts on the CEN, resulting in
increased, sustained attention to irrelevant stimuli, and the DMN, resulting in aberrant consolidation of information.

4.4 Cognition and aberrant salience

So far, the discussion of aberrant salience has focussed on simple stimuli and basic neural mechanisms of association. However, a key component of the aberrant salience hypothesis is the cognitive explanation for the salience of irrelevant stimuli (Kapur, 2003). Two potential means by which aberrant salience may contribute to such cognitive explanations are discussed below. I then explore how impaired cognitive function (discontinuity) may contribute to aberrant salience leading to symptoms (self-disorders). Finally, I review evidence supporting the argument that extension of the mechanisms underlying aberrant salience provides an explanation within the aberrant salience hypothesis for the formation of negative symptoms.

4.4.1 Explaining irrelevant stimuli

Anselme and James (2015) argued that conscious explanations are used to rationalise thoughts, beliefs, and actions. In schizophrenia, neural mechanisms signal (Boehme et al., 2015; Ceaser & Barch, 2016; Esslinger et al., 2013) and maintain (Andersen et al., 2016; W P Horan et al., 2013) irrelevant stimuli as important. However, irrelevant stimuli have no predictive value. The failure of stimuli to predict the expected outcome results in a mismatch between expectation and outcome, expressed as a prediction error signalled by dopamine (Anselme & James, 2015). Deficits in updating information associated with schizophrenia (Gradin et al., 2011; Waltz et al., 2009) may contribute to a rigidity in beliefs about stimulus associations, leading patients to formulate cognitive explanations that facilitate the development of symptoms, such as delusions and hallucinations.

Unexpected outcomes that disconfirm beliefs trigger neural responses in regions associated with reward processing, salience, and cognition. Schwartenbeck, FitzGerald, and Dolan (2016) investigated neural regions associated with Bayesian surprise, the shift in belief about outcomes due to a difference between prior and subsequent beliefs. An example of Bayesian
surprise is the change in predictive value of a stimulus, that is always rewarded, after an unfavourable outcome. Bayesian surprise elicits a strong attentional response to the stimulus in question (Itti & Baldi, 2009). Schwartenbeck et al. (2016) found Bayesian surprise activated regions in the midbrain (VTA and substantia nigra pars compacta), inferior frontal cortex, posterior parietal cortex, and ACC. Thus, the shift in outcome impacted not only reward regions but also those associated with the highest levels of cognitive processing.

4.4.2 Aberrant salience and self-disorders

Mishara et al. (2016) argue that self-disorders—disruptions to a coherent, stable sense of self that are evident in schizophrenia—can also be explained within the aberrant salience framework. Reductions in temporal linking (continuity) can result in discarding information from past experiences, causing attribution of self-generated actions to external agents, and so dysfunction of cognitive explanations. Due to the discontinuity between perceived action and outcome, future such events are then unexpected, triggering a prediction error that further disrupts explanation. Reduced continuity may also lead to previously encountered novel events being subsequently assigned importance due to the occurrence of neural activation that indicates salience. The experienced aberrant salience then further contributes to self-disorders.

4.4.3 Aberrant salience and negative symptoms

The inclusion of self-referential and salience processing networks, which are disrupted during reward processing in schizophrenia and linked to aberrant salience, may offer a potential explanation for the negative symptoms of schizophrenia. Maeda, Takahata, Muramatsu, and Okimura (2013) found negative symptoms of schizophrenia were associated with a reduced sense of agency. However, paranoid schizophrenia was associated with increased sense of agency, even when the external event (tone) preceded action (button press). Dysregulated activation in the DMN is indicated during reward and salience processing and linked to symptoms. Attenuated resting-state activation in the DMN is associated with positive symptoms (Anticevic et al., 2015) whereas hyperactivation during positive symptoms is associated with negative symptoms (Mingoia et al., 2012). Activation in the DMN, due to failure of the SN, may
therefore play a key role in the expression of symptoms that arise from a common aberrant processing of salience.

### 4.4.4 Summary

Cognitive explanations are affected by, and affect, aberrant salience. Current mechanisms underlying aberrant salience focus on the influence of dopamine on motivational salience. Cognitive disruptions also contribute to aberrant salience leading to a disrupted sense of self. Inclusion of neural networks involved in self-referential processing and salience processing extends the aberrant salience hypothesis and may provide an explanation for the development of negative symptoms.

### 4.5 Conclusion

Schizophrenia is associated with reduced adaptive and increased aberrant salience. Specifically, increased motivated behaviour has been reported for irrelevant (Freeman et al., 2013; R. Morris et al., 2013) and neutral cues (Anticevic et al., 2011) and decreased motivated behaviour for relevant cues (Currie et al., 2017). Activation in a key reward-related region, the VS, also signals salience (Ceaser & Barch, 2016; Moessnang et al., 2012). In schizophrenia, VS activation is attenuated for reinforcer (gain or loss) salience (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Juckel, Schlagenhauf, Koslowski, Wüstenberg, et al., 2006; Nielsen et al., 2012; Radua et al., 2015; Schlagenhauf et al., 2009) and increased for irrelevant stimuli (Andersen et al., 2016), with irrelevant stimuli enhancing the salience of negative stimuli (WP Horan et al., 2013).

Kapur (2003) suggested that dysfunctional motivational salience mediates the aberrant assignment of importance to irrelevant stimuli. The proposed underlying mechanism is the effect of hyperdopaminergic activation in creating salience of irrelevant stimuli. Motivational salience is the level of desire to obtain or avoid a stimulus (Berridge, 2013; Le Pelley et al., 2014). Neurological, cognitive, and behavioural evidence suggests deficits in motivational salience, reward processing, and salience processing in schizophrenia (see Chapter 3, section 3.4). These deficits take the form of...
reduced adaptive salience and increased aberrant salience (Anticevic et al., 2011; Currie et al., 2017; Doll et al., 2014; Dowd et al., 2016; R. Morris et al., 2013). However, there is an inconsistent pattern of activation in the striatum, a key dopaminergic, reward-related region. Whereas atypical activation in the striatum predicts reduced adaptive salience in UHR (A. Schmidt, Antoniades, et al., 2016), FEP (Esslinger et al., 2012), and schizophrenia (Ceaser & Barch, 2016), there is no such relationship with aberrant salience. Indeed, the relationship between aberrant salience and enhanced striatal activation only appears evident in schizophrenia (Andersen et al., 2016; W P Horan et al., 2013). Thus, the effect of motivational salience, as a function of reward-related regions alone, cannot account for aberrant salience in schizophrenia.

Atypical activation in networks associated with salience and self-referential processing may better explain the development of aberrant salience. Activation in the CEN sustains aberrant salience, impairing filtering of irrelevant stimuli (Anticevic et al., 2011). Task-related activation in the DMN in schizophrenia increases aberrant and reduces adaptive salience (Anticevic et al., 2011; Moessnang et al., 2012). Central to both the DMN and CEN, is the SN, which is responsible for switching between the DMN and SN networks. Attenuated activation in the SN is associated with increased aberrant (A. Schmidt, Palaniyappan, et al., 2016) and decreased adaptive salience (Smieskova et al., 2015). The failure of the SN to deactivate the DMN results in a lack of continuity in self-agency, leading to erroneous explanations about the origin of action. The relationship between self-agency and action may provide an account for the negative symptoms of schizophrenia within the aberrant salience hypothesis (Maeda et al., 2013).

There is limited support for the idea that dysfunctional motivational salience mediates the development of aberrant salience. The current evidence is primarily based on dysregulated neural activation associated with atypical behavioural outcomes for the individual constructs. No available studies have directly investigated the relationship between measures of aberrant salience and motivational salience. Kapur’s (2003) hypothesis that motivational salience mediates aberrant salience, therefore, remains untested. Understanding the relationship between aberrant salience and motivational salience will inform
investigations into the neural mechanisms underlying aberrant salience. Anchoring of aberrant salience in neural systems may address some of the current limitations of the aberrant salience hypothesis. Furthermore, although specific measures of aberrant salience have been developed, they have not been compared. It is important to establish whether the construct of aberrant salience is common to measures and whether these constructs are unique to schizophrenia. Thus, whereas current findings appear to support the aberrant salience hypothesis, the current projects seek to ascertain whether indices of aberrant salience are measuring the same construct, are related to indices of motivational salience, and are unique to schizophrenia.
Chapter Five

The relationships among aberrant salience, reward motivation and reward sensitivity

5.1 Abstract

Change in reward processing and motivation may mediate the relationship between dopaminergic dysregulation and positive symptoms of schizophrenia. We sought to investigate the measurement of aberrant salience and its relationship with behavioural measures of reward and motivation. Participants \( (n = 82) \) completed measures of aberrant salience (Aberrant Salience Inventory, Salience Attribution Task), motivation (Effort Expenditure for Rewards Task), reinforcer sensitivity (Stimulus Chase Task). Hypotheses were tested using correlation and generalised linear modelling. Results indicated no relationship between aberrant salience measures. The ASI was positively related to effort expenditure for lower less likely rewards and predicted the use of probability alone in decision-making. The only significant relationship between reward and motivation was a positive relationship between gain sensitivity and motivated behaviour for higher more likely rewards. Although some support for a relationship between measures of reward motivation and aberrant salience was found, there was no evidence the aberrant salience measures had concurrent validity. Our results suggest caution is warranted when interpreting measures of aberrant salience.

5.2 Introduction

Dysregulation of the neurotransmitter dopamine has long been linked with the symptoms of schizophrenia. One prominent hypothesis on the role of dopamine in the development of symptoms is that of aberrant salience. According to Kapur (2003), dopaminergic dysregulation leads to the aberrant assignment of importance to, or salience of, external objects and internal representations, such as thoughts. In turn, many of the consequent epiphenomena, or subjective
experiences, require explanation in order to make sense of the world (Howes & Nour, 2016; Kapur, 2003). These experiences and concomitant explanations constitute the positive symptoms of psychosis. Although not fully understood, many regard the reward system and motivation as key mediators in the link between dopaminergic dysregulation and psychosis (Kapur, 2003).

Dopaminergic firing is associated with processing of reward-related stimuli (Bromberg-Martin et al., 2011; L. Zhang et al., 2009; Zweifel et al., 2009). It is critical in the evaluation of appetitive (Balconi & Crivelli, 2010; Jahn et al., 2014; McNaughton, 2004; Salamone et al., 2005, 1997; Wardle et al., 2011) and aversive (Matsumoto & Hikosaka, 2009) stimuli and is involved in the production of motivated behaviour, as seen in reward-based learning paradigms. For example, sensitivity to reward or punishment (or reinforcer sensitivity; Corr & McNaughton, 2012) has been shown to influence motivated behaviour (Cooper et al., 2014; Unger, Heintz, & Kray, 2012). Contextual factors have also been implicated in motivated behaviour: Motivated behaviour is influenced by the likelihood and magnitude of associated reward (Sambrook & Goslin, 2015; Schultz, 2010), whether gain or loss is immediate or delayed (Berridge, 2013; Smith et al., 2016), and how much effort is required for a reward (Bardgett, Depenbrock, Downs, Points, & Green, 2009; Salamone & Correa, 2002).

Schizophrenia is associated with anomalous reward-related behaviour and cognitive differences in reward processing, especially when tasks require adaptation to changing stimuli or value assessments. Differences include an impaired ability to adapt learning strategies based on changing contingencies (Waltz & Gold, 2007), greater sensitivity to loss (Scholten, van Honk, Aleman, & Kahn, 2006), and a preference for smaller, more immediate rewards over larger, delayed rewards (Heerey et al., 2007). Behavioural differences include reduced willingness to expend effort for reward (Green & Horan, 2015; Reddy et al., 2015), especially for larger, more likely rewards (Barch, Treadway, & Schoen, 2014; Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013), and an increased willingness to expend effort on low incentive outcomes (Fervaha, Graff-Guerrero, et al., 2013). The difference in behaviour across high and low
incentive scenarios may indicate impairments in effort-cost computation in schizophrenia (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013).

However, several limitations affect this literature. First, there is little if any research into if, or how, factors contributing to motivated behaviour relate to aberrant salience. Second, although some evidence has emerged consistent with the aberrant salience hypothesis of schizophrenia (Haralanova et al., 2012; J Jensen et al., 2008; Micoulaud-Franchi et al., 2012), findings are inconsistent. For example, although increased aberrant salience has been found in schizophrenia (Pankow, Katthagen, et al., 2015) and those at risk of psychosis (Cicero et al., 2010), other findings indicate no significant difference compared to unaffected individuals (Ceaser & Barch, 2016; Roiser et al., 2009). Third, there is a dearth of evidence that diverse measures of aberrant salience do, indeed, measure the same thing or relate to well-grounded measures of reinforcer sensitivity. Before discrepancies in schizophrenia research can be understood, it is important to ascertain the validity of aberrant salience measures in unaffected individuals. Therefore, our aim was to investigate the relationships among measures of aberrant salience, effort expenditure, and reinforcer sensitivity to better understand the construct validity of two prominent tests of aberrant salience: The Salience Attribution Test (SAT; Roiser et al., 2009) and the Aberrant Salience Inventory (ASI; Cicero et al., 2010).

The SAT is a computerised task that yields measures of implicit and explicit aberrant and adaptive salience. Implicit salience is inferred from response time differences across task conditions whereas explicit salience is based on awareness of predictors of reward. The ASI is a self-report measure of subjective experiences and beliefs attributed to aberrant salience. ASI scores correlate with psychotic experiences (Lelli et al., 2015). Patients with schizophrenia and those identified as at-risk of psychosis have higher ASI ratings than control participants (Cicero et al., 2010).

Performance on the SAT and ASI was compared with that on the Effort-Expenditure for Rewards Task (EEfRT; Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009) and the Stimulus Chase Task (SCT; Hall, Chong, McNaughton, & Corr, 2011). The EEfRT is a measure of decision-making under conditions of differential effort expenditure and differential outcome potentials.
Those with schizophrenia choose hard tasks less often than unaffected individuals (Green et al., 2015), especially when the value and likelihood of rewards are higher (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013; Reddy et al., 2015). However, when reward value and likelihood are low, patients choose hard tasks more often (Brown et al., 2013; Fervaha, Graff-Guerrero, et al., 2013).

The SCT is grounded in reinforcer sensitivity theory (Corr, 2001; Gray & McNaughton, 2000; McNaughton & Corr, 2004), which explains variations in goal directed behaviour in terms of the sensitivity of approach, avoidance, and conflict resolution systems (McNaughton & Corr, 2014). The SCT provides indices of sensitivity of the responder to gain and loss outcomes under different conditions of approach and avoidance (Hall et al., 2011). Previous research using SCT indicates individuals tend to exhibit loss aversion and a stronger approach than avoidance tendency (Hall et al., 2011).

We hypothesised that measures of aberrant salience would be positively correlated with each other, negatively related to effort in high-reward high-probability scenarios, and positively related to effort in low-reward low-probability scenarios. Given evidence of higher sensitivity to loss in schizophrenia (Scholten et al., 2006), it was hypothesised that aberrant salience would predict an increase in sensitivity to loss relative to sensitivity to gain. We also expected that effort expenditure would predict greater approach vs. avoidance tendencies under conditions of high reward likelihood and value but predict greater gain sensitivity under conditions of low reward likelihood and value.
5.3 Methods

5.3.1 Participants

Undergraduates ($n = 82$) in introductory courses on psychology volunteered as participants. For large effects in correlational analysis ($r = 0.50$) where $\alpha = 0.05$, a sample of 82 affords power of $> 0.99$. Participants were aged 17 to 57 years ($m = 20.0, SD = 5.7$) and most were female (68%). Most participants identified as New Zealand European (71%) with smaller numbers identifying as Māori (16%) or other ethnic identity (23%). Having completed participation, volunteers could earn a small amount of course credit based on assessment of learning about the study. Participants provided written informed consent. The study was approved by the University of Otago Human Ethics Committee (Health).

5.3.2 Measures

**Aberrant Salience Inventory (ASI)**

The ASI (Cicero et al., 2010) was used as an orally-administered self-report measure of aberrant salience. The ASI contains 29 questions, each requiring a yes or no response in reference to lifetime experiences. Respondents are directed to ignore experiences that occurred under the influence of drugs or alcohol. The ASI yields a single score calculated as number of yes responses. ASI shows high internal consistency ($\alpha = .89$; Cicero et al., 2010; Lelli et al., 2015) and test-retest reliability (.96 over 15 days; Lelli et al., 2015)

**Effort-Expenditure for Rewards Task (EEfRT)**

The EEfRT (Treadway et al., 2009) is a computerised performance task that uses decision-making as a measure of motivation. The EEfRT consists of a series of trials in which the respondent must choose between undertaking a hard and an easy task, each of which is associated with different reward values. At the start of each trial, participants are advised the probability of winning (12%, 50% or 88%) and the amount of reward for the decision alternatives. They are then to choose to complete either the easy or hard task. The easy task reward is set at $1 and requires participants to complete 30 button presses with the
dominant index finger within 7 seconds. The hard task reward varies between $1.24 and $4.30 and requires participants to complete 100 button presses with the non-dominant little finger. Feedback at the end of each trial advises whether money was available for that trial and how much won.

The task runs for 20 minutes so the number of trials undertaken depends on the proportion of hard- versus easy-task decisions. For each trial, the probability of reinforcement and the reward value for the hard task vary. Over the task, the probabilities of reinforcement are equalised, with each possible combination of probability and reward value occurring at least once. The dependent variable is task choice.

Factor analysis of data collected from 94 schizophrenia patients on five motivational effort paradigms, including the EEfRT, revealed a single factor explained 53% of observed variance. The correlation between the factor score and EEfRT reward magnitude was strong ($r = .66$; William P. Horan et al., 2015).

**Salience Attribution Test (SAT)**

The SAT (Roiser et al., 2009) is a computerised learning paradigm that uses stimulus reinforcement to assess implicit and explicit aberrant and adaptive salience. The task consists of two 64-trial blocks. In each trial, a fixation cross appears centre screen. Then, after 1000 ms, a line drawing of an object or animal appears in duplicate, centred above and below the fixation cross. A black box then replaces the fixation cross and participants are required to press a button as soon as the black box appears but before it disappears. After each trial, auditory and visual feedback indicate whether the trial was reinforced and the amount of money earned.

Participants are advised that reward is probabilistically related to the stimulus type whereas speed of response determines the amount of money that can be earned (between 10¢ and $1). Participants are assigned one of four possible contingencies that remain consistent throughout the task. The contingencies are whether the dimension of colour (red or blue) or shape (household object or animal) of the picture is relevant. For the task relevant dimension, one level (e.g. household object) has a high probability (87.5%) of being reinforced while the other (e.g. animal) has a low probability (12.5%). For
the task irrelevant dimension, both levels (e.g. blue and red) have a 50% probability of being reinforced. Participants are instructed to try and identify which dimension yields the highest probability of reward. After each trial-block, participants complete a VAS indicating how often (%) they believed each dimension was reinforced.

SAT output for each participant includes single measures for explicit and implicit adaptive salience and aberrant salience. Implicit salience is measured using response time (ms) while explicit salience is measured using a VAS rating (mm). Adaptive salience is calculated as the difference between mean response time (RT) for low (10%; e.g. household object) versus high (90%; e.g. animal) reinforcement probability trials while aberrant salience was calculated as the absolute difference in RT between the two task-irrelevant dimensions (e.g. blue and red; Roiser et al., 2009).

In unaffected individuals, the SAT shows good discriminant validity. Implicit aberrant salience was independent of learned irrelevance, reinforcement sensitivity, working memory and probabilistic learning (K. Schmidt & Roiser, 2009). Although explicit measures were related to operant learning, explicit aberrant salience was not associated with schizotypy (K. Schmidt & Roiser, 2009).

**Stimulus Chase Task (SCT)**

The SCT (Hall et al., 2011) is a computerised task that uses reinforcement to assess relative sensitivity to gain and loss and relative tendency to engage in approach and avoidance behaviour. In each of two phases of the task, participants start with a balance of $180 and are advised how much they can gain or lose at the start of each trial, with the probability of gain or loss fixed at 50%. The value of gain and loss is manipulated in increments of 2 between 8 and 0. For example, in Block 1 the gain and loss amounts are +$8, -$8, Block 2 +$8, -$6, Block 5 +$8, -$0, Block 11 +$6, -$8, and Block 12 +$8, -$8. Each block consists of 5 trials. With 50 blocks per phase, each incremental gain and loss value combinations are presented in two blocks (10 trials) in both phases. In Phase 1, participants must click on the blue box (approach behaviour) to take a chance on gaining or losing the stated values whereas choosing not to click
(avoid behaviour) will incur no change in balance. In Phase 2, avoidance behaviour (not clicking) instigates the chance of winning or losing whereas approach behaviour leads to no change in balance. Feedback is provided by a change in the colour of the blue box (to red for loss, green for gain, and grey for no change) and the balance, which is presented next to the box.

As with the SAT, the rationale underlying the SCT is that response time will vary with the value a respondent gives to a trial outcome (Hall et al., 2011). Behaviour on the SCT adheres to predictions based on the matching law (Hall et al., 2011). Therefore, the matching law is used to estimate gain:loss sensitivity and approach:avoidance tendency ratios, using modelling with the Microsoft® Excel Solver. Participants whose data does not conform to the matching law are excluded from further analysis.

5.3.3 Procedure

Having provided written informed consent, participants completed a demographics questionnaire and the ASI followed by the three computerised tasks (EEfRT, SAT, and SCT). Computer tasks were administered in counterbalanced order across participants. Following completion of all the tasks, participants were debriefed, paid the money they won ($4 = NZ$1), and thanked for their time.

5.3.4 Data Analysis

For each participant, EEfRT effort was calculated as the proportion of hard task choices by dividing the number of hard task choices by the total number of trials (Treadway et al., 2009; Treadway & Zald, 2013; Wardle et al., 2011). The number of hard choices for each probability level, each reward magnitude ($\leq$ $2$, $2$ to $3$, $\geq$ $3$), and each probability-magnitude combination was divided by number of corresponding trials. The estimated value was calculated by multiplying probability by reward magnitude to provide the proportion of small (< 1), medium ($\geq 1$ and < 2) and large ($\geq 2$) estimated values for hard task choices.

Mixed effects modelling was used to calculate group and individual beta coefficients for models of EEfRT decisions. Modelling included random intercepts and random slopes for reward magnitude, probability, and cross-
level reward magnitude × probability interactions. For each participant, beta coefficients for reward magnitude, probability, and their interaction were calculated then linear modelling was used to assess whether the effect of these variables on task choice during EEfRT was related to measures of ASI, SAT and SCT. As assumptions of normality were not met, Kendall’s tau was used for correlational analysis. Analysis was completed using the psych (Revelle, 2016) and lme4 (Bates, Maechler, Bolker, & Walker, 2015) packages in R (R Development Core Team, 2016) and Hmisc (Harrell Jr et al., 2016).

5.4 Results

Data from 3 participants were excluded from analyses because these participants demonstrated they did not understand task requirements. Data from another 4 participants were excluded because of equipment failures. Table 5.1 shows the descriptive statistics from the key measures.

SCT measures of interest were overall gain:loss and approach:avoidance ratios, where a gain:loss ratio over 1 indicates reduced loss sensitivity and an approach:avoidance ratio over 1 indicates an approach tendency.

There was no evidence that ASI scores correlated with SAT indices of adaptive or aberrant salience, whether measured implicitly or explicitly, or with gain:loss or approach:avoidance ratios from the SCT (Table 5.2). No significant correlations were found between SCT ratios and SAT indices (Table 5.2). On the SAT, greater implicit aberrant salience predicted greater implicit adaptive salience. The relationships among ASI and SAT indices remained unchanged when analyses were restricted to those reporting no mental health issues (n = 69).
### Table 5.1
Demographic variables for ASI, SAT, EEfRT and SCT indices

<table>
<thead>
<tr>
<th>Demographic</th>
<th>ASI, SAT, EEfRT (n = 82)</th>
<th>SCT (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56 (68)</td>
<td>36 (65)</td>
</tr>
<tr>
<td>Male</td>
<td>26 (32)</td>
<td>19 (35)</td>
</tr>
<tr>
<td><strong>Age in years m (SD)</strong></td>
<td>20 (5.71)</td>
<td>20 (5.29)</td>
</tr>
<tr>
<td><strong>Ethnicity n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>58 (71)</td>
<td>43 (78)</td>
</tr>
<tr>
<td>Maori</td>
<td>5 (6)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (23)</td>
<td>9 (16)</td>
</tr>
<tr>
<td><strong>Currently Employed n (%)</strong></td>
<td>12 (15)</td>
<td>10 (18)</td>
</tr>
<tr>
<td><strong>Household income n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 200k</td>
<td>8 (10)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>101-150</td>
<td>23 (28)</td>
<td>15 (27)</td>
</tr>
<tr>
<td>76-100k</td>
<td>20 (24)</td>
<td>15 (27)</td>
</tr>
<tr>
<td>51-75k</td>
<td>14 (17)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>26-50k</td>
<td>7 (9)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>&lt;25k</td>
<td>1 (1)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Mental Health Diagnosis n (%)</strong></td>
<td>12 (15)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (5)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>3 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Depression and Anxiety</td>
<td>2 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Eating Disorder</td>
<td>1 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Note: ASI = Aberrant Salience Inventory; SAT = Salience Attribution Test; EEfRT = Effort Expenditure for Reward Task; SCT = Stimulus Chase Task; Percent rounded to nearest whole number; Household income in NZ$
In the mixed effects modelling of EEfRT decisions, effort was predicted by the reward magnitude × probability interaction ($\beta = 1.89, z = 9.30, p < .001$; Figures 5.1 & 5.2) but not by reward magnitude ($\beta = 0.04, z = 0.30, p = .77$) or probability ($\beta = -1.15, z = -1.90, p = .06$).

Table 5.3 shows the correlation between measures of aberrant salience, effort, and SCT. There was a positive relationship between ASI ratings and effort at each level of the EEfRT variables except low probability. ASI positively correlated with effort for lower more likely rewards, higher less likely rewards and with all reward magnitudes when the likelihood of winning was 50%. There was a negative relationship between SAT implicit aberrant salience and effort for larger more likely rewards. There were no significant correlations between effort expenditure and explicit aberrant salience. Higher implicit adaptive salience correlated with less effort for higher rewards and both low and high rewards when likelihood of winning was high.

**Table 5.2**

Correlations (Kendall’s tau) among ASI, SAT, and SCT indices

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aberrant Salience Inventory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. SAT implicit aberrant salience</td>
<td>-.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. SAT explicit aberrant salience</td>
<td>-.06</td>
<td>.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. SAT implicit adaptive salience</td>
<td>-.06</td>
<td>.21</td>
<td>.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. SAT explicit adaptive salience</td>
<td>-.10</td>
<td>.08</td>
<td>-.15</td>
<td>-.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. SCT approach:avoidance ratio</td>
<td>-.01</td>
<td>.03</td>
<td>-.19</td>
<td>.03</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>7. SCT: gain:loss ratio</td>
<td>.02</td>
<td>.06</td>
<td>-.02</td>
<td>.06</td>
<td>.04</td>
<td>-.27</td>
</tr>
</tbody>
</table>

*Note:* ASI = Aberrant Salience Inventory; SAT = Salience Attribution Test; SCT = Stimulus Chase Task.

**p < .01**
Figure 5.1. Beta coefficient for reward magnitude on task choice during EEfRT by probability of winning. Error bars represent 95% confidence intervals.

Figure 5.2. Beta coefficient for probability of winning on task choice during EEfRT by reward magnitude. Shaded area represents 95% confidence intervals.
### Table 5.3

Correlation Coefficients (Kendall’s tau) for EEfRT with ASI, SAT and SCT indices.

<table>
<thead>
<tr>
<th>Measure</th>
<th>ASI</th>
<th>Implicit</th>
<th>Explicit</th>
<th>Implicit</th>
<th>Explicit</th>
<th>Approach</th>
<th>Gain:</th>
</tr>
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<tbody>
<tr>
<td>Hard choices</td>
<td>.28**</td>
<td>-.08</td>
<td>.05</td>
<td>-.11</td>
<td>-.19*</td>
<td>Avoid</td>
<td>.04</td>
</tr>
<tr>
<td>L Pr</td>
<td>.11</td>
<td>-.13</td>
<td>.14</td>
<td>-.04</td>
<td>-.23**</td>
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<td>.10</td>
</tr>
<tr>
<td>M Pr</td>
<td>.28**</td>
<td>.00</td>
<td>.04</td>
<td>-.03</td>
<td>-.09</td>
<td>.02</td>
<td>.21’</td>
</tr>
<tr>
<td>H Pr</td>
<td>.19*</td>
<td>-.13</td>
<td>.05</td>
<td>-.12</td>
<td>-.13</td>
<td>-.12</td>
<td>.09</td>
</tr>
<tr>
<td>L $</td>
<td>.18*</td>
<td>-.04</td>
<td>.05</td>
<td>-.17*</td>
<td>-.03</td>
<td>-.04</td>
<td></td>
</tr>
<tr>
<td>M $</td>
<td>.19*</td>
<td>-.02</td>
<td>.11</td>
<td>-.04</td>
<td>-.13</td>
<td>-.06</td>
<td>.12</td>
</tr>
<tr>
<td>H $</td>
<td>.27***</td>
<td>-.08</td>
<td>.06</td>
<td>-.17*</td>
<td>-.13</td>
<td>-.02</td>
<td>.15</td>
</tr>
<tr>
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<td>.07</td>
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<td>.01</td>
<td>-.01</td>
<td>-.13</td>
<td>-.04</td>
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<tr>
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<td>-.10</td>
<td>.11</td>
<td>-.03</td>
<td>-.15</td>
<td>-.07</td>
<td>.01</td>
</tr>
<tr>
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<td>.17*</td>
<td>-.11</td>
<td>.08</td>
<td>-.06</td>
<td>-.22**</td>
<td>-.04</td>
<td>.12</td>
</tr>
<tr>
<td>M Pr, L $</td>
<td>.18*</td>
<td>.06</td>
<td>.10</td>
<td>-.13</td>
<td>-.12</td>
<td>.07</td>
<td>.06</td>
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<tr>
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<td>.16*</td>
<td>.03</td>
<td>.04</td>
<td>-.07</td>
<td>-.04</td>
<td>.04</td>
<td>.19</td>
</tr>
<tr>
<td>M Pr, H $</td>
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<td>.01</td>
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<td>-.09</td>
<td>-.01</td>
<td>.25**</td>
</tr>
<tr>
<td>H Pr, L $</td>
<td>.17*</td>
<td>-.07</td>
<td>.01</td>
<td>-.16*</td>
<td>-.10</td>
<td>-.06</td>
<td>-.09</td>
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<tr>
<td>H Pr, M $</td>
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<td>-.09</td>
<td>.06</td>
<td>-.05</td>
<td>-.12</td>
<td>-.11</td>
<td>.15</td>
</tr>
<tr>
<td>H Pr, H $</td>
<td>.13</td>
<td>-.17*</td>
<td>.09</td>
<td>-.18*</td>
<td>-.07</td>
<td>-.17</td>
<td>.19</td>
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<tr>
<td>L EV</td>
<td>.15</td>
<td>-.07</td>
<td>.11</td>
<td>.04</td>
<td>-.24**</td>
<td>-.02</td>
<td>.09</td>
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<tr>
<td>M EV</td>
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<td>-.02</td>
<td>.04</td>
<td>-.06</td>
<td>-.14</td>
<td>-.02</td>
<td>.14</td>
</tr>
<tr>
<td>H EV</td>
<td>.13</td>
<td>-.10</td>
<td>.01</td>
<td>-.08</td>
<td>-.03</td>
<td>-.07</td>
<td>.14</td>
</tr>
</tbody>
</table>

**Note:** L = low; M = medium; H = high; Pr = probability; $ = reward magnitude; EV = expected value; ASI = Aberrant Salience Inventory Score. EEfRT tasks are based on proportion of hard task choices for three Pr levels (L = .12, M = .5, H = .88); for three levels of RM (< $2.00, $2.00 to $3.00, ≥ $3.00). EV = Pr × $.

*p < .05, **p < .01, ***p < .001
The effects of probability on task choice during the EEfRT were predicted by ASI ratings, \( R^2 = 0.05, F(1, 80) = 4.56, p = .04 \). Evidence that ASI ratings predicted the effects of reward magnitude, \( R^2 = 0.05, F(1, 80) = 3.77, p = .06 \), or the probability \( \times \) magnitude interaction, \( R^2 = 0.04, F(1, 80) = 2.10, p = .09 \), was marginal. In contrast, there was no evidence that EEfRT task parameters predicted SAT implicit aberrant salience: for reward magnitude, \( R^2 = 0.00, F(1, 80) = 0.34, p = .56 \); for probability, \( R^2 = 0.00, F(1, 80) = 0.29, p = .60 \); and for their interaction, \( R^2 = 0.00, F(1, 80) = 0.24, p = .63 \).

There was a positive relationship between SCT gain:loss ratio and EEfRT effort for high rewards with a 50% probability of winning (Table 5.3). When probability of winning was 50%, the relationship between gain:loss and effort for high reward magnitudes accounted for 49.9% of the variance, with 43.6% for medium reward and 24.2% for low reward. There was no evidence that linear EEfRT variable coefficients were significant predictors of gain:loss ratio.

5.5 Discussion

Contrary to our expectations, there was no evidence that measures of aberrant salience were correlated. Furthermore, measures of aberrant salience did not correlate with measures of reward sensitivity. Although aberrant salience correlated with EEfRT as hypothesised, ASI positively correlated with effort for small, improbable rewards while SAT implicit aberrant salience negatively correlated with willingness to exert effort for large, probable rewards. Effort was related to the SCT gain:loss ratio in the direction hypothesised but only for uncertain rather than low probability trials. Finally, there was no evidence of a relationship between effort and approach:avoidance behaviour.

The failure to find a relationship between the aberrant salience measures raises the question of validity of one or both measures. Previous research utilising the SAT has yielded inconsistent patterns of results in the sensitivity of explicit versus implicit aberrant salience to differentiate healthy participants from those on the schizophrenia spectrum (Pankow, Katthagen, et al., 2015; Roiser et al., 2013, 2009). Furthermore, evidence suggests this cannot simply be attributed to differences in cognitive ability (Katthagen et al., 2016). One issue with the SAT is the assumption that aberrant salience results in all
irrelevant stimuli becoming salient. Given the aberrant salience hypothesis suggests an errant pairing of dopaminergic firing and irrelevant stimuli, the inconsistent findings using SAT may indicate individual differences in the salience attributed to specific irrelevant stimuli. Similarly, the ASI may lack discriminant validity. The ASI measures a trait associated with schizophrenia, labelled aberrant salience. However, there is no evidence that the ASI measures a trait that is unique to schizophrenia. Furthermore, the ASI questions are open to interpretation and a high ASI score may, for example, reflect the openness personality trait.

The difference in the relationships of the EFfRT with the ASI and SAT further support that the two measures of aberrant salience are measuring either different constructs or different aspects of aberrant salience. Implicit aberrant and adaptive SAT measures were positively related and both associated with less effort for large, probable rewards. These findings suggest implicit SAT measures are measuring a similar construct (e.g., speed of response). The construct validity of SAT is further challenged by the lack of evidence supporting a relationship between EFfRT and explicit aberrant salience or predictive associations between the weighting of EFfRT variables during task choice and SAT measures.

In contrast, higher ASI scores were associated with aberrant decision making during the EFfRT that appears to be based on mental effort. For example, higher ASI was associated with hard task choice for high value low probability trials as well as high probability low value trials. The weight assigned to variables during EFfRT supports an association between ASI score and reduced mental effort. Overall, participants appeared to use combined reward magnitude and probability to determine task choice. However, participants with higher ASI scores were more likely to use probability alone in deciding task choice during the EFfRT. Task selection based on one of three probabilities arguably requires less mental effort than the evaluation of a combined probability and reward magnitude or even determining the subjective value of a continuous reward magnitude. The greater weight given to probability also explains the lack of evidence supporting the predicted negative relationship between ASI and hard task choices during high reward high
probability trials. These findings are interesting considering evidence from previous research suggesting an impaired cost-effort computation in schizophrenia (Fervaha, Foussias, et al., 2013) and, overall, indicate the ASI may be a more informative measure of aberrant salience than the SAT.

It is unclear whether the lack of evidence supporting a relationship between aberrant salience and loss sensitivity is due to the sample population or measures. However, evidence supported an association between reward sensitivity and reward motivation. Given that the SCT outcome probability is constant (50%) and the EEfRT does not include loss (deduction of reward) outcomes, the correlations between the gain:loss ratio and hard task choice during 50% probability EEfRT trials suggest an increased gain sensitivity rather than loss sensitivity. The results, therefore, indicate that higher gain sensitivity is related to increased willingness to expend effort for higher value rewards.

Although a healthy sample was required to ascertain baseline relationships between the measures, this is one of the key limitations of the study. The current evidence suggests no relationship between the measures of aberrant salience. One explanation for the null relationship is that the different constructs of aberrant salience, employed by the SAT and ASI, are associated with differences in sensitivity. Therefore, although the current study had adequate power, a case-control design may show a relationship between these measures that was masked by a restricted range of scores from the student sample. Interpretation of the results within the framework of an association between aberrant salience and schizophrenia should, therefore, be cautiously applied.

Future research should include additional measures of reward and motivation, such as probabilistic learning and learned irrelevance, and neurological measures, such as EEG. These additional measures would help to clarify the relationship between SAT indices and reward processing. Furthermore, explanations for inconsistent findings from the SAT focus primarily on medication and stage of symptom development (e.g. at risk, prodromal, or active). The inclusion of schizotypy measures would assist in understanding whether specific schizotypy factors or sub scales predict the relationship between the ASI and the SAT. In future research, the relationship
between measures should be assessed in individuals with active symptoms (schizophrenia). Finally, it is important to note that the current findings may have wider implications. Although the aberrant salience hypothesis has been applied to schizophrenia, reward processing is affected in other disorders and diseases, such as Parkinson’s disease and addictions. Thus, research is needed to ascertain whether the aberrant salience hypothesis is unique to schizophrenia.
Chapter Six
Aberrant salience and reward processing: A comparison of measures in schizophrenia and anxiety

6.1 Abstract

Aberrant salience may contribute to the development of schizophrenia symptoms via alterations in reward processing and motivation. However, tests of this hypothesis have yielded inconsistent results. These inconsistencies may reflect problems with the validity and specificity of measures of aberrant salience in schizophrenia. Therefore, we investigated relationships among measures of aberrant salience, reward, and motivation in schizophrenia and anxiety. Individuals with schizophrenia (n = 30), anxiety (n = 33), or unaffected by mental disorder (n = 30) completed measures of motivation (Effort Expenditure for Reward Task), reinforcer sensitivity (Stimulus Chase Task), and aberrant salience (Aberrant Salience Inventory [ASI] and Salience Attribution Test [SAT]). Schizophrenia participants scored higher than anxiety (d = .71) and unaffected (d = 1.54) groups on the ASI and exhibited greater aberrant salience (d = .60) and lower adaptive salience (d = .98) than anxious participants on the SAT. There was no evidence of a correlation between measures of aberrant salience. Schizophrenia was associated with related deficits in motivated behaviour and maladaptive reward processing. However, these differences in reward processing did not correlate with aberrant salience measures. The results suggest key measures of aberrant salience have limited specificity and validity. These problems may account for inconsistent findings reported in the literature.
6.2 Introduction

Aberrant salience is a prominent explanation for the development of psychosis symptoms. According to Kapur (2003), dysregulated dopaminergic firing results in the creation, or exaggeration, of the importance of external objects or events and internal thoughts or perceptions. Dopaminergic firing is associated with motivational salience, the cognitive process of directing attention and behaviour. In the absence of a relevant stimulus context, Kapur (2003) proposes dopaminergic firing leads to impairments in motivational salience and the assignment of importance to irrelevant stimuli. Kapur (2003) suggested delusions serve an explanatory function for patients, explaining the importance of aberrant stimuli, whereas hallucinations manifest from aberrant visual and auditory percepts.

There is some evidence for aberrant salience in schizophrenia, however results are inconsistent. Studies show increased emotional arousal (Haralanova et al., 2012) and neural activation (W P Horan et al., 2013) to neutral stimuli in schizophrenia—a pattern that is observed in unaffected individuals who are exposed to negative stimuli. Compared to unaffected individuals, those with schizophrenia rate environmental sounds as more invasive, and artificial abstract sounds as more familiar (Micoulaud-Franchi et al., 2012). Data from measures of aberrant salience, such as the ASI (Cicero et al., 2010) and SAT (Roiser et al., 2009), show heightened aberrant salience in schizophrenia compared to controls (Cicero et al., 2010; Katthagen et al., 2016; Pankow, Katthagen, et al., 2015). Additionally, aberrant salience is associated with abnormal beliefs (Roiser et al., 2013), perceptual aberration, and magical ideation (Cicero et al., 2013, 2010) in individuals with no history of psychosis, suggesting a link between aberrant salience and psychosis risk. Conversely, SAT data from other studies suggest salience is normal in schizophrenia (Abboud et al., 2016; Roiser et al., 2009).

Reasons for inconsistent findings vary. Aberrant salience may be more prominent during the prodromal phase than other illness phases (Roiser et al., 2013) or be attenuated by medication (Roiser et al., 2009). However, these accounts have not been replicated (Smieskova et al., 2015; Walter et al., 2016).
Alternatively, there is limited evidence of the validity of aberrant salience measures in schizophrenia. ASI scores correlate with psychotic-like experiences, such as magical ideation, in unaffected individuals and discriminate schizophrenia from other psychopathologies, such as bipolar disorder (Cicero et al., 2010). The SAT shows good construct validity in unaffected individuals (K. Schmidt & Roiser, 2009) and concurrent validity (Katthagen et al., 2016). However, more robust validity studies are needed, examining whether aberrant salience measures correlate with cognitive processes associated with dopamine function, such as motivational salience and reinforcer sensitivity.

Schizophrenia is associated with impairments in motivational salience, such as a reduced ability to unlearn previous associations (Waltz et al., 2007), aberrant reward-related behaviour (Barch et al., 2014; Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013; McCarthy, Treadway, Bennett, & Blanchard, 2016; Reddy et al., 2015; Strauss et al., 2011), and disrupted loss sensitivity (Currie et al., 2017; Scholten et al., 2006; Trémeau et al., 2008). Reduced activation of reward-related neural regions in schizophrenia is associated with reward receipt (Gradin et al., 2013; Schlagenhauf et al., 2009), impaired reward anticipation (Radua et al., 2015), and reward-seeking behaviour (Wolf et al., 2014).

Kapur (2003) proposed that motivational salience mediates aberrant salience. However, evidence of an association between motivational salience and measures of aberrant salience is limited. Ceaser and Barch (2016) found incorrect identification of a distractor stimulus as salient was associated with increased dorsal striatal activation in schizophrenia, with the degree of activation positively correlating with ASI score. Boehme et al. (2015) found high SAT implicit aberrant salience in unaffected individuals was associated with reduced ventral striatum activation during reward prediction error.

We previously reported finding no evidence that the ASI and SAT indices are correlated among undergraduates with no history of psychosis (Neumann & Linscott, 2018). At most, the ASI and SAT indices predicted aspects of willingness to expend effort under different task conditions. For example, higher ASI scores predicted greater willingness to expend effort for small, less
likely rewards, and the SAT behavioural measure of aberrant salience predicted less effort for large, more likely rewards. The primary finding, that the ASI and SAT were unrelated, may reflect: (a) the effects of range restriction in aberrant salience in unaffected individuals; or (b) a typical pattern of reinforcer sensitivity and motivation in unaffected individuals compared to that seen in individuals with schizophrenia.

Therefore, our aim was to investigate relationships among measures of aberrant salience, motivation, and reinforcer sensitivity in schizophrenia and anxiety groups. We elected to compare schizophrenia and anxiety because of evidence that anxiety results from the conflict of competing goals during reward processing (Corr & McNaughton, 2012; Gray & McNaughton, 2000). That is, although reward processing is associated with anxiety and psychosis, the sources of symptom development are thought to differ between these disorders. If aberrant salience is specific to schizophrenia, predicted relationships between measures should be evident in schizophrenia but not in anxious and unaffected individuals.

Participants with schizophrenia, anxiety, and unaffected individuals completed measures of motivational salience (Effort Expenditure for Rewards Task [EEfRT]; Treadway et al., 2009) and reinforcer sensitivity (Stimulus Chase Task [SCT]; Hall et al., 2011) along with the ASI and SAT. We predicted that the schizophrenia group would exhibit greater aberrant salience on the ASI and SAT than would unaffected or anxiety groups (Cicero et al., 2010; Katthagen et al., 2016; Pankow, Katthagen, et al., 2015). We expected greater variance of aberrant salience in schizophrenia, resulting in relationships between measures of aberrant salience that would not be present in the unaffected and anxiety groups. We also examined the relationship between measures of motivation and aberrant salience. We hypothesised that, in schizophrenia, aberrant salience would predict comparatively greater and lesser engagement in hard tasks when these were poorly and richly rewarded, respectively (Fervaha, Graff-Guerrero, et al., 2013). Finally, we predicted that relative sensitivity to gain and loss would correlate with aberrant salience indices (Currie et al., 2017; Scholten et al., 2006; Trémeau et al., 2008). We also explored whether relationships among measures were consistent across groups or specific to schizophrenia.
6.3 Methods

6.3.1 Participants

Patients (n = 34) with working diagnoses of schizophrenia, schizoaffective disorder, schizophreniform disorder, or first episode psychosis were recruited by referral from mental health clinicians. Patients with anxiety (n = 37) and individuals with no mental disorder (n = 31) were recruited using posters in hospital staff areas and an online advertisement in a local newspaper. Inclusion criteria for the anxiety group were meeting diagnostic criteria for an anxiety disorder and reporting no prior or current psychotic symptoms. The inclusion criterion for the unaffected group was the absence of current or past experience of mental health issues. All participants were aged 18 to 65 years and indicated no history of neurological injury or disease. For the large effects (f2 = 0.35) expected between measures of the same construct, where α = 0.05, a sample of 30 per group affords a power of ~0.84. For large effects (r = 0.5) between measures within groups, where α = 0.05, a sample of 30 affords a power of ~0.83.

In the clinical groups, the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 2010) was used, in conjunction with other measures and clinical evidence, to confirm the current working diagnosis and shed light on symptom expression. The schizophrenia group included one participant who met criteria for schizoaffective disorder; and two who did not meet the MINI diagnostic criteria for schizophrenia but were retained on the basis of working diagnosis. Five referrals to the schizophrenia group were excluded: one who stated he had faked symptoms of psychosis; two who met criteria for mood disorder with psychotic symptoms; one with current (< 3 months) alcohol dependency; and one who was unable to complete the assessment. All anxiety participants met the MINI diagnostic criteria for an anxiety disorder. However, two were reassigned to the schizophrenia group as they met the MINI diagnostic criteria for schizophrenia and two others were excluded because of age or current alcohol dependence. One unaffected individual was excluded due to prior diagnosis of mental health issues. Table 6.1 shows demographics characteristics of participants included in final analysis. Table 6.2 shows MINI
output and current positive symptom summary for schizophrenia and anxiety participants.

The study was approved by the University of Otago Human Ethics Committee (H16/026). All participants provided written informed consent. Participants were offered payment of $25 per appointment.

Table 6.1
Demographics for unaffected, anxiety, and schizophrenia groups.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Unaffected (n = 30)</th>
<th>Anxiety (n = 33)</th>
<th>Schizophrenia (n = 30)</th>
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</thead>
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<tr>
<td>Female n (%)</td>
<td>19 (63)</td>
<td>25 (76)</td>
<td>6 (20)</td>
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<td>Age in years M (SD)</td>
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<td>35 (02)</td>
<td>44 (11)</td>
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<td>Ethnicity n (%)</td>
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<td></td>
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<tr>
<td>NZ European</td>
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<td>26 (79)</td>
<td>21 (70)</td>
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<tr>
<td>Maori</td>
<td>1 (3)</td>
<td>3 (9)</td>
<td>4 (13)</td>
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<tr>
<td>Other</td>
<td>9 (30)</td>
<td>4 (12)</td>
<td>5 (16)</td>
</tr>
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<td>Currently employed n (%)</td>
<td>22 (73)</td>
<td>20 (61)</td>
<td>6 (20)</td>
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<td>Household income n (%)</td>
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<tr>
<td>&gt; 200k</td>
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<tr>
<td>151-200</td>
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<td>-</td>
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<td>76-100k</td>
<td>4 (13)</td>
<td>4 (12)</td>
<td>1 (4)</td>
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<td>26-50k</td>
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<td>7 (21)</td>
<td>1 (4)</td>
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<tr>
<td>&lt;25k</td>
<td>8 (27)</td>
<td>11 (33)</td>
<td>21 (84)</td>
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<td>First degree relative mental health diagnosis n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Schizophrenia spectrum</td>
<td>-</td>
<td>1 (3)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>2 (7)</td>
<td>8 (24)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (10)</td>
<td>4 (12)</td>
<td>3 (10)</td>
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Table 6.2
MINI diagnosis and symptom summary for anxiety and schizophrenia groups.

<table>
<thead>
<tr>
<th>Diagnosis/Symptoms</th>
<th>Anxiety (n = 33)</th>
<th>Schizophrenia (n = 30)</th>
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<tbody>
<tr>
<td><strong>Primary Diagnosis n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic Disorder</td>
<td>-</td>
<td>28 (93)</td>
</tr>
<tr>
<td>Mood Disorder with Psychotic features</td>
<td>-</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Positive Symptoms</td>
<td>-</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Delusions</td>
<td>-</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Auditory Hallucinations</td>
<td>-</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Visual Hallucinations</td>
<td>-</td>
<td>6 (20)</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>33 (100)</td>
<td>-</td>
</tr>
<tr>
<td>General Anxiety Disorder</td>
<td>17 (51.5)</td>
<td>-</td>
</tr>
<tr>
<td>Social Phobia/Disorder</td>
<td>5 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>3 (9)</td>
<td>-</td>
</tr>
<tr>
<td>Non-Anxiety Primary Disorder</td>
<td>7 (21)</td>
<td>-</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>1 (3)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Secondary Diagnosis (current) n</strong></td>
<td></td>
<td></td>
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<tr>
<td>General Anxiety Disorder</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Social Phobia/Disorder</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>PTSD</td>
<td>1</td>
<td>-</td>
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<tr>
<td>Major Depressive Disorder</td>
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<td>1</td>
</tr>
<tr>
<td>Bipolar Disorder I</td>
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<td>2</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
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<td>4</td>
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<tr>
<td><strong>Secondary Diagnosis (past/recurrent) n</strong></td>
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<td></td>
</tr>
<tr>
<td>Major Depressive Disorder (recurrent)</td>
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<td>4</td>
</tr>
<tr>
<td>Major Depressive Disorder (past)</td>
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<td>2</td>
</tr>
<tr>
<td>Bipolar Disorder I</td>
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<td>3</td>
</tr>
<tr>
<td>Bipolar Disorder II</td>
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<td>-</td>
</tr>
<tr>
<td>Manic/hypomanic episode</td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>

*Note.* MINI = Mini-International Neuropsychiatric Interview.
6.3.2 Measures

The Alcohol and Drug Abuse and Dependence Screen (ADDS; Muthén, 1995) was used to screen for problematic substance use. The ADDS contains items that address quantity and impact of consumption of drugs and alcohol. Outcome scores range from 0 (no use) to 240 (severe dependency).

The Depression Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1995) were used to quantify mood and anxiety symptoms. The DASS contains 42 self-report items that respondents rate from $0 = \text{did not apply at all}$ to $3 = \text{applied most of the time}$, with 14 items relating to each of depression, anxiety, and stress.

Nine items comprising the Anxiousness facet of the Personality Inventory for DSM-5 (PID-5A; American Psychiatric Association, 2013b) were used to assess anxious temperament. Respondents rate items from $0 = \text{very false or often false}$ to $3 = \text{very true or often true}$.

The DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure (L1SM; American Psychiatric Association, 2013a) was used to screen for current mental health issues. The L1SM is a 23-item screen for key features of depression, anger, mania, anxiety, somatic symptoms, suicidal ideation, psychosis, sleep problems, memory impairment, repetitive thoughts and behaviours, dissociation, personality functioning, and substance use experienced in the past two weeks. Respondents rate items from $0 = \text{none / not at all}$ to $4 = \text{severe / nearly every day}$.

The MINI (Sheehan et al., 2010) was used to evaluate current and past diagnoses. The MINI is a semi-structured brief interview covering DSM-5 and ICD-10 Axis I psychiatric disorders.

The ASI and SAT were used as measures of aberrant salience, the EEfRT as a measure of decision making, and the SCT to assess relative sensitivities to gain and loss and relative tendencies for approach and avoidance. These measures are described in Chapter 5.

6.3.3 Procedure

Clinical group participants attended two ~90-min sessions. In the first, participants completed a demographics questionnaire and the ASI, SAT, EEfRT,
and SCT. Performance task order was counterbalanced across participants. During the second session, conducted within a week of the first, participants completed the AADS, DASS, PID-5A, L1SM, and MINI. Unaffected participants attended one 2-hr session during which they completed all measures except the MINI.

6.3.4 Data Analysis

Planned comparisons and ANOVA with Games-Howell post hoc analysis were used to test group differences in measures. Pearson’s correlation coefficient (2-tailed unless otherwise stated), with Holm adjusted significance level, was used to assess relationships among measures within each group. Holm correction for multiple comparisons was carried out on each within-group measure pair. For planned comparisons, ANOVA, and correlations, bias-corrected and accelerated bootstrapped confidence intervals (95%, 10 000 samples) were computed using SPSS version 25 (IBM Corp, 2017). SCT ratios were log-transformed for analysis. Holm’s correction was applied to families of hypotheses using R psycho package (Makowski, 2018).

EEfRT trials were categorised by probability (12%, 50%, 88%) and reward (low < $2, medium $2 to $2.99, high ≥ $3), yielding 9 trial types, and the proportion of hard task choices (effort) was obtained for each trial type. Mixed-effects modelling was used to calculate the effects of probability, reward, and reward × probability on task choice. Models included random slopes and intercepts. Mixed-effects analyses were conducted using R (R Development Core Team, 2016) with the Hmisc (Harrell et al., 2016), lme4 (Bates et al., 2015), and psych (Revelle, 2016) packages.

6.4 Results

One outlier in the schizophrenia group singularly skewed results, creating a correlation between ASI and SAT aberrant salience. Data from this outlier were excluded. SCT data from n = 41 participants did not fit the matching law. There was no difference between SCT fit and non-fit group means for other indices (all p > .10) and non-fitting behaviour was not associated with group, $\chi^2(2) = 5.63$, p = .06. SCT data were analysed for: schizophrenia, n = 12; anxiety, n = 23; and
unaffected, \( n = 17 \). The mean number of trials completed during the EEfRT was: schizophrenia, \( m = 65 \); anxiety, \( m = 68 \); and unaffected, \( m = 67 \).

### 6.4.1 Group differences

Compared to anxiety, schizophrenia was associated with higher ASI and SAT implicit aberrant salience scores and lower explicit adaptive salience scores (Table 6.3 and Appendix A, Figure A1). The schizophrenia group also had higher ASI scores and lower explicit adaptive salience scores than the unaffected group. The anxiety group had higher on ASI scores than the unaffected group.

Both SCT ratios differed across groups (Figure 6.1(b)). Ratios over 1 indicate greater sensitivity to gain than loss and greater tendency to approach than avoid, respectively. Compared to the unaffected group, schizophrenia was associated with a higher approach-avoidance ratio.

During the EEfRT task, the schizophrenia group chose the hard task more often with lower less likely rewards; and less often for higher, more certain rewards and for medium and high combinations of probability and reward (Figure 1(e)). There was also an effect of group, with the schizophrenia group selecting the hard task less often than the unaffected and anxiety groups. The effects of reward and reward × probability were also significantly decreased in the schizophrenia group compared to the unaffected and anxiety groups (Table 6.4). There were no main effects of probability.

The number of males and females differed across groups, \( \chi^2(2) = 21.29, p < .001 \). Additionally, the mean age of the psychosis group (\( M = 43.5, SE = 2.06 \)) was higher than the unaffected (\( M = 32.10, SE = 1.83 \)), \( t(58) = -4.14, p < .001, r = .47 \), and anxiety (\( M = 34.82, SE = 1.83 \)) groups, \( t(59.37) = -3.16, p = .003, r = .37 \). Multiple regression with bootstrapped confidence intervals (95%, 10 000 samples) were computed to investigate the effect of age and sex covariates on group differences. Controlling for age and sex did not make any substantive difference except that there was no longer any evidence of a schizophrenia group difference on low-probability low-reward EEfRT scores (\( \beta = 0.07, 95\% CI -.02, 0.16 \)).
**Figure 6.1.** Mean group scores showing significant differences in planned comparisons for (a) Aberrant Salience Inventory (b) Stimulus Chase Task gain-loss and approach-avoidance ratios, (c) SAT Attribution Test implicit and explicit aberrant salience, and (d) Salience Attribution Test implicit and explicit adaptive salience; and ANOVA and post hoc differences for significant group differences in (e) reward × probability combinations of the Effort Expenditure for Reward Task. Error bars show standard error of the mean.
### Table 6.3

Means and their bootstrapped (BCa) 95% confidence intervals (CI) for the ASI, SAT, SCT and EEfRT.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Unaffected</th>
<th>Anxiety</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$n = 30$</td>
<td>$n = 33$</td>
<td>$n = 30$</td>
</tr>
<tr>
<td></td>
<td>9.5 (7.34, 11.73)</td>
<td>13.6 (11.10, 15.89)</td>
<td>17.7 (16.11, 19.12)</td>
</tr>
<tr>
<td><strong>SAT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implicit AS</td>
<td>$n = 30$</td>
<td>$n = 33$</td>
<td>$n = 30$</td>
</tr>
<tr>
<td></td>
<td>17.3 (13.32, 21.84)</td>
<td>14.5 (11.24, 18.16)</td>
<td>24.0 (17.80, 30.72)</td>
</tr>
<tr>
<td>Explicit AS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.8 (5.20, 11.25)</td>
<td>10.2 (7.42, 13.33)</td>
<td>8.8 (5.63, 12.33)</td>
</tr>
<tr>
<td>Implicit AdS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.2 (3.58, 14.63)</td>
<td>10.1 (3.97, 16.33)</td>
<td>1.5 (-5.78, 8.76)</td>
</tr>
<tr>
<td>Explicit AdS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40.3 (30.26, 50.58)</td>
<td>39.2 (28.15, 49.84)</td>
<td>12.8 (5.73, 20.75)</td>
</tr>
<tr>
<td><strong>SCT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$n = 17$</td>
<td>$n = 23$</td>
<td>$n = 12$</td>
</tr>
<tr>
<td>A:A ratio</td>
<td>.50 (.45, .55)</td>
<td>.54 (.50, .58)</td>
<td>.65 (.58, .73)</td>
</tr>
<tr>
<td>G:L ratio</td>
<td>-.34 (-.45, -.25)</td>
<td>-.34 (-.41, -.27)</td>
<td>-.53 (-.70, -.38)</td>
</tr>
<tr>
<td><strong>EEfRT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$n = 30$</td>
<td>$n = 33$</td>
<td>$n = 30$</td>
</tr>
<tr>
<td>Hard Choices</td>
<td>.42 (.37, .47)</td>
<td>.38 (.34, .43)</td>
<td>.26 (20.33)</td>
</tr>
<tr>
<td>L Pr</td>
<td>.18 (.12, .25)</td>
<td>.13 (.10, .18)</td>
<td>.21 (15.28)</td>
</tr>
<tr>
<td>M Pr</td>
<td>.43 (.37, .49)</td>
<td>.35 (.28, .42)</td>
<td>.24 (18.31)</td>
</tr>
<tr>
<td>H Pr</td>
<td>.63 (.56, .70)</td>
<td>.66 (.58, .73)</td>
<td>.33 (24.42)</td>
</tr>
<tr>
<td>L $</td>
<td>.14 (.09, .19)</td>
<td>.17 (.12, .22)</td>
<td>.18 (11.26)</td>
</tr>
<tr>
<td>M $</td>
<td>.36 (.30, .42)</td>
<td>.34 (.29, .40)</td>
<td>.24 (18.31)</td>
</tr>
<tr>
<td>H $</td>
<td>.59 (.53, .66)</td>
<td>.53 (.47, .60)</td>
<td>.31 (24.38)</td>
</tr>
<tr>
<td>L Pr L $</td>
<td>.06 (.02, .10)</td>
<td>.07 (.02, .13)</td>
<td>.19 (11.29)</td>
</tr>
<tr>
<td>L Pr M $</td>
<td>.19 (.12, .27)</td>
<td>.13 (.09, .18)</td>
<td>.20 (14.27)</td>
</tr>
<tr>
<td>L Pr H $</td>
<td>.25 (.17, .35)</td>
<td>.18 (.12, .25)</td>
<td>.23 (15.31)</td>
</tr>
<tr>
<td>M Pr L $</td>
<td>.13 (.07, .20)</td>
<td>.12 (.08, .16)</td>
<td>.12 (06.18)</td>
</tr>
<tr>
<td>M Pr M $</td>
<td>.38 (.29, .48)</td>
<td>.34 (.24, .45)</td>
<td>.26 (17.34)</td>
</tr>
<tr>
<td>M Pr H $</td>
<td>.66 (.57, .74)</td>
<td>.50 (.40, .61)</td>
<td>.32 (24.41)</td>
</tr>
<tr>
<td>H Pr L $</td>
<td>.24 (.16, .33)</td>
<td>.31 (.22, .42)</td>
<td>.24 (14.36)</td>
</tr>
<tr>
<td>H Pr M $</td>
<td>.60 (.48, .73)</td>
<td>.65 (.54, .76)</td>
<td>.30 (20.41)</td>
</tr>
<tr>
<td>H Pr H $</td>
<td>.86 (.78, .93)</td>
<td>.86 (.77, .93)</td>
<td>.39 (30.49)</td>
</tr>
</tbody>
</table>

**Note.** ASI = Aberrant Salience Inventory; SAT = Salience Attribution Test; SCT = Stimulus Chase Task; EEfRT = Effort Expenditure for Reward Task; AS = aberrant salience; AdS = adaptive salience; A:A = approach-avoid; G:L = gain-loss; L = low; M = medium; H = high; Pr = probability; $ = reward.
Table 6.4
Effect of reward, probability, and reward × probability on task choice.\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-4.62\textsuperscript{***}</td>
<td>0.67</td>
<td>-5.92</td>
<td>-3.31</td>
</tr>
<tr>
<td>Reward</td>
<td>0.77\textsuperscript{***}</td>
<td>0.19</td>
<td>0.39</td>
<td>1.14</td>
</tr>
<tr>
<td>Probability</td>
<td>0.21</td>
<td>0.88</td>
<td>-1.51</td>
<td>1.93</td>
</tr>
<tr>
<td>Anxiety Group</td>
<td>0.81</td>
<td>0.90</td>
<td>-0.95</td>
<td>2.57</td>
</tr>
<tr>
<td>Schizophrenia Group</td>
<td>2.42\textsuperscript{**}</td>
<td>0.88</td>
<td>0.70</td>
<td>4.15</td>
</tr>
<tr>
<td>Reward × Probability</td>
<td>1.30\textsuperscript{***}</td>
<td>0.27</td>
<td>0.77</td>
<td>1.81</td>
</tr>
<tr>
<td>Reward × Anxiety Group</td>
<td>-0.48</td>
<td>0.27</td>
<td>-1.00</td>
<td>0.04</td>
</tr>
<tr>
<td>Reward × Schizophrenia Group</td>
<td>-0.63\textsuperscript{*}</td>
<td>0.26</td>
<td>-1.13</td>
<td>-0.13</td>
</tr>
<tr>
<td>Probability × Anxiety Group</td>
<td>0.12</td>
<td>1.19</td>
<td>-2.20</td>
<td>2.45</td>
</tr>
<tr>
<td>Probability × Schizophrenia Group</td>
<td>-0.73</td>
<td>1.15</td>
<td>-3.00</td>
<td>1.53</td>
</tr>
<tr>
<td>Reward × Probability × Anxiety</td>
<td>0.23</td>
<td>0.36</td>
<td>-0.49</td>
<td>0.94</td>
</tr>
<tr>
<td>Reward × Probability × Schizophrenia</td>
<td>-0.78\textsuperscript{*}</td>
<td>0.34</td>
<td>-1.45</td>
<td>-0.11</td>
</tr>
</tbody>
</table>

\textit{Note.} \textsuperscript{a} Unaffected individuals and hard task choice are baseline
\textsuperscript{*} \textit{p} < .05, \textsuperscript{**} \textit{p} < .01, \textsuperscript{***} \textit{p} < .001.

6.4.2 Within-group correlations

There was no evidence that the ASI correlated with any other measure in the schizophrenia group. SAT implicit and explicit adaptive salience positively correlated, however correlations between SAT, EEFRT and SCT indices did not survive the Holm correction (Appendix A, Table A1). Similarly, none of the correlations between measures in the anxiety group survived the Holm correction (Appendix A, Table A2). In the unaffected group, ASI and explicit aberrant salience predicted relatively lower gain:loss sensitivity (Appendix A, Table A3). No other correlations survived Holm correction.

6.5 Discussion

There was partial support for the idea that, compared to anxiety, schizophrenia is associated with greater expressed aberrant salience. Schizophrenia was
associated with higher ASI and higher SAT implicit aberrant salience scores. However, contrary to our hypotheses, the ASI and SAT aberrant salience indices were negatively correlated, albeit not significantly. We found no evidence for a relationship between aberrant salience indices and reinforcer sensitivity in schizophrenia and correlations between aberrant salience and motivational salience did not survive corrections for multiple testing. Support for the construct validity of aberrant salience indices against reward processing measures was also limited in unaffected and anxiety groups.

The results have several implications for the interpretation of ASI and SAT data. First, they cast doubt on the validity of the ASI and, to a lesser extent, the SAT. The intermediate rating of the anxiety group suggests the ASI measures a trait that is not unique to schizophrenia. Furthermore, the failure to find a relationship between the ASI and EEfRT indicates that the construct measured with the ASI is not related to motivational salience. There was no evidence that implicit aberrant salience predicted effortful decision-making in the schizophrenia group. These findings rest in stark contrast to what would be expected given even modest construct validity and specificity. The lack of relationship could be due to construct validity issues with the EEfRT. However, this is unlikely given the current data from the EEfRT are in line with a body of literature suggesting maladaptive behaviour in schizophrenia in contrast to the adaptive behaviour found in unaffected individuals (Barch et al., 2014; Fervaha, Graff-Guerrero, et al., 2013; McCarthy et al., 2016; Strauss, Waltz, & Gold, 2014).

This notwithstanding, the schizophrenia group did exhibit a pattern of inefficient, maladaptive behaviour not seen in the anxiety or unaffected groups. Schizophrenia was associated with lower adaptive but higher aberrant reinforcement learning. During the EEfRT, the schizophrenia group exhibited less adaptive behaviour, pursuing the hard task when it was less likely to yield higher rewards but not when higher more likely rewards were available. Impaired cost and effort computations in schizophrenia have previously been linked to impairments in working memory, value representations, and cost calculations (Strauss et al., 2014). The current findings indicate reduced cognitive effort during cost and effort computations in schizophrenia. Specifically, stimuli that required greater cognitive effort (e.g., determining
reward value from a scale and calculating the reward by probability interaction) had less effect on task choice in the schizophrenia compared to other groups. These findings are in line with evidence suggesting reduced activation in the striatum, a region associated with acquired salience (Esslinger et al., 2013), contributes to impaired reward processing (Gradin et al., 2013; Radua et al., 2015; Roiser et al., 2010; Schlagenhauf et al., 2009) and effortful behaviour (Wolf et al., 2014) in schizophrenia.

Several alternative explanations may account for these findings. First, aberrant salience may be more evident in the prodromal phase but dampened in subsequent illness phases due to medication or symptom development (Abboud et al., 2016). If that were the case, the relationship between aberrant salience and motivational salience may also reduce. Secondly, it may be that the schizophrenia participants here exhibited intact reinforcement learning and motivational salience. However, in line with previous findings (Fervaha, Graff-Guerrero, et al., 2013), the schizophrenia group exhibited aberrant effortful behaviour.

The findings should be considered in light of several limitations. First, given we examined aberrant salience indices obtained using different measurement methods, our expectation of obtaining large effects may have been unreasonable or a larger sample should have been used. However, we are confident our expectations were reasonable and our key interpretation is safe for several reasons. The SAT implicit and explicit measures, which involve performance and global judgement methodologies (respectively), did show some evidence of significant within-group relationships; despite common methods for the SAT explicit and ASI measures, the magnitude of observed relationships were no greater than those for the SAT implicit measures; and the SAT implicit aberrant salience measure was negatively related to ASI ratings, albeit not significantly.

We did not record information on current medication for schizophrenia or anxiety group participants. A large proportion of the current schizophrenia group, however, reported current psychotic symptoms. Antipsychotic medication is not universally effective (e.g. Gotfredsen et al., 2017) and, among those for whom it is effective, is often not completely effective. However, future
research should examine the effect of antipsychotics. All but one participant in the schizophrenia group were receiving treatment within a health care system at the time of participation whereas the anxiety group were not recruited via health services and many had not sought formal treatment. Furthermore, although unaffected participants underwent screening for current mental health experiences, there may have been undiagnosed or unreported mental health issues. However, participants were asked about past mental health in the demographics questionnaire and excluded if one recorded.

The implications of data loss due to chaotic behaviour, resulting in exclusion from SCT analysis, are also worth considering. Higher than expected exclusion rates may be explained if limited to individuals with schizophrenia, where impairments in reward processing and motivational salience may result in chaotic behaviour (e.g. Currie et al., 2017; Gold et al., 2013; Reddy et al., 2015; Strauss et al., 2011). However, all groups had much higher SCT exclusion rates, suggesting modifications to the way the SCT is calculated is needed to include non-fitting behaviour. Finally, the groups were not well matched on age and sex. Although there was little evidence that the pattern of effects seen in the schizophrenia group was attributable to sex or age, matching would allow more accurate analysis of the effect.

The current findings suggest a variance in construct definition among measures of aberrant salience and challenge the construct validity of the measures. Caution should be applied when interpreting findings from measures of aberrant salience. Further research is needed to understand whether the relationships among measures are dependent on stage of psychosis, medication, or common comorbidities such as anxiety.
Chapter Seven
Discussion

The current research project investigated the validity and specificity of measures of aberrant salience. Across two studies, I examined whether measures of aberrant salience: correlated with each other; were related to measures of motivational salience; and measured a construct unique to schizophrenia.

I found increased aberrant salience and reduced adaptive behaviour in schizophrenia compared to other psychopathologies, namely anxiety disorders, as well as unaffected individuals. This extends previous research (Chapters 2 and 3). The schizophrenia group had higher ASI scores than both control groups and higher SAT implicit aberrant salience scores than the anxiety group. Reduced adaptive behaviour in schizophrenia was evident in lower SAT explicit adaptive salience scores and inefficient choices made during the EEFRT. The SCT data revealed a shift in relative approach:avoidance tendencies in schizophrenia, with an increased tendency to approach or a decreased tendency to avoid, but no difference in sensitivity to loss or gain compared to the other groups. The data for the anxiety and unaffected groups were comparable for all indices except the ASI, where elevated scores were also found in anxiety.

Conversely, across the groups, there was no evidence of convergent validity between aberrant salience measures. There was also very little evidence to support an association between aberrant salience and motivational salience. Indeed, the minimal evidence of relationships among measures in undergraduates was absent in schizophrenia.

Below, I highlight key similarities and differences in the findings from the current study compared to the literature, looking first at the individual measures and then their interactions. I suggest implications of the current findings. Finally, I highlight limitations and identify key research questions facing the field.
7.1 Aberrant and adaptive salience in schizophrenia

The current findings suggest individuals with schizophrenia experience aberrant salience. However, aberrant salience was also present in unaffected and anxious individuals. The sensitivity and specificity of the ASI and SAT differed. There was also a pattern of maladaptive motivated behaviour in schizophrenia but not unaffected and anxious individuals.

7.1.1 The ASI

The ASI is used to measure an individual’s subjective experience of aberrant salience. This is based on yes/no responses to 29 questions designed to ascertain each of the five common experiences Cicero et al. (2010) thought reflected aberrant salience: attention to previously irrelevant stimuli, heightened perception, sense of understanding, enhanced emotionality, and heightened cognition.

Higher ASI scores are not unique to schizophrenia. Individuals considered at risk of developing schizophrenia (i.e. high schizotypy scores) and individuals with schizophrenia or schizoaffective disorder (Cicero et al., 2010) scored higher on the ASI than unaffected individuals. However, the current study found elevated ASI scores in anxiety. Whereas participants with schizophrenia scored significantly higher on the ASI than both the anxiety and unaffected groups, the anxiety group scored significantly higher than the unaffected group. The current findings may, therefore, indicate aberrant salience is not unique to schizophrenia, the ASI is measuring something else, or the ASI is measuring an aspect of aberrant salience that is present in other psychopathologies (e.g., hyperarousal).

7.1.2 The SAT

The SAT uses a reinforcement learning paradigm to measure implicit salience based on speed of response and explicit salience based on subjective reflection about outcomes of trials in the task. Adaptive and aberrant salience were distinguished by the objective relationship of stimuli with available outcomes. The task relevant stimulus type (e.g., colour) predicts high (87.5%) or low (12.5%) probability of winning based on level (e.g. blue or red). Conversely, the
other stimulus type (e.g., shape) is task irrelevant, as the probability of winning from either level (e.g., household object or animal) is chance (50%). An assumption of the task is that participants will learn from the feedback which stimulus type and level predicts reward most often. This knowledge will be evident in faster speed of response to high compared to low probability outcomes and greater accuracy in recalling the probability of reward for each level. For the aberrant stimulus types, speed of response and probability estimates should be similar as both are rewarded at chance.

The SAT aberrant salience indices yield inconsistent results. Previous studies have found no difference in implicit or explicit aberrant salience between unaffected individuals and individuals with schizophrenia (Abboud et al., 2016; Roiser et al., 2009) and, conversely, higher implicit aberrant salience in schizophrenia (Katthagen et al., 2016; Pankow, Katthagen, et al., 2015). In the current study, higher SAT implicit aberrant salience in the schizophrenia group compared to the anxiety group seemed to indicate that SAT may differentiate between psychopathologies. However, the current project yielded no support for the SAT in differentiating between schizophrenia and unaffected individuals in implicit or explicit aberrant salience.

There is no consistent relationship among SAT indices. In line with previous findings (Katthagen et al., 2016; Pankow, Katthagen, et al., 2015; Roiser et al., 2009, 2010), there was no evidence of a relationship between explicit and implicit aberrant salience indices in undergraduates, anxiety, schizophrenia, or unaffected individuals (after correction for multiple comparisons). The relationship between SAT adaptive salience indices was also inconsistent. The only relationship to survive adjustment for multiple comparison in schizophrenia was the positive relationship between explicit and implicit adaptive salience. This finding was, however, not evident in undergraduates, the anxiety group, or unaffected individuals. Prior research has found a positive relationship between SAT adaptive salience indices in unaffected individuals (Roiser et al., 2010) and for schizophrenia and unaffected individuals when data not grouped (Katthagen et al., 2016; Roiser et al., 2010). The findings suggest that explicit and implicit indices are not measuring the same constructs.
Reward-related impairments in schizophrenia may confound results obtained using the SAT. Schizophrenia is associated with: impaired reward-related reinforcement learning (Dowd et al., 2016; Serra et al., 2001); diminished reward valuation (Ahn et al., 2011; Brown et al., 2018; Heerey et al., 2007; Weller et al., 2014); an inability to rapidly adjust behaviour to optimise outcomes (Schlagenhauf et al., 2014; Waltz & Gold, 2007); impaired working memory (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014; Lee & Park, 2005); and reduced motivation (Green et al., 2015; Reddy et al., 2015). Such impairments in schizophrenia would reduce the ability to differentiate between high and low reward probability (relevant) stimuli, leading to less disparity in speed of response (impaired adaptive salience). These behavioural findings are in line with evidence that attenuated VS activation in schizophrenia disrupts reward-related function (Gradin et al., 2013; Koch et al., 2010; Schlagenhauf et al., 2014; Waltz et al., 2010). Furthermore, atypical neural activation during reward-processing in schizophrenia interrupts salience tracking (e.g., Koch et al., 2010; Waltz et al., 2010), impairing the ability to utilise relevant information, and contributing to reduced motivated behaviour.

The operationalisation of SAT aberrant salience lacks sensitivity and specificity. All groups exhibited implicit aberrant salience, measured as the absolute difference, in speed of response or subjective rating, between the two irrelevant stimulus types. In line with some previous findings (Abboud et al., 2016; Roiser et al., 2009; Smieskova et al., 2015) but in contrast to others (Katthagen et al., 2016; Pankow et al., 2015), unaffected individuals did not significantly differ from schizophrenia in aberrant salience. If the SAT aberrant salience indices measure the construct of aberrant salience, the collective findings suggest aberrant salience is not unique to schizophrenia. However, the differences in implicit and explicit indices of aberrant salience could be due to a number of other factors, such as individual response strategies or guessing. Other sources of systematic measurement error could have included the effects of cognitive abilities (e.g., memory) and knowledge (e.g., how percentiles work) on the accuracy of explicit indices. Furthermore, there was a positive relationship between SAT implicit indices in undergraduates, that was not replicated in anxiety, schizophrenia, or unaffected individuals. Whereas this
may be a spurious correlation, it serves to highlight the inconsistent results obtained from the SAT.

The labelling of SAT explicit and implicit indices as measures of one construct is misleading and unsupported. Roiser et al. (2009) argued the failure to find heightened aberrant salience in schizophrenia was due to the effect of antipsychotics on dampening aberrant salience. However, evidence to support this argument is mixed (Abboud et al., 2016; Smieskova et al., 2015). Overall, a more likely conclusion is that the SAT lacks sensitivity and specificity. A similar pattern of inconsistent results across groups was found when comparing the SAT with specific measures of motivational salience.

7.1.3 Aberrant motivated behaviour in schizophrenia

The EEfRT provides indices of the willingness to expend effort relative to reward value and probability of winning. Levels of probability were low (12%), moderate (50%), or high (88%) and levels of reward magnitude were small, medium, or large. Effort was defined as the willingness to choose the hard task and was calculated across all magnitude-probability combinations, as well as magnitude and probability levels.

The SCT provides orthogonal measures of gain relative to loss sensitivity and approach relative to avoidance behaviour. The SCT is expressed as ratios, where ratios over 1 indicate greater sensitivity to gain than loss and a greater tendency to approach than avoid respectively. The probability of any outcome is 50%. The SCT measures are calculated using the matching law (see Section 5.3.2). Therefore, participants who did not behave in a manner consistent with the matching law, such that the speed of response (including choosing not to respond) was relative to the outcome value, were excluded from further analysis.

Schizophrenia was associated with maladaptive behaviour that was distinct from anxiety and unaffected individuals. The schizophrenia group had higher approach relative to avoidance tendency but were less willing to exert effort for reward. Consistent with previous findings (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013), schizophrenia was associated with reduced adaptive and increased aberrant motivated behaviour during the EEfRT. These findings
may reflect devaluation of reward (Ahn et al., 2011; H. E. Brown et al., 2018; Heerey et al., 2007; Weller et al., 2014) or difficulties with cost and effort computations (Fervaha, Foussias, et al., 2013; Morris et al., 2011). Alternatively, individuals with schizophrenia may have been responding without considering outcome likelihood.

### 7.1.4 Observations during motivational measures

Comments from participants with schizophrenia during the SCT revealed a potential effect of aberrant salience on motivated behaviour. One participant described focusing on either the loss or gain amount but not both. For example, if they could win $6 or lose $8, they commented on how they wanted to win the $6 and responded to the task accordingly. Other times, participants would focus purely on avoiding the loss, no matter how minimal, without considering potential gain. These observations are in line with behavioural evidence suggesting attenuated responses to reward but intact responses to aversive outcomes. Importantly, such data was excluded from SCT analysis as the response pattern was inconsistent with the matching law.

The reduced use of all available information was also observed during the EEFRT. For example, one participant asked a number of times why they did not get any money following an unrewarded hard task. Their comment suggests they were focusing more on reward magnitude than probability. As suggested by Fervaha (2013), decision-making will be impaired where participants were not using all available information. This notwithstanding, the attention to just one aspect of a stimulus is also indicative of reduced adaptive salience.

Other observations suggested symptoms impacted decision-making. One participant, who advised they were hearing voices at the start of the session, stated that the SCT was measuring their psychic abilities. They appeared to ignore the information given during the task, and verbalised their choices based on their intuition. Another participant stated that the computer would take away their money once they got to a certain level. Therefore, whereas the motivational salience indices provided evidence for reduced adaptive behaviour, observations suggest such findings may also reflect response
patterns based on task-irrelevant information. In other words, aberrant salience.

7.2 The absence of convergent validity

A key finding from the current research was the lack of relationships among the ASI and the SAT aberrant salience indices. The failure to find convergent validity may be due, in part, to the differing operationalisation of aberrant salience. The ASI is a retrospective, self-report measure of the experience of aberrant salience that is subject to memory and related biases. The SAT is a behavioural measure that relies on reward-related processing (implicit) and working memory (explicit). The explicit SAT measure of aberrant salience, while self-report, is limited to the stimuli presented during the task. Therefore, the ASI and the SAT implicit and explicit indices appear to be measuring very different things, which may or may not reflect different aspects of aberrant salience. However, their lack of convergence with motivational salience indices challenges the validity of the ASI and SAT as measures of aberrant salience.

7.2.1 The ASI and motivational salience

Among undergraduates there was an association between the ASI and aberrant motivated behaviour. Analysis of the EEfRT and ASI variables revealed higher ASI scores were associated with: more effort for higher less likely rewards; lower more likely rewards; and rewards where the likelihood of winning was chance. Additionally, participants scoring high on the ASI were less likely to use all the available information to determine effort. Undergraduates with a low ASI score used both probability and reward magnitude to determine task choice. In contrast, undergraduates who scored high on the ASI were more likely to use probability of winning alone to determine task choice. However, a higher ASI score was also associated with an overall increased willingness to exert effort (choose the hard task more often) and increased effort for high value outcomes, including when the outcome was uncertain. Conversely, there was no association between ASI score and SCT indices. The findings provide some support for an association between the ASI and aberrant motivational salience.
However, the findings were far from the consistent outcome that would be expected based on the aberrant salience hypothesis.

There was no association between the ASI and aberrant motivated behaviour in schizophrenia. Despite elevated ASI scores in schizophrenia, the expected increase in evidence of a relationship between the ASI and motivational salience was not found. Even prior to correction for multiple comparisons, there was no evidence of a relationship between the ASI and motivated behaviour in schizophrenia. In fact, the only relationship to survive correction was the negative relationship between the ASI and the SCT gain:loss ratio in unaffected individuals. Given the relationship between aberrant motivated behaviour and ASI in undergraduates, it is unlikely that the different data collection methods for the measures account for the lack of relationship.

7.2.2 Does the ASI measure aberrant salience?

The ASI has good face validity but lacks construct validity. The failure to find a positive relationship with the SAT aberrant salience indices may be due to issues with the SAT. However, the failure to find a relationship between the ASI and aberrant motivational behaviour suggests that what the ASI is measuring is not related to motivational salience. Kapur (2003) proposed deficits in motivational salience underlie the relationship between dopaminergic dysregulation and aberrant salience. The failure to find evidence of this relationship in schizophrenia, therefore, challenges the ASI as a measure of aberrant salience. However, other factors need to be considered.

Observations during the administration of the ASI indicated that the language used in the questionnaire is complicated, ambiguous, and may confound results. The wording used was not always clear to participants. During the current studies, participants (from all groups) often asked for clarity. For example, “Do you often become fascinated by the little things around you?” would elicit a request for clarification on what type of little things. A number of participants did not understand the words ominous and trivial. Participants sometimes verbalised their thought processes prior to providing a response, highlighting another key issue: interpretation. Some participants talked about how their beliefs or spirituality related to their heightened awareness and
understanding, and even to the assignment of importance to things that previously were unimportant. Another time a participant diagnosed with schizophrenia responded to the question, “Do you sometimes feel like you are finding the missing piece to a puzzle?”, by stating that when they did puzzles, they often found the missing piece so responded with yes. I also observed that some participants took longer to think about questions than others, which may reflect issues with comprehension and interpretation.

The ASI could be improved by a number of changes. The wording needs clarifying and simplifying. The use of a scale, rather than simply yes or no, would also aid in determining the degree of variability in experience. Participants would frequently ponder the words sometimes and ever. There was no benchmark against which a participant could determine their experience. For example, ever may have been taken to mean once, sometimes as more than once, or the two words interpreted interchangeably. The use of a scale, for example never, rarely, once in a while, sometimes, almost always, would better enable participants to quantitively evaluate frequency. Such a scale would also provide useful information on the variability of experience and whether this variance predicted schizophrenia. For example, some participants may be very extreme on the presence or absence of an experience, whilst others may have a more consistent, mid-level experience range that is not accurately captured by the current ASI.

### 7.2.3 The SAT and motivational salience

Implicit SAT indices were associated with aberrant motivated behaviour in undergraduates. Students with higher implicit aberrant salience were less likely to exert effort for higher, more likely rewards. Thus, implicit aberrant salience predicted reduced adaptive behaviour. However, higher implicit adaptive salience was also associated with less effort for high reward value, including when there was a low or high probability of winning. These findings were unsurprising given the positive relationship between the SAT implicit measures in undergraduates. Conversely, higher explicit adaptive salience predicted adaptive motivated behaviour, but only when there was a low expectation of success. There was no evidence of an association between explicit aberrant
salience and maladaptive motivational salience. Furthermore, none of the SAT indices were predicted by the effect of value or likelihood of reward on task choice or SCT indices. These findings reflect the inconsistent relationships reported between the SAT indices.

There was no evidence of a relationship between the SAT and EEfRT or SCT in the schizophrenia. The weak inverse association between adaptive behaviour and aberrant salience failed to survive adjustment for multiple comparisons. Indeed, none of the relationships between the SAT and EEfRT in schizophrenia, anxiety, or unaffected individuals survived correction for multiple comparison. Prior to correction, however, the correlations between indices in anxious individuals did suggest an association between aberrant salience and both loss sensitivity and maladaptive motivated behaviour. The only robust finding between the SAT and SCT was the relationship between loss sensitivity and aberrant salience in unaffected individuals. Combined, these findings further highlight issues with the utility of the SAT. Kapur (2003) proposed that motivational salience mediates the relationship between hypodopaminergic activation and aberrant salience in schizophrenia. According to Roiser et al. (2009), the SAT measures aberrant and adaptive salience. If both these statements hold true, there should be a relationship between aberrant salience and maladaptive motivated behaviour that is enhanced in schizophrenia. The current projects found no evidence of this.

7.2.4 Does the SAT measure aberrant salience?

The SAT indices yield inconsistent results for aberrant salience (Abboud et al., 2016; Katthagen et al., 2016; Pankow, Katthagen, et al., 2015; Roiser et al., 2009) and adaptive salience (Abboud et al., 2016; Katthagen et al., 2016; Pankow, Deserno, et al., 2015; Roiser et al., 2009) in schizophrenia. Differences in SAT data obtained from individuals with schizophrenia may reflect impairments in reward processing (e.g., Dowd et al., 2016; Serra et al., 2001) rather than salience. For example, reported increased aberrant and reduced adaptive salience SAT indices in schizophrenia may reflect the effect of outcome value on behaviour.
Flaws in the underlying assumptions of the SAT may also confound results in schizophrenia. The task-irrelevant stimuli are rewarded 50% of the time, thus are not actually task irrelevant. Another issue is the assumption that there will be a difference between irrelevant stimulus types, rather than specific stimuli. The SAT aberrant salience is calculated based on a difference between levels (e.g., household objects and animals) of each stimulus type (e.g., shape). This assumes that participants with schizophrenia will group stimuli in a similar manner, based on the type of picture (as instructed). However, as argued by Berridge (1996), all stimuli are not equal when it comes to motivation. The contingencies in the SAT control for bias towards a stimulus type (e.g., prefer red over blue) but they cannot account for the personal identification of stimulus relevance in schizophrenia. Participants with schizophrenia may focus on the combined stimulus characteristics or adopt a response strategy that has very little to do with reinforcement schedules. For example, a participant may respond to a blue gorilla and blue chair more quickly than any other stimuli. If colour is relevant, and blue is rewarded only 12.5% of the time, this will lead to less difference between irrelevant cues (reduced aberrant salience) while also reducing adaptive salience. Attempts to generalise a pattern of behaviour in schizophrenia, based on a set of stimuli that show differentiation in unaffected individuals is, therefore, limited.

The SAT should be used with caution as a measure of aberrant salience. The SAT has yielded a decade of inconsistent results and lacks sufficient evidence of construct validity. Continued use of a measure that has poor construct validity does little to advance understanding of aberrant salience in schizophrenia and, at worst, may mislead the field. This situation is comparable to the BIS/BAS scale (Carver & White, 1994). The BIS/BAS scale is still in use, despite being an inadequate measure of BIS and BAS as defined by reinforcer sensitivity theory. Continued publication of studies using the BIS/BAS scale over the last 25 years has facilitated self-perpetuating validity and very little critique as to whether the measure is fit for purpose.

In summary, there is limited evidence of aberrant salience in schizophrenia using the SAT indices. Conversely, the SAT highlights issues with reduced adaptive salience. The SAT indices of aberrant and adaptive salience
may be subject to confounds, such as cognitive impairments in schizophrenia or the failure to account for the personal specificity of aberrant salience. However, the continued use of the SAT as a measure of aberrant salience is not supported by the current findings.

7.2.5 Relationship between motivational salience indices

Evidence of relationships among motivational salience indices was limited. In undergraduates, reduced loss sensitivity correlated with increased willingness to exert effort when there was only a chance of obtaining the reward. This relationship was strengthened when the reward value was high. The correlations between the SCT and EEfRT in schizophrenia, anxiety, and unaffected individuals failed to survive correction for multiple comparisons. However, the pattern of significant relationships prior to correction is worth noting. Unaffected individuals with higher relative approach tendency were more willing to exert effort for low probability trials across all reward values. In anxiety, greater relative approach tendency inversely related to increased reward value, whereas reduced loss sensitivity related to effort under conditions of lower probability of rewarding outcome. Conversely, there was no pattern of related behaviour between the EEfRT and the SCT in schizophrenia. Therefore, even though only those individuals whose behaviour fitted the law of effect were included in SCT analysis, schizophrenia was still associated with atypical patterns of motivated behaviour.

7.2.6 Summary

The SAT and ASI are purported to be measures of aberrant salience with no convergent validity and questionable sensitivity and specificity. Whereas individuals with schizophrenia scored higher on the ASI and SAT implicit aberrant salience, there was no relationship between the indices. Furthermore, there was no relationship between aberrant motivated behaviour and measures of aberrant salience in schizophrenia. Issues with each of the measures may have contributed to the lack of convergence. However, the combined findings challenge the construct validity of the SAT and, to a lesser degree, the ASI as measures of aberrant salience. There is, however, an alternative explanation to
consider: that motivational salience does not mediate the relationship between dopaminergic dysregulation and aberrant salience in schizophrenia.

### 7.3 Does motivational salience mediate aberrant salience?

Kapur (2003) argued that motivational salience mediates the relationship between dopaminergic dysregulation and aberrant salience in schizophrenia. The current findings do not support this hypothesis. One explanation is that the SAT and ASI are not measuring aberrant salience. However, an alternative explanation, that motivational salience does not mediate aberrant salience, cannot be ruled out.

Motivational salience requires dopaminergic activation (Berridge & Robinson, 1998; Hebart & Gläscher, 2015), which signals both reward value (Schultz, 2015) and salience (Horvitz, 2000; Jimmy Jensen & Walter, 2014) within the mesocorticolimbic system (Bromberg-Martin et al., 2011). Furthermore, dopaminergic firing facilitates the maintenance and updating of stimulus-outcome associations (Cooper et al., 2014; Hird et al., 2018; Sambrook & Goslin, 2015; Talmi et al., 2013; Walsh & Anderson, 2012) and motivated behaviour (Boksem et al., 2006; Holroyd & Coles, 2002; Ventouras et al., 2011).

Atypical dopaminergic firing is associated with reward processing impairments (Di Rosa et al., 2015; Moody et al., 2010; Szamosi et al., 2012) but not necessarily motivated behaviour (Goerendt et al., 2004). Schizophrenia is associated with impaired reward processing (Ahn et al., 2011; Brown et al., 2018; Dowd et al., 2016; Heerey et al., 2007; Schlagenhauf et al., 2014; Serra et al., 2001; Waltz & Gold, 2007; Weller et al., 2014) and maladaptive motivated behaviour (Fervaha, Graff-Guerrero, et al., 2013; Gold et al., 2013; Green et al., 2015; Reddy et al., 2015; Treadway et al., 2009). However, neuro imaging data yields inconsistent evidence of atypical activation in key reward processing regions in schizophrenia (Esslinger et al., 2012; Gradin et al., 2011; Hägele et al., 2014; Juckel, Schlagenhauf, Koslowski, Wüstenberg, et al., 2006; Waltz et al., 2010; Wolf et al., 2014). The inconsistent findings suggest neural activation outside the reward pathways is affecting motivated behaviour in schizophrenia.
Atypical activation in the SN, CEN, and DMN contributes to aberrant salience. Activation in the SN signals motivational salience and informs goal-directed behaviour (Lamichhane & Dhamala, 2015). The SN regulates the relative activation in the CEN and DMN (Chand & Dhamala, 2016a; Goulden et al., 2014; Sridharan et al., 2008; Uddin, 2017c). Increased activation in the CEN, which predicts task related performance, was found in response to salient (aversive) stimuli in unaffected individuals but to irrelevant (neutral) stimuli in schizophrenia (Anticevic et al., 2011). Activation in the DMN usually signals self-referential processing and is attenuated during task-related processing (Buckner et al., 2008; Crone et al., 2011; Scheibner et al., 2017). In schizophrenia, DMN hyperactivation contributes to reduced task performance (Whitfield-Gabrieli et al., 2009), symptom severity (T. P. White, Wigton, et al., 2016; Whitfield-Gabrieli et al., 2009), and aberrant salience (Anticevic et al., 2011). Atypical SN activation in schizophrenia may, therefore, result in reduced processing of salient stimuli and increased self-agency and importance of irrelevant stimuli. In other words, the SN may be central to reduced adaptive salience and increased aberrant salience in schizophrenia.

The failure to find a relationship between motivational salience and aberrant salience may reflect a directional difference in the relationship between motivational salience and aberrant salience. Specifically, impaired functioning of the SN in schizophrenia may mediate aberrant salience, which then affects motivational salience. The effect of impaired SN functioning, in reducing adaptive salience and increasing aberrant salience, fits with the maladaptive pattern of behaviour found in schizophrenia. The effect of antipsychotics on regulating SN and DMN activation is also related to reduction in symptom severity (Wang et al., 2017). Therefore, the link between dopaminergic activation, aberrant salience, and symptoms is not inconsistent within the amended framework.

7.4 Limitations

The current research has limitations. Information about current medication, including antipsychotics, was not obtained. As antipsychotics dampen dopaminergic activation, antipsychotics may have had an effect on motivational
salience, aberrant salience, or both. ASI scores do not appear to be affected by antipsychotics (Tofani et al., 2016). In regards to the SAT, individuals on antipsychotics who did not experience delusions or negative symptoms scored lower explicit aberrant salience compared to unaffected individuals and those experiencing delusions and negative symptoms (Roiser et al., 2009). No such effect was found for hallucinations, implicit aberrant salience, or adaptive salience indices. In the current study, 20 of the participants with schizophrenia reported current positive symptoms, including delusions and hallucinations. Comparison of individuals with and without positive symptoms, however, revealed no group differences in the ASI or SAT scores, minimal effect on the EEfRT, but higher gain relative to loss sensitivity in the positive symptom group. Sample sizes were too small for a meaningful comparison of current delusions versus hallucinations. Whereas, the combined evidence suggests it is unlikely that antipsychotic dose would have affected the results, inclusion of current medication would have been beneficial for comparison with previous and future research and generalisability.

Cognitive ability may have confounded between-group results. Schizophrenia is associated with impaired cognitive functioning that affects reward processing. The inclusion, for example, of working memory and decision-making indices would have facilitated analysis of the effect of cognitive ability on SAT, SCT, and EEfRT performance.

Data from participants whose behaviour on the SCT did not fit with the law of effect were excluded from analyses. The number of excluded participants, from all groups, was higher than expected. Further research into the parameters used during SCT analysis is therefore indicated. Additionally, as evident in the current research findings for the EEfRT, schizophrenia is associated with maladaptive motivated behaviour. Future research should, therefore, also explore variations in approach:avoidance tendency and gain:loss sensitivity in individuals who do not fit the model, including across groups and between measures.

The reduced sample size for SCT analysis may have contributed to the lack of consistent relationship between the SCT and EEfRT. However, it may also be that the SCT and EEfRT are measuring unrelated aspects of motivated
behaviour. Future research should explore this relationship and include additional measures of motivational salience.

Participants were not demographically matched across groups. This was partly due to endemic differences in schizophrenia, such as gender and the impact of on-going engagement with mental health services on socioeconomic variables. Indeed, there is evidence of a matching fallacy effect, whereby matching groups on factors such as education or IQ creates a mismatch (Kremen et al., 1995; Kremen, Seidman, Faraone, & Tsuang, 2008). However, anxious and unaffected individuals were fairly evenly matched for age, employment, and household income.

Finally, the MINI was not administered to unaffected individuals. However, unaffected individuals did complete the DSM-5 Self-Rated Cross-Cutting Symptom Measure Level 1 and, where applicable, Level 2. All of the unaffected individuals rated 0 for psychosis and did not have clinical levels of anxiety. Given this, it is unlikely that administration of the MINI would have identified clinically significant symptoms in unaffected individuals.

7.5 Future research ideas

The current findings raise issues with the two published measures of aberrant salience, the SAT and ASI. In future research, investigators should seek to assess whether changes in wording could improve the utility of the ASI as a measure of aberrant salience. However, as with many self-report measures, scores on the ASI are affected by factors such as memory, self-reflection, and subjective interpretation. Inconsistencies in SAT data suggest future measures should avoid, or control for, known confounds such as the effect of reward-related impairments in schizophrenia. Alternative measures of aberrant salience are needed to ascertain whether aberrant salience is evident in, and unique to, schizophrenia.

Investigators could build on existing methodologies used during behavioural and neuroimaging studies indicating aberrant salience to formulate and develop new measures of aberrant salience. Existing methodologies fall into two broad categories, namely distractor interference and arousal. For example, schizophrenia was associated with higher distractibility during task
performance, especially from irrelevant neutral stimuli (Anticevic et al., 2011). Compared to negative stimuli, neutral stimuli were associated with higher self-reported emotional arousal (Haralanova et al., 2012; Okruszek et al., 2016) and physiological arousal in schizophrenia (Haralanova et al., 2012; W P Horan et al., 2013). Both distractor and arousal tasks would benefit from the inclusion of appetitive as well as neutral and aversive stimuli. This would provide further insight into the effect of reduced reward value on the salience of irrelevant stimuli, which may further the understanding of the aversive undertone of positive symptoms. The use of eye-tracking for visual stimuli tasks would also assist in ascertaining the relationship between attention to stimuli and behavioural or self-report responses.

The argument that aberrant salience contributes to symptom development has yet to be investigated. One approach would be to assess the association between sensory specific aberrant salience and symptoms. For example, an association between auditory hallucinations and task interference from irrelevant auditory stimuli would strengthen the argument that aberrant salience contributes to symptom development. Future research could use auditory and visual stimuli in the same paradigm to ascertain whether such a relationship is evident.

Further research is needed to confirm whether or not there is an association between aberrant salience and motivational salience in schizophrenia. The failure to find a relationship in the current study may reflect either the study limitations or the complexity and number of the EEfRT variables. A more simplistic measure of motivational salience, and more robust measure of aberrant salience, may reveal an association. Furthermore, the direction of the relationship between aberrant salience and motivational salience needs to be understood and clarified.

Finally, investigators should seek to anchor the construct of aberrant salience, as it contributes to symptoms of schizophrenia, to known neural systems and their functions. For example, the relationship between aberrant salience and the SN in schizophrenia warrants further investigation. Neurological evidence suggests key regions involved in self-referential processing may influence aberrant salience (Pauly, Kircher, Schneider, & Habel,
The ASI (Cicero et al., 2013) and the SAT aberrant salience (Roiser et al. 2010) are associated with self-identity and self-referential processing, respectively. In future studies, investigators should seek to clarify whether atypical activation in SN leads to a failure to switch between DMN and CEN during self-referential and task-related activities. If so, the relationship between activation in each of the networks and aberrant salience should be examined to clarify which of these networks, if any, contributes to aberrant salience in schizophrenia.

### 7.6 Conclusion

The current findings suggested increased aberrant salience and reduced adaptive behaviour in schizophrenia. This is in line with previous behavioural and neurological evidence. However, the lack of relationship between motivational salience and aberrant salience in schizophrenia challenges Kapur's (2003) argument that motivational salience mediates the relationship between dopaminergic hyperactivation and aberrant salience in schizophrenia. However, there was no evidence of convergent validity between the ASI and SAT, and minimal evidence of the expected relationships between aberrant salience and motivational salience indices. Whereas amendments to the ASI may improve its validity, the SAT is confounded by reward-related impairments in schizophrenia. However, it may be that there is no relationship between motivational salience and aberrant salience. Instead, atypical activation in the salience network may disrupt the functional connectivity between the DMN and CEN, leading to increased aberrant salience and reduced adaptive salience. Further research is, therefore, needed to understand the cognitive and neural mechanisms underlying aberrant salience in schizophrenia.
## Appendix A
### Chapter 6 Supplementary Material

**Table A1**

Correlation between variables for Schizophrenia Group

<table>
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<th></th>
<th>ASI</th>
<th>Aberrant Salience</th>
<th>Adaptive Salience</th>
<th>A:A</th>
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<td>-.23</td>
<td>-.21</td>
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<td>-.55</td>
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</tr>
<tr>
<td>$ Coef</td>
<td>.01</td>
<td>.02</td>
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<td>.31</td>
<td>-.33</td>
</tr>
<tr>
<td>Pr Coef</td>
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<td>-.26</td>
<td>-.23</td>
<td>-.20</td>
<td>-.37*</td>
</tr>
<tr>
<td>$ \times Pr Coef</td>
<td>.03</td>
<td>.15</td>
<td>.21</td>
<td>.35</td>
<td>.54**</td>
</tr>
</tbody>
</table>

*Note: ASI = Aberrant Salience Inventory; Aberrant Salience = Salience Attribution Test Aberrant Salience; Adaptive Salience = Salience Attribution Test Adaptive Salience; A:A = Stimulus Chase Task approach-avoid ratio; G:L = Stimulus Chase Task gain-loss ratio. For Effort Expenditure for Reward Task variables: L = low; M = medium; H = high; Pr = probability; $ = reward; Coef = coefficient.*

* p < .05. ** p < .01. *** p < .001.

Only highlighted correlations survived Holm correction for multiple comparisons.
Table A2

Correlation between variables for Anxiety Group

<table>
<thead>
<tr>
<th></th>
<th>ASI Implicit</th>
<th>ASI Explicit</th>
<th>AdS Implicit</th>
<th>AdS Explicit</th>
<th>A:A</th>
<th>G:L</th>
</tr>
</thead>
<tbody>
<tr>
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<td>-.32†</td>
<td></td>
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<td></td>
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<tr>
<td>Explicit AS</td>
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<td>-.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implicit AdS</td>
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<td>-.10</td>
<td>.01</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Explicit AdS</td>
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<td>-.45**</td>
<td>-.23</td>
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<tr>
<td>A:A</td>
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<td>.03</td>
<td>.17</td>
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<td>.08</td>
<td></td>
</tr>
<tr>
<td>G:L</td>
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<td>-.03</td>
<td>-.53**</td>
<td>.24</td>
<td>-.16</td>
<td>-.53**</td>
</tr>
<tr>
<td>Hard Choices</td>
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<td>.02</td>
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<td>-.08</td>
<td>-.10</td>
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<td>-.41</td>
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<td>.24</td>
<td>.40</td>
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<tr>
<td>L $</td>
<td>.05</td>
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<td>.17</td>
<td>-.23</td>
<td>-.17</td>
<td>.54**</td>
</tr>
<tr>
<td>M $</td>
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<td>-.09</td>
<td>.04</td>
<td>.12</td>
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<td>-.02</td>
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<td>.14</td>
<td>-.03</td>
<td>-.48*</td>
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<td>.00</td>
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<td>-.15</td>
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<tr>
<td>L Pr, H $</td>
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<td>.07</td>
<td>-.02</td>
<td>-.13</td>
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<td>-.19</td>
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<td>-.13</td>
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<td>-.14</td>
<td>.15</td>
<td>-.09</td>
<td>-.52*</td>
</tr>
<tr>
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<td>-.04</td>
<td>.58**</td>
</tr>
<tr>
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<td>.01</td>
<td>.24</td>
<td>.41*</td>
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<tr>
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<td>-.05</td>
<td>-.21</td>
<td>-.45**</td>
<td>-.12</td>
</tr>
<tr>
<td>M EV</td>
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<td>.09</td>
<td>.07</td>
<td>-.09</td>
<td>.01</td>
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<tr>
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<td>-.01</td>
<td>.15</td>
<td>.47**</td>
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<tr>
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<td>.12</td>
<td>.46**</td>
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<td>-.28</td>
<td>.35</td>
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<tr>
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<td>-.40*</td>
<td>.31</td>
<td>.49**</td>
<td>-.29</td>
</tr>
</tbody>
</table>

Note: ASI = Aberrant Salience Inventory; Aberrant Salience = Salience Attribution Test Aberrant Salience; Adaptive Salience = Salience Attribution Test Adaptive Salience; A:A = Stimulus Chase Task approach-avoid ratio; G:L = Stimulus Chase Task gain-loss ratio. For Effort Expenditure for Reward Task variables: L = low; M = medium; H = high; Pr = probability; $ = reward; Coef = coefficient.
† p < .05. 1-tailed
* p < .05. ** p < .01. *** p < .001 two-tailed
No correlations survived Holm correction for multiple comparisons
Table A3
Correlation between variables for Unaffected Group

<table>
<thead>
<tr>
<th></th>
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<th>Aberrant Salience</th>
<th>Adaptive Salience</th>
<th>A:A</th>
<th>G:L</th>
</tr>
</thead>
<tbody>
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<td>.33†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Implicit AdS</td>
<td>.09</td>
<td>-.05</td>
<td>.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explicit AdS</td>
<td>-.03</td>
<td>-.20</td>
<td>.00</td>
<td>.17</td>
<td></td>
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<td>A:A</td>
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<td>.25</td>
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<td>.69**</td>
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<td>Hard Choices</td>
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<td>.09</td>
<td>-.13</td>
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<td>L Pr</td>
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<td>.02</td>
<td>.05</td>
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<td>-.38*</td>
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<tr>
<td>M Pr</td>
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<td>-.10</td>
<td>-.13</td>
<td>-.20</td>
</tr>
<tr>
<td>H Pr</td>
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<td>.27</td>
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<td>-.08</td>
<td>.02</td>
<td>-.25</td>
<td>.40</td>
</tr>
<tr>
<td>M $</td>
<td>-.11</td>
<td>-.05</td>
<td>.00</td>
<td>-.18</td>
<td>.30</td>
</tr>
<tr>
<td>H $</td>
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<td>-.03</td>
<td>.09</td>
<td>-.09</td>
<td>.01</td>
</tr>
<tr>
<td>L Pr, L $</td>
<td>.02</td>
<td>-.04</td>
<td>.14</td>
<td>.35</td>
<td>-.17</td>
</tr>
<tr>
<td>L Pr, M $</td>
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<td>-.02</td>
<td>.00</td>
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<td>L Pr, H $</td>
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<td>.48*</td>
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<tr>
<td>M Pr, L $</td>
<td>-.29</td>
<td>-.06</td>
<td>-.04</td>
<td>.14</td>
<td>-.38*</td>
</tr>
<tr>
<td>M Pr, M $</td>
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<td>-.08</td>
<td>-.24</td>
<td>-.06</td>
</tr>
<tr>
<td>M Pr, H $</td>
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<td>-.19</td>
<td>-.08</td>
<td>-.14</td>
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</tr>
<tr>
<td>H Pr, L $</td>
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<td>-.15</td>
<td>-.04</td>
<td>.19</td>
<td>-.02</td>
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<tr>
<td>H Pr, M $</td>
<td>-.22</td>
<td>-.13</td>
<td>.02</td>
<td>.10</td>
<td>.08</td>
</tr>
<tr>
<td>H Pr, H $</td>
<td>-.20</td>
<td>-.19</td>
<td>.09</td>
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</tr>
<tr>
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<td>.01</td>
<td>.03</td>
<td>.16</td>
<td>-.45*</td>
</tr>
<tr>
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<td>-.06</td>
<td>-.09</td>
<td>-.08</td>
</tr>
<tr>
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<td>-.01</td>
<td>.12</td>
<td>.17</td>
<td>.37*</td>
</tr>
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<td>-.01</td>
<td>-.22</td>
<td>-.18</td>
</tr>
<tr>
<td>Pr Coef</td>
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<td>-.26</td>
<td>-.01</td>
<td>-.20</td>
<td>-.13</td>
</tr>
<tr>
<td>$x Pr Coef</td>
<td>-.03</td>
<td>.24</td>
<td>.01</td>
<td>.17</td>
<td>.28</td>
</tr>
</tbody>
</table>

Note: ASI = Aberrant Salience Inventory; Aberrant Salience = Salience Attribution Test Aberrant Salience; Adaptive Salience = Salience Attribution Test Adaptive Salience; A:A = Stimulus Chase Task approach-avoid ratio; G:L = Stimulus Chase Task gain-loss ratio. For Effort Expenditure for Reward Task variables: L = low; M = medium; H = high; Pr = probability; $ = reward; Coef = coefficient. † p < .05. 1-tailed
* p < .05. ** p < .01. *** p < .001.
Only highlighted correlations survived Holm correction for multiple comparisons.
Figure A1. Mean group scores showing non-significant differences in planned comparisons for reward × probability combinations of the Effort Expenditure for Reward Task. Error bars show standard error of the mean.
Appendix B
R Code used for Data Analysis

General information

The R programme uses various packages and commands. I have included a list of the packages used for each of the analyses along with the master code. Within each master code the dataframe filename has been replaced with `dataframe`. The variable name (e.g., ASI score, SAT implicit aberrant salience) has been replaced with numbered variables (e.g. Variable1). Columns within the dataframe are selected using the `c()` command.

For the EEfRT dataframe, the definitions of columns identified in the code are as follows: `Participant` is participant ID; `Choice_Hard_1` is whether hard task was chosen (hard task choice coded as 1 and easy task choice coded as 0); `RM_Hard` is the reward magnitude (monetary value) for the hard task choice; and `Probability` is the probability of winning (0.12, 0.5, 0.88).

R Commands: Chapter 5

Correlation analysis

Packages used: Hmisc

The master command for undertaking correlational analysis between each of the variables was:

```
cor.test(dataframe$variable, dataframe$variable, method = "kendall")
```

Mixed effects modelling of EEfRT data

Packages used: lme4; mlmRev; ggplot2; reshape2; sjPlot

Modelling was then undertaken sequentially using the steps presented in Table B.1. Where multiple models calculated for a step, only the model with the best fit was used in subsequent comparisons.
Table B.1
Mixed effects models, and R code, used in analysing the EEfRT data

<table>
<thead>
<tr>
<th>Step</th>
<th>Purpose</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Calculate Null Model</td>
<td>NullModel &lt;- glmer(Choice_Hard_1 ~ 1 + (1</td>
</tr>
</tbody>
</table>
| 2.   | Calculate the fixed effects models (known variables of reward magnitude and probability) | RewardMagnitude <- glm(formula = Choice_Hard_1 ~ RM_Hard, data = dataframe, family = "binomial")  
Probability <- glm(formula = Choice_Hard_1 ~ Probability, data = dataframe, family = "binomial")  
RewardMagnitudeXProbability <- glm(formula = Choice_Hard_1 ~ RM_Hard*Probability, data = dataframe, family = "binomial")  
Fixed <- glm(formula = Choice_Hard_1 ~ Probability + RM_Hard, data = dataframe, family = "binomial") |
| 3.   | Compare fixed effects models | anova(NullModel, RewardMagnitude, Probability, RewardMagnitudeXProbability, Fixed) |
| 4.   | Calculate random effects model | Random <- glmer(Choice_Hard_1 ~ (1|Participant), family = "binomial", data = dataframe) |
| 5.   | Compare null, fixed, and random effects models |
6. Calculate varying slopes and intercepts for each variable (reward magnitude and probability):
   a) fixed variable with varying intercept for each participant
      ```r
      Model1 <- glmer(Choice_Hard_1 ~ Variable + (1|Participant), family = "binomial", data = dataframe)
      ```
   b) fixed variable with varying slopes
      ```r
      Model2 <- glmer(Choice_Hard_1 ~ Variable + (0+RM_Hard|Participant), family = "binomial", data = dataframe)
      ```
   c) fixed variable with varying intercepts and slopes
      ```r
      Model3 <- glmer(Choice_Hard_1 ~ Variable + (1+RM_Hard|Participant), family = "binomial", data = dataframe)
      ```

7. Compare slopes and intercepts models for each variable
   ```r
   anova(Model3, Model2, Model1)
   ```

8. Calculate slopes and intercepts for interaction between variables:
   a) fixed variables with varying intercept for each participant
      ```r
      Int1 <- glmer(Choice_Hard_1 ~ RM_Hard + Probability + RM_Hard:Probability +(1|Participant),
                     control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)
      ```
   b) fixed variable with varying slopes
      ```r
      Int2 <- glmer(Choice_Hard_1 ~ RM_Hard + Probability + RM_Hard:Probability + (0+RM_Hard*Probability|Participant),
                     control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)
      ```
   c) fixed variable with varying intercepts and slopes
Int3 <- glmer(Choice_Hard_1 ~ RM_Hard + Probability + RM_Hard:Probability + (1+RM_Hard*Probability|Participant),
control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)

9. Compare slopes and intercept models for interaction between variables
   anova(Int3, Int2, Int1)

10. Calculate independent random effects model:
    effortFinalModel1 <- glmer(Choice_Hard_1 ~ RM_Hard + Probability + RM_Hard:Probability +
                                 (1|Participant) + (0+RM_Hard|Participant) + (0+Probability|Participant) + (0+RM_Hard:Probability|Participant),
                                 control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)

11. Calculate models that fall between independent random and correlated random effects:
    effortFinalModel2 <- glmer(Choice_Hard_1 ~ RM_Hard + Probability + RM_Hard:Probability +
                                       (1|Participant) + (0+RM_Hard|Participant) + (0+Probability|Participant),
                                       control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)
    effortFinalModel3 <- glmer(Choice_Hard_1 ~ RM_Hard + Probability + RM_Hard:Probability + (1+RM_Hard|Participant),
                                control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)
    effortFinalModel4 <- glmer(Choice_Hard_1 ~ RM_Hard + Probability + RM_Hard:Probability + (1+Probability|Participant),
                                control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)
    effortFinalModel5 <- glmer(Choice_Hard_1 ~ RM_Hard + Probability + RM_Hard:Probability + (1+RM_Hard+Probability|Participant),
                                control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)
12. Calculate correlated random effects model:

\[
\text{effortFinalModel6} \leftarrow \text{glmer}(\text{Choice\_Hard\_1} \sim \text{RM\_Hard} + \text{Probability} + \text{RM\_Hard}\cdot\text{Probability} + \\
(1+\text{RM\_Hard}+\text{Probability}+\text{RM\_Hard}\cdot\text{Probability}|\text{Participant}), \\
\text{control} = \text{glmerControl(\text{optimizer="bobyqa"), family = "binomial", data = dataframe)}
\]

13. Compare models to ascertain best fit

\[
\text{AIC(\text{effortFinalModel1, effortFinalModel2, effortFinalModel3, effortFinalModel4, effortFinalModel5, effortFinalModel6})}
\]

*Note:* In steps where models are compared, the model with the best fit is identified in bold. For step 7, the highlighted model was the same for both reward magnitude and probability.
Individual beta coefficients for EEfRT

For each individual, logistic regression coefficients for choice during the EEfRT predicted from reward magnitude, probability, and reward magnitude x probability were calculated.

Packages used: ggplot2; lme4; reshape2

The following master function was used to select individual participant data:

```
subXEff <- dataframe[dataframe$Participant == "1", c("Participant", "Choice_Hard_1", "RM_Hard", "Probability")]
```

where: $X$ refers to the participant ID within the EEfRT data dataframe;

Beta coefficients were then calculated using the following master code:

```
SubXglm <- glm(Choice_Hard_1 ~ Probability + RM_Hard + Probability:RM_Hard, data = subXEff, family = binomial("logit"))
```

R Commands: Chapter 6

Mixed effects modelling of EEfRT data

Packages used: lme4; mlmRev; ggplot2; reshape2; sjPlot

Modelling was then undertaken sequentially using the steps presented in Table B.2. Where multiple models calculated for a step, only the model with the best fit was used in subsequent comparisons.

Individual beta coefficients for EEfRT

For each individual, logistic regression coefficients for choice during the EEfRT predicted from reward magnitude, probability, and reward magnitude x probability were calculated. The R codes used were the same as those used for Chapter 5 analysis.
Table B.1
Mixed effects models, and R code, used in analysing the EEfRT data

<table>
<thead>
<tr>
<th>Step</th>
<th>Purpose</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Calculate Null Model</td>
<td>`NullModel &lt;- glmer(Choice_Hard_1 ~ 1 + (1</td>
</tr>
</tbody>
</table>
| 2.   | Calculate the fixed effects models (known variables of reward magnitude, probability, and group) | `RewardMagnitude <- glm(formula = Choice_Hard_1 ~ RM_Hard, data = dataframe, family = "binomial")`  
`Probability <- glm(formula = Choice_Hard_1 ~ Probability, data = dataframe, family = "binomial")`  
`Group <- glm(formula = Choice_Hard_1 ~ Group, data = dataframe, family = "binomial")`  
`RewardMagnitudeXProbability <- glm(formula = Choice_Hard_1 ~ RM_Hard*Probability, data = dataframe, family = "binomial")`  
`RewardMagnitudeXGroup <- glm(formula = Choice_Hard_1 ~ RM_Hard*Group, data = dataframe, family = "binomial")`  
`ProbabilityXGroup <- glm(formula = Choice_Hard_1 ~ Probability*Group, data = dataframe, family = "binomial")`  
`Fixed <- glm(formula = Choice_Hard_1 ~ Probability + RM_Hard, data = dataframe, family = "binomial")` |
| 3.   | Compare fixed effects models | `anova(NullModel, RewardMagnitude, Probability, Group, RewardMagnitudeXProbability, RewardMagnitudeXGroup, ProbabilityXGroup, Fixed)` |
4. Calculate random effects model
   Random <- glmer(Choice_Hard_1 ~ (1|Participant), family = "binomial", data = dataframe)

5. Compare null, fixed, and random effects models
   anova(NullModel, Fixed, Random)

6. Calculate varying slopes and intercepts for each variable (reward magnitude, probability, group):
   d) fixed variable with varying intercept for each participant
      Model1 <- glmer(Choice_Hard_1 ~ Variable + (1|Participant), family = "binomial", data = dataframe)
   e) fixed variable with varying slopes
      Model2 <- glmer(Choice_Hard_1 ~ Variable + (0+RM_Hard|Participant), family = "binomial", data = dataframe)
   f) fixed variable with varying intercepts and slopes
      Model3 <- glmer(Choice_Hard_1 ~ Variable + (1+RM_Hard|Participant), family = "binomial", data = dataframe)

7. Compare slopes and intercepts models for each variable (reward magnitude and probability only as group slopes and intercepts had negligible effect)
   anova(Model3, Model2, Model1)
8. Calculate slopes and intercepts for interaction between variables:
   d) fixed variables with varying intercept for each participant
      \[ \text{Int1} <- \text{glmer(Choice\_Hard\_1} \sim \text{RM\_Hard + Probability + RM\_Hard:Probability + (1|Participant),} \]
      \[ \quad \text{control=} \text{glmerControl(optimizer=\text{``bobyqa''}, family = \text{``binomial''}, data = dataframe)} \]
   e) fixed variable with varying slopes
      \[ \text{Int2} <- \text{glmer(Choice\_Hard\_1} \sim \text{RM\_Hard + Probability + RM\_Hard:Probability + (0+RM\_Hard*Probability|Participant),} \]
      \[ \quad \text{control=} \text{glmerControl(optimizer=\text{``bobyqa''}, family = \text{``binomial''}, data = dataframe)} \]
   f) fixed variable with varying intercepts and slopes
      \[ \text{Int3} <- \text{glmer(Choice\_Hard\_1} \sim \text{RM\_Hard + Probability + RM\_Hard:Probability + (1+RM\_Hard*Probability|Participant),} \]
      \[ \quad \text{control=} \text{glmerControl(optimizer=\text{``bobyqa''}, family = \text{``binomial''}, data = dataframe)} \]

9. Compare slopes and intercept models for interaction between variables
   \[ \text{anova(Int3, Int2, Int1)} \]

10. Calculate independent random effects model:
    \[ \text{effortFinalModel1} <- \text{glmer(Choice\_Hard\_1} \sim \text{RM\_Hard + Probability + Group + RM\_Hard:Probability + RM\_Hard:Group +} \]
    \[ \quad \text{Probability:Group + RM\_Hard:Probability:Group + (1|Participant) + (0+RM\_Hard|Participant) +} \]
    \[ \quad (0+Probability|Participant) + (0+RM\_Hard:Probability|Participant), \]
    \[ \quad \text{control=} \text{glmerControl(optimizer=\text{``bobyqa''}, family = \text{``binomial''}, data = dataframe)} \]
11. Calculate models that fall between independent random and correlated random effects:

\[
\text{effortFinalModel2} \leftarrow \text{glmer(Choice\_Hard\_1 \sim RM\_Hard + Probability + Group + RM\_Hard:Probability + RM\_Hard:Group + Probability:Group + RM\_Hard:Probability:Group + (1|Participant) + (0+RM\_Hard|Participant) + (0+Probability|Participant), control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)}
\]

\[
\text{effortFinalModel3} \leftarrow \text{glmer(Choice\_Hard\_1 \sim RM\_Hard + Probability + Group + RM\_Hard:Probability + RM\_Hard:Group + Probability:Group + RM\_Hard:Probability:Group + (1+RM\_Hard|Participant), control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)}
\]

\[
\text{effortFinalModel4} \leftarrow \text{glmer(Choice\_Hard\_1 \sim RM\_Hard + Probability + Group + RM\_Hard:Probability + RM\_Hard:Group + Probability:Group + RM\_Hard:Probability:Group + (1+Probability|Participant), control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)}
\]

\[
\text{effortFinalModel5} \leftarrow \text{glmer(Choice\_Hard\_1 \sim RM\_Hard + Probability + Group + RM\_Hard:Probability + RM\_Hard:Group + Probability:Group + RM\_Hard:Probability:Group + (1+RM\_Hard+Probability|Participant), control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)}
\]

12. Calculate correlated random effects model (failed to converge):

\[
\text{effortFinalModel6} \leftarrow \text{glmer(Choice\_Hard\_1 \sim RM\_Hard + Probability + Group + RM\_Hard:Probability + RM\_Hard:Group + Probability:Group + RM\_Hard:Probability:Group + (1+RM\_Hard+Probability+RM\_Hard:Probability|Participant), control=glmerControl(optimizer="bobyqa"), family = "binomial", data = dataframe)}
\]
13. Compare models to ascertain best fit

\[ \text{AIC(} \text{effortFinalModel}_1, \text{effortFinalModel}_2, \text{effortFinalModel}_3, \text{effortFinalModel}_4, \text{effortFinalModel}_5) \]

---

**Notes:** In steps where models are compared, the model with the best fit is identified in bold. For step 7: group was excluded as slopes and intercepts had negligible effect; the highlighted model was the same for both reward magnitude and probability. Final model 6 was best fit but failed to converge so was excluded from final model best fit.
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