Brain mechanisms underlying sensation-seeking in humans

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I, Agnes Norbury, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Only part of us is sane: only part of us loves pleasure and the longer day of happiness, wants to live to our nineties and die in peace, in a house that we built, that shall shelter those who come after us. The other half of us is nearly mad. It prefers the disagreeable to the agreeable, loves pain and its darker night despair, and wants to die in a catastrophe that will set back life to its beginnings and leave nothing of our house save its blackened foundations.

Rebecca West, *Black Lamb and Grey Falcon*, Penguin 1994, p. 1102.

Abstract

Sensation-seeking is a personality trait concerned with motivation for intense and unusual sensory experiences, that has been identified as risk factor for a variety of psychopathologies with high social cost; in particular gambling and substance addictions. It has previously proved difficult to tease out neural mechanisms underlying sensation-seeking in humans, due to a lack of cognitive-behavioural paradigms probing sensation-seeking-like behaviour in the lab.

The first aim of this thesis was to develop such a behavioural paradigm. Within, we present evidence from this novel task and a combination of psychopharmacological, functional imaging and computational approaches to argue that sensation-seeking behaviour in humans is driven by inter-individual differences in the activation of dopaminergic approach-withdrawal tendencies, when faced with the opportunity to experience intense and unusual sensory stimulation. In a parallel research stream, we investigate the relationship between self-reported sensation-seeking, D2-type dopamine receptor function and risky decision-making, motivated by the common implication of sensation-seeking personality and D2ergic drugs in disorders involving excessive risk-taking.

Together, the findings presented here may aid investigation of various psychopathologies for which more extreme sensation-seeking scores constitute a vulnerability factor. In particular, a more precise understanding of sensation-seeking behaviour might aid in the identification of at-risk individuals and the development of individualised therapies and prevention strategies.

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Note to examiners

A version of the Introduction to this thesis (Chapter 1) has appeared in print as Norbury, A. & Husain, M. (2015). Sensation-seeking: dopaminergic manipulation and risk for psychopathology. *Behavioural Brain Research*

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Introduction

The point of diving in a lake is not immediately to swim to the shore;

it's to be in the lake, to luxuriate in the sensation of water.

(Campion, 2009)

Is there a hedonic drive to seek out 'sensations', above and beyond more traditionally conceived rewards? For example, what is it that motivates some people to devote large amounts of time, money, and effort in search of such – often fleeting – experiences as sky-diving, a rollercoaster ride, the thrill of fast driving or really spicy food?

Sensation-seeking (SS) has been described as "a trait defined by the need for *varied, novel, complex* and *intense* sensations and experiences, and willingness to take physical and social risks for the sake of such experiences" (Zuckerman, 1974, 1994). Tendency to engage in these kind of behaviours has been found not to be modality-specific, but rather to cluster across the senses, various kinds of social behaviour, and other classes of risky activity (Zuckerman, 1971). Indeed, it has been shown that degree of engagement in various SS activities (particularly licit and illicit recreational drug consumption, and risky driving or sexual behaviours) covaries in both adults and adolescents (Carmody et al., 1985; Caspi et al., 1997; Miles et al., 2001; King et al., 2012; Terry-McElrath et al., 2014). The study of this intriguing individual difference can be traced from mid-century homeostatic theories regarding optimal levels of sensory stimulation (Hebb, 1949) through to

the rise of personality psychology in the 1970s (Zuckerman, 1974, 1994). Recently, it has been greatly advanced via the use of cognitive neuroscience techniques in both humans and animal models.

As well as describing an interesting dimension of behaviour in and of itself, SS trait has been shown to be significantly related to health outcomes across a variety of domains, and has been identified as a relevant individual difference for several psychopathologies (Roberti, 2004). Specifically, high trait SS is considered to be both a vulnerability factor and predictor of poorer prognosis in substance and gambling addictions (e.g. Crawford et al., 2003; Kosten et al., 1994; Fortune and Goodie, 2009). Conversely a putative role in stress-resiliency may explain preliminary findings of higher SS status being a protective factor against psychopathologies resulting from exposure to high-intensity stressors, e.g. post-traumatic stress disorder (Smith et al., 1992; Solomon et al., 1995; Neria et al., 2000).

The brain basis of this personality trait therefore has high relevance for understanding both healthy human behaviour and several prevalent disease states. In this introduction, we first discuss insights into the neurobiology of SS behaviour derived from studies in both humans and animal models, particularly with respect to midbrain dopamine systems. Evidence for how these differences might relate to differential risk for addictive and gambling disorders is then considered, as well as the role high SS may play in more functionally adaptive behaviour such as exploration and stress resiliency.

1.1 Measuring sensation-seeking in humans

1.1.1 Self-report measures of sensation-seeking in humans

SS personality has to date been measured in humans via questionnaires. The most commonly used instrument is the Sensation-Seeking Scale form V (the SSS-V), originally developed in the 1970s by Zuckerman and colleagues (Zuckerman, 1974). The SSS-V has four subscales (Zuckerman, 1994):

1. *Thrill and adventure-seeking*: desire to participate in physically risky activities that involve novel sensations and experiences. Sample item: "I think I would enjoy the sensation of skiing very fast down a high mountain slope".
2. *Experience-seeking*: search for new experiences. Sample item: "I like to try new foods that I have never tasted before".
3. *Disinhibition*: interest in socially and sexually disinhibited activities. Sample item: "I like to have new and exciting experiences, even if they are a little frightening, unconventional, or illegal".
4. *Boredom susceptibility*: intolerance of routines and repetitiveness. Sample item: "I often get very restless if I have to stay around home for any length of time".

These four subscales have been shown to exhibit high internal reliability across a large number of samples (Roberti et al., 2003), including from non English-speaking cultures (Zuckerman, 1994). Recently, a slightly updated version of this measure was produced using factor analysis, which has increased contemporary

internal validity via exclusion of several more dated-sounding items (referring to 'queers', 'swingers' etc; Gray and Wilson, 2007).

Evidence from self-report measures supports the assertion that SS trait is a robust and valid individual difference in humans. SS scores have moderate to high heritability estimates (40-80%; Fulker et al., 1980; Koopmans et al., 1995; Stoel et al., 2006; Harden et al., 2012), and rank order differences in scores are highly stable over time (Terracciano et al., 2011). Moreover, SS scores from a variety of instruments have repeatedly been shown to predict propensity to engage in real-life 'sensation-seeking behaviours' including licit and illicit substance use, participation in high impact sports, and risky driving or sexual behaviours (Zuckerman, 1994; Roberti, 2004; Perry et al., 2011; see **section 1.3**). This is apparent even when the measure used (unlike the SSS-V) deliberately omits any reference to such behaviours (Arnett, 1994; Roth and Hammelstein, 2011). Self-reported SS scores have also been linked to a variety of markers of individual difference in brain function (particularly in the dopamine system, see **section 1.2.1**).

1.1.1 Relationship to other constructs: impulsivity and novelty-seeking

SS has previously been described as a component of *impulsive behaviour* (Whiteside and Lynam, 2001). However, analysis of both cross-sectional and longitudinal samples has demonstrated that the two constructs are somewhat distinct, as self-report scores exhibit divergent developmental trajectories

(Steinberg et al., 2008; Harden and Tucker-Drob, 2011; Collado et al., 2014). In addition, there are only modest or non-significant correlations between SS and (other) impulsivity scores in adults (Whiteside et al., 2005; Ersche et al., 2010; Harden and Tucker-Drob, 2011). For example, on the factor-analysis derived UPPS measure of impulsivity (which indexes Urgency, Premeditation, Perseverance and Sensation seeking), SS subscale scores do not correlate well with other impulsivity subscores in either healthy volunteer or patient samples (Whiteside and Lynam, 2001; Whiteside et al., 2005; Smith et al., 2007). Thus trait SS possesses the potential to provide separate explanatory capacity from other forms of impulsivity, e.g. with regard to propensity to develop psychopathological symptoms.

Novelty-seeking has been described as a key component of SS personality (Cloninger et al., 1993; Blanchard et al., 2009) – a fact often reflected in the structure of self-report SS measures (e.g. Arnett, 1994). Thus, scores on questionnaire measures of novelty-seeking and SS have been shown to be significantly correlated (Zuckerman and Cloninger, 1996), and, on self-report instruments at least, the degree of overlap between constructs may be significant. However, the two traits are somewhat conceptually distinct. In theory, high SS individuals may be motivated to continue to sample a particular high intensity sensory stimulus across repeated episodes of exposure, whereas in high novelty-seeking individuals this tendency may habituate over time (for relevant examples from the animal literature see Lloyd et al., 2012; Olsen and Winder, 2012). This distinction may be relevant to different behavioural models of SS in the animal literature (see **section 1.2**), and is one reason why analogous behavioural

paradigms are needed in order to dissect out different aspects of sensation-seeking personality in humans.

1.2 Operational measures of sensation-seeking in animals

In animal models, sensation-seeking trait has mainly been operationalized in terms of extent and vigour of interaction with novel objects or environments. For example, on one of the oldest measures, the hole-board test, the animal is placed in a novel environment, on a board with several viewing apertures or holes. The frequency of 'head-dip' responses below the surface of the board is then interpreted as an index of exploratory tendency or novelty-seeking (Boissier and Simon, 1962; Boissier et al., 1964). It should be noted that in the animal literature, the terms novelty and sensation-seeking are often used somewhat interchangeably, although as noted in the previous section there are at least subtle distinctions between the two behaviours.

Three of the most commonly-used approaches to operationalising SS trait in animals (primarily in rodent models) are outlined below and in **Figure 1**.

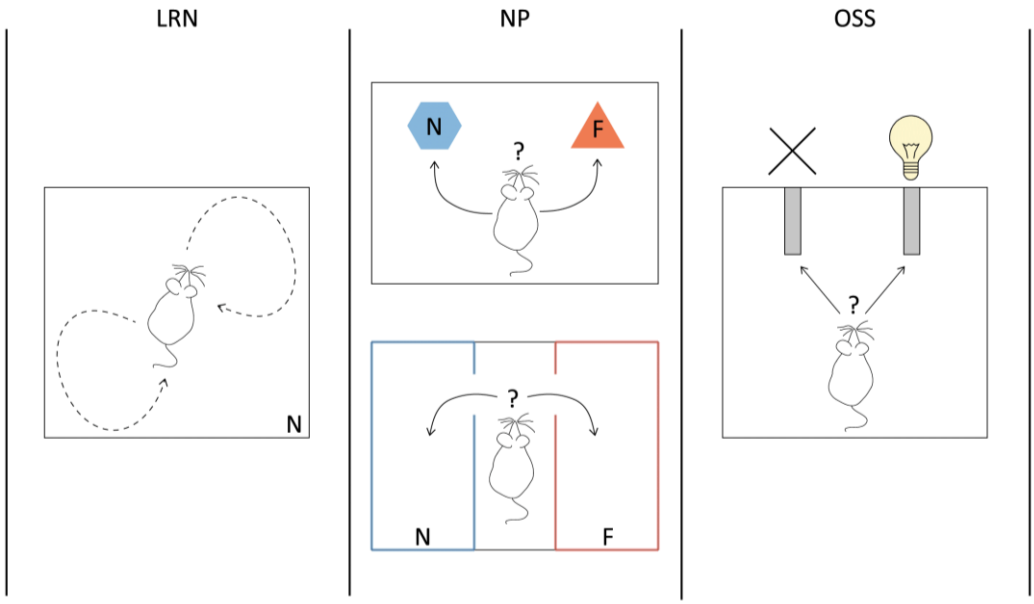

Figure 1 Three commonly-used behavioural measures of 'sensation-seeking' in rodents.

1) Locomotor response to novelty (LRN): general exploratory motor activity exhibited when an animal is placed in a novel environment for a set period of time.

2) Novelty preference (NP): commonly-used choice measures of novelty preference include novel object preference (relative time spent exploring a novel object in preference to a familiar one), and novelty-induced place preference (relative preference for a novel over a previously familiarised environment).

3) The operant sensation-seeking (OSS) paradigm: animals are presented with two operant levers: an 'active' lever, which results in the display of sensory stimuli (e.g. a light onset), and an 'inactive' lever, which has no consequences. The ratio of active:inactive lever presses measures the animal's relative preference for the sensory stimulus. N=novel; F=familiarised.

1.2.1 Locomotor reactivity to novelty (LRN)

Perhaps the most established animal model of SS is 'locomotor reactivity to novelty' (LRN), i.e. general exploratory motor activity exhibited when an animal is placed in a novel environment (Piazza et al., 1989; Dellu et al., 1996). This has been proposed as a model of SS as rodents classed as having 'high reactivity to novelty' (HR animals, usually classified as such on the basis of median split of group scores) show several similarities to human high sensation-seekers (for a review see Blanchard et al., 2009). Specifically, they demonstrate increased sensitivity to the activating and rewarding effects of psychostimulant drugs, which might relate to common factors involving the dopamine D2 system function (see **section 1.2.2**).

However it is debatable how well this measure maps onto human trait SS, at least in terms of face validity. In particular, although part of the original definition of the phenotype, it is often not empirically demonstrated in studies utilising the LRN model that increased 'locomotor reactivity' is specific to novel contexts. Thus it is somewhat unclear in these studies the extent to which HR grouping may be driven by general locomotor activity levels. A further concern is that LRN can also be viewed to some extent as simply the inverse of rodent models of 'anxiety'. The latter is commonly indexed as time spent exploring exposed ('potentially threatening') areas on the open field test or elevated plus maze (environments to which the animal is often naïve). Thus, it is not surprising that HR rats show lower 'anxiety-like' behaviour on a variety of tests (Dellu et al., 1996; Kabbaj et al., 2000).

1.2.2 Novelty preference (NP)

SS trait has also been operationalized in rodents in terms of measures of novelty-preference (NP). Most commonly this is indexed by novel object preference (relative time spent exploring a novel object in preference to a familiar one), and various forms of novelty-related environment preference (usually simple relative preference for a novel over a familiarised space; Bardo et al., 1996; Cain et al., 2005; Belin et al., 2011; Belin and Deroche-Gamonet, 2012). It has been argued that *choice*-based measures of response to novelty may represent better models of SS than simple locomotor activity in an (unescapably) novel environment, on the basis that novelty is viewed in the rodent literature as activating contradictory approach-avoidance motivational systems (see **section 1.2.3**) (Bardo et al., 1996). Thus, active approach of the novel option may constitute a better rodent model of the higher risk or intensity-preference exhibited by human higher sensation-seekers than simple locomotor response to a novel environment (Deroche-Gamonet and Piazza, 2014).

1.2.3 Operant sensation-seeking (OSS)

A range of animals have been observed to work to receive purely sensory rewards – in the absence of association (or history of association) with any other primary reinforcer (Stewart, 1960; Kish, 1966; Blatter and Schultz, 2006; Olsen and Winder, 2009). In the 'operant sensation-seeking' (OSS) paradigm (Olsen and Winder, 2009), animals are presented with a choice between two operant levers:

one, termed the 'active' lever, which results in the display of sensory stimuli (often a simple light onset, but sometimes a more complex audiovisual stimulus), and one which has no consequences (the 'inactive' lever). The key dependent variable is the animal's relative preference for the stimulus-producing lever (i.e. ratio of active:inactive lever presses; although sometimes the somewhat less valid measure of total active lever presses is reported).

OSS behaviour has been shown, at least in some hands, to be fairly robust: persisting over extended sessions, in extinction (when the sensory reward is no longer presented) and on demanding schedules where a progressively increasing number of responses are required to gain a single presentation of the sensory stimulus (Olsen and Winder, 2009). Thus, despite evidence that response rate on the active lever is positively related to variation in (or novelty content of) the sensory stimulus (Olsen and Winder, 2012), it is unlikely that behaviour on this task can be explained purely by appetitive responses to 'novelty' alone. Although currently less extensively explored, this paradigm may have the most face validity with respect to the human trait of SS.

The three behavioural measures discussed above have been inconsistently inter-related. Specifically, LRN may be associated with total lever responses on OSS paradigm (i.e. general levels of responding), but not with specific responses for the active (sensory-associated) lever (Olsen and Winder, 2009; Gancarz et al., 2012a, 2012b). While some studies have found that HR rats show greater

preference for a novel environment (Dellu et al., 1996; Marusich et al., 2011), others find no relationship between LRN and indices of novel object preference (e.g. Bardo et al., 1996; Cain et al., 2005). This suggests that these different behavioural operationalisations of SS trait may depend upon at least partially different neurobiological systems. Furthermore, this might be reflected in differential relationship of these indices to different aspects of drug-related behaviour (see **section 1.3.1**).

1.2 Role of dopamine in individual differences in trait sensation-seeking

1.2.1 Evidence from studies in humans

Almost all data relating SS trait to neurotransmitter systems in humans concerns the dopamine system. Specifically, evidence from genetic and PET radioligand displacement studies suggests that individuals higher in SS personality may exhibit both higher endogenous dopamine (DA) levels and greater dopaminergic responses to cues of upcoming reward in striatal regions (Zuckerman, 1985; Riccardi et al., 2006; Derringer et al., 2010; Gjedde et al., 2010; O'Sullivan et al., 2011).

Higher sensation-seekers have been reported to show lower platelet levels and carry lower activity isoforms of monoamine oxidase (MAO), an enzyme responsible for the breakdown of DA (Zuckerman, 1985; Carrasco et al., 1999; Verdejo-García et al., 2013). They also exhibit relatively higher activity of dopa

decarboxylase (DDC, a rate-limiting enzyme for DA synthesis) in the striatum, both via variation in the *DDC* gene itself (Derringer et al., 2010) and the Taq1a polymorphism (Ratsma et al., 2001; Eisenberg et al., 2007; Laakso et al., 2005). Thus, it might be expected that higher SS individuals have greater overall DAergic tone, particularly in striatal regions.

Individuals higher in SS trait also show increased physiological and subjective responses to dopaminergic stimulants such as amphetamine (Hutchison et al., 1999; Kelly et al., 2006; Stoops et al., 2007). This also holds for drugs which may not directly target the DA system, such as oxycodone, diazepam and alcohol (Kelly et al., 2006; Fillmore et al., 2009; Zacny, 2010; Scott and Corbin, 2014). However, this may be the result of a final common pathway for these substances which results in increased DA levels in the ventral striatum (Pierce and Kumaresan, 2006). Further, self-reported SS score correlates positively with both amphetamine-induced DA release in the striatum (Leyton et al., 2002; Riccardi et al., 2006), and the magnitude of dopaminergic response to cues of forthcoming rewards (O'Sullivan et al., 2011).

SS trait has also been linked to variation in function in the D2 class of dopamine receptors (D2, D3, and D4 receptors) (Eisenberg et al., 2007; Hamidovic et al., 2009; Campbell et al., 2010). Gjedde and colleagues have recently argued on the basis of the above findings and PET evidence that higher sensation-seekers have lower D2/D3 receptor 'availability' due to higher endogenous DA levels than their high SS counterparts. Thus, they argue that the 'gain' (reactivity to the presence of dopamine) of the D2 system in the striatum might be inversely

related to SS score (Gjedde et al., 2010). Specifically, this hypothesis would predict greater amplification of the postsynaptic signalling cascade following DA binding in higher gain lower sensation-seekers, and a lower sensitivity post-binding cascade (due to higher tonic levels of synaptic DA) in lower gain higher sensation-seekers.

1.2.2 Evidence from animal models

Data from the animal literature also supports the involvement of both a hyper-responsive striatal DA system and variation in D2-type receptor function in individual differences in SS-like behaviour. Performance on all three animal models of SS described in **section 1.2** are sensitive to manipulation of brain DA function.

For example, rodents with higher than average locomotor reactivity to novelty (HR animals) have been shown to exhibit increased DA levels in the ventral striatum and a higher overall basal firing rate of midbrain DA neurones, in addition to decreased concentrations of D2 receptors overall in the striatum (Blanchard et al., 2009). Selectively bred HR animals also have lower nucleus accumbens D2 mRNA levels than selectively bred low responders, and show a greater frequency of spontaneous dopaminergic transient currents in this brain region (Flagel et al., 2010).

A different line of research has revealed that disruption of the dopamine transporter (DAT) *Dat1* gene attenuates novelty-related behaviour in mice (Pogorelov et al., 2005). High novelty-preferring rats may have reduced DAT affinity for DA (Marusich et al., 2011), and therefore increased synaptic DA levels, due to decreased efficiency of synaptic DA clearance (Jones et al., 1998). In male minipigs, higher novel object exploration has been associated with greater dopaminergic response to amphetamine in the striatum, as measured using [^{11}C]raclopride PET (Lind et al., 2005). Further, the D2 receptor antagonist haloperidol produces a dose-dependent attenuation of novelty-preference in free choice tests in rats (Bardo et al., 1989). D4 receptor knock-out mice exhibit reduced exploration of novel objects (Dulawa et al., 1999), and the association between individual differences in novelty-seeking and D4 receptor polymorphisms previously observed in humans (Munafò et al., 2008) has recently been replicated in non-human primates (Bailey et al., 2007).

On the OSS paradigm, amphetamine injections to the ventral striatum increase relative responses on the active (sensory stimulus-associated) lever in a dose-dependent manner, an effect reduced by pre-application of the D2/D3 receptor antagonist sulpiride (Shin et al., 2010). Mutant mice with disrupted function in particular dopamine D1 receptor-containing neurones fail to develop a preference for the active lever when it is associated with sensory reward, whilst ability to develop preference for a food reward remains intact (Olsen and Winder, 2009). By contrast, mice receiving low systemic doses of the DA antagonist flupenthixol (a mixed D1 and D2-type receptor antagonist) show *increased* responding on the active lever, an effect the authors argue is consistent with

decreased sensory reward efficacy under these conditions (Olsen and Winder, 2009).

The evidence presented above suggests that there may be at least partially shared neural pathways regulating behaviour across these three paradigms. In support of this interpretation, a mouse model with targeted inactivation of excitatory glutamate receptors in DA receptor-expressing neurones showed reduced instrumental responses on the OSS paradigm, reduced locomotor activity when placed in a novel environment, and decreased interaction with a novel object compared to control animals (Parkitna et al., 2013). Importantly, there were no detectable behavioural deficits or abnormal learning abilities, suggesting these effects were not due to some generalised deficit.

1.2.3 Do individual differences in dopaminergic approach-avoidance tendencies contribute to individual differences in trait sensation-seeking?

It has been proposed that the core basis for individual differences in trait SS is the differential activation of *approach* versus *withdrawal* mechanisms in response to novel and intense stimuli (Zuckerman, 1990; Lang et al., 2005) (**Figure 2**). A candidate neural mechanism for this difference is variation in efficacy of striatal DA transmission, a pathway thought to be involved in the *vigour* of approach-type behaviours (Salamone and Correa, 2002; Robbins and Everitt, 2007; Ikemoto, 2007; Hoffmann and Nicola, 2014).

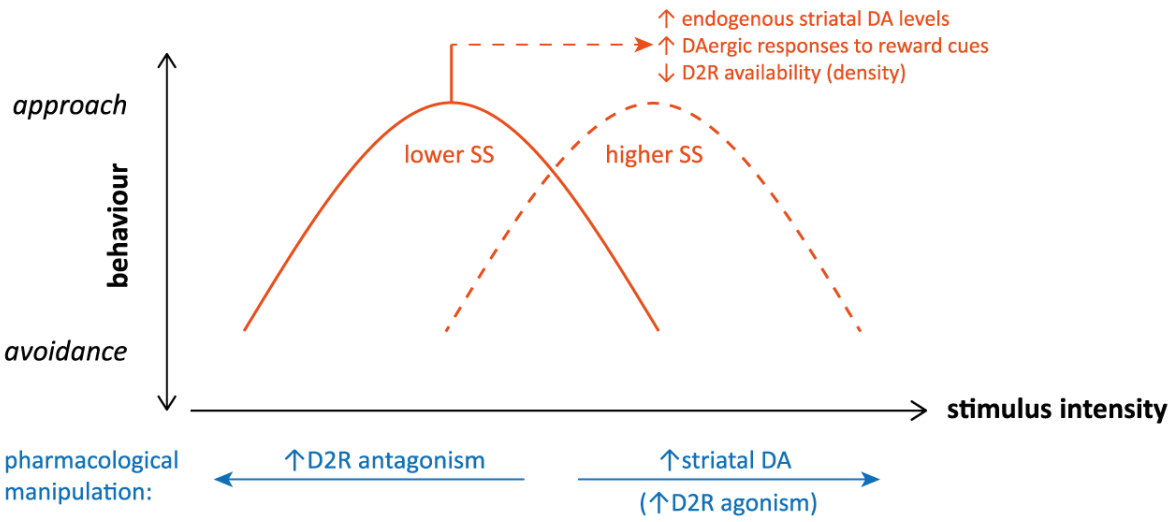

Figure 2. Schematic of how differential activation of approach-avoidance tendencies in lower and higher sensation-seekers (SSs) may result in opposite behavioural reactions to the same intensity sensory stimulus.

For example; a stimulus of an intensity that excites peak approach reactions in a lower sensation-seeker may be insufficient to elicit such a reaction in a higher sensation-seeker; whereas a stimulus of an intensity that elicits peak approach behaviour in higher SSs may be aversive and evoke an avoidance response in lower SSs.

Higher SS trait is associated with differences in striatal dopamine (DA) function (*orange text*). Behavioural measures of SS preference are also affected by drugs which affect synaptic dopamine levels (e.g. amphetamine) or that target D2-type (D2/D3/D4) dopamine receptors (e.g. sulpiride), which are prevalent in the striatum (*blue text*). D2Rs = D2-type dopamine receptors.

In favour of this hypothesis, there is some evidence to suggest that high sensation-seekers may show both increased appetitive responses and reduced defensive reactions to intense sensory stimuli (Lissek and Powers, 2003; De Pascalis et al., 2007; Freeman and Beer, 2010). For example, human high sensation-seekers have a greater response to intense auditory stimuli on EEG measures (Brocke et al., 1999) and prefer both positive and negative affective stimuli to neutral ones, regardless of valence (Zaleski, 1984). Conversely, low SS individuals exhibit greater affective startle potentiation, including during anticipation of aversive stimuli (Lissek and Powers, 2003; Lissek et al., 2005). In the animal literature, rats selectively bred over many generations for low *vs* high expression of avoidance behaviour on the shuttlebox paradigm (RHA and RLA strains) also express marked differences in sensation-seeking-like behaviours (such as novelty-preference and reactivity to drug rewards; Giorgi et al., 2007).

As outlined in the previous section, evidence from a variety of sources implicates individual variation in striatal dopamine function (particularly at D2-type receptors) in differences in SS personality in both humans and animals. Inconsequential, non-novel, but 'intense' or otherwise physically salient sensory stimuli have been shown to evoke robust responses in midbrain DA neurons in a variety of animal models (Freeman and Bunney, 1987; Horvitz, 2000; Schultz, 2010). Indeed it has been argued that dopaminergic transmission in the ventral striatum may govern the vigour of approach-type behaviours in response to salient stimuli (Robbins and Everitt, 2007; Ikemoto, 2007). Individual differences in the efficacy of dopaminergic neurotransmission in this pathway might

therefore contribute to interindividual variation in responsivity to these kinds of salient stimuli, constituting a quantitative trait of novelty or intensity preference.

Using this conceptual framework, it can be proposed that inappropriately high activation of *approach* tendencies towards intense stimuli may result in adverse outcomes, particularly where the 'intensity' of such experiences is inextricably bound up with or indeed derived from a risk of physical danger or damage to health. Conversely, inappropriately high activation of *avoidance* tendencies may hamper the ability to engage with potentially advantageous novel environments or experiences, and result in over-expression of anxiety-like responses to such stimuli. In the next section we consider the relationship of individual differences in trait SS to health and psychopathology.

1.3 Role of sensation-seeking trait in general health outcomes and psychopathology

Links have been established in healthy individuals between high trait SS and increased engagement in various 'health risk' behaviours that may endanger the self or others (Roberti, 2004; Arnett, 1994; Zuckerman, 1994; Hoyle et al., 2000; Charnigo et al., 2013; Oshri et al., 2013). Specifically, SS scores exhibit medium effect sizes for predicting alcohol consumption and medium-to-high effect sizes for illicit substance use, across many studies (for reviews and meta-analyses see Roberti, 2004; Hittner and Swickert, 2006; Perry et al., 2011; Stautz and Cooper, 2013), including in non-Western cultures (e.g. Huang et al., 2013).

Higher SS score is also associated with greater likelihood of regular smoking (Ersche et al., 2010; Doran et al., 2013), and increased rates of nonmedical use of prescription stimulants (Lookatch et al., 2012). Further, self-reported SS has been associated with increased frequency of risky driving or sexual practices (Arnett, 1994; Jonah, 1997; Charnigo et al., 2013; Oshri et al., 2013), as well as increases in antisocial behaviour, shop-lifting, and truancy during adolescence (Harden et al., 2012). However, it should be noted high SS score is also associated with increased incidence of 'pro-social' risk-taking among professions such as fire fighters, police, and bomb disposal experts, (e.g. Gomà-i-Freixanet, 1995) (see **section 1.3.3**). Finally, high trait SS has been also been specifically identified as a vulnerability factor for a variety of psychopathologies that have been associated with changes in brain DA function, in particular substance and gambling addictions.

1.3.1 High sensation-seeking and substance use disorders

High SS scores have consistently been identified in people with diagnoses of substance use disorders (individuals with compulsive drug use, persisting in the face of recurrent adverse consequences, American Psychiatric Association, 1994), across several classes of drug – including alcohol, psychostimulants, and opiates (Kosten et al., 1994; Franques et al., 2003; Whiteside et al., 2005; Ersche et al., 2010; Adams et al., 2012). In particular, convincing data from longitudinal studies has shown that high trait SS in adolescence predicts risk for substance

use disorders later in life, especially for alcohol and tobacco (Crawford et al., 2003; Sargent et al., 2010).

Although there has been some debate about the primacy of SS in risk for *pathological* substance use (Ersche et al., 2010) (e.g. heightened SS scores also occur in non-addicted recreational drug users, Ersche et al., 2013), it is likely that SS trait has at least moderate clinical relevance for drug-addicted populations. Among individuals with a diagnosis of substance use disorder, higher SS score is associated with earlier age of onset, increased polysubstance use, more severe functional impairment, poorer overall treatment outcome, and more greatly impaired decision-making (Kosten et al., 1994; Ball et al., 1994; Staiger et al., 2007; Noël et al., 2011; Lackner et al., 2013; Patkar et al., 2004). Similarly, high SS trait may relate to increased risk for substance misuse problems comorbid in other psychopathological populations (Fornaro et al., 2013). For example, amongst individuals with a diagnosis of unipolar or bipolar depression, high sensation seekers are more likely to be poorly compliant to prescribed medications or become demanding for drugs with perceived mood-elevating properties (Ekselius et al., 2000; Liraud and Verdoux, 2001; Åkerblad et al., 2008).

Interestingly, attempts to tease out the role of trait SS in addiction using animal models have revealed different relationships to aspects of substance addiction psychopathology, depending on the particular model of SS employed. Specifically, recent studies in rodents report that heightened *novelty preference* is associated with increased motivation to work for stimulant drug infusions, increased

likelihood of progression to 'compulsive' drug use, and higher scores for 'addiction-like' behaviour (operationalized DSM-IV criteria for substance addiction, over several different measures), but not initial acquisition of drug self-administration behaviour (Belin et al., 2011; Molander et al., 2011; Peña et al., 2014).

Conversely, increased *locomotor reactivity* to a novel environment has been associated with increased initial sensitivity to drugs (both ease of initiation of self-administration and range of dose supporting self-administered, Piazza et al., 1989; Blanchard et al., 2009) – but not with progression to an addiction-like state (Belin et al., 2008). Thus, LRN has been linked to initial propensity to try out drugs of abuse, but not predisposition to 'addiction' *per se*, and *vice versa* for choice measures of novelty-preference (Belin and Deroche-Gamonet, 2012). Interestingly, it has recently been reported that preference for an environment established via pairing with cocaine administration (cocaine-induced conditioned place preference), which is subsequently allowed to extinguish in the absence of drug, is selectively reinstated after a priming dose of cocaine in high novelty-preferring mice (Montagud-Romero et al., 2014) – possibly representing an increased risk of relapse in these animals.

The operant sensation-seeking (OSS) model has thus far been less well studied with respect to addiction vulnerability. Manipulations that fairly selectively affect OSS behaviour also affect drug self-administration, whilst leaving intact measures of learning and performance on operant tasks where food is the rewarding outcome. These findings, some have argued, suggest a common neural

substrate of sensory and drug rewards (Olsen and Winder, 2009; Olsen et al., 2010; Parkitna et al., 2013). In one recent study, mice with targeted inactivation of metabolic glutamate (mGluR5) receptors on D1 receptor-expressing neurons showed normal anxiety-like behaviour and learning abilities, but decreased SS-like behaviour on OSS, LRN *and* NP indices. Unlike control animals, these low SS mice did not escalate alcohol intake after enforced absence, perhaps indicating decreased risk of relapse upon drug re-exposure (Parkitna et al., 2013).

What underlies these findings? As described above, both human self-report and animal models of SS have been linked to variation in D2-type receptor function. In particular high trait SS has often been associated with low striatal D2 receptor 'availability' – due to increased endogenous DA levels, lower receptor density, or some combination of both these factors. In healthy humans, both high trait SS and low striatal D2 receptor availability have been linked to greater *'liking'* of stimulant drug effects (Kelly et al., 2006; Volkow et al., 1999). This may therefore explain the increased likelihood of initial drug use or experimentation in high sensation-seekers, as paralleled by increased ease of acquisition of drug self-administration in by HR animals on the LRN model of SS.

Low striatal D2 receptor availability has consistently also been found in both individuals with *pathological* or compulsive substance use (including in withdrawal; Volkow et al., 1993, 2002), and in animals who exhibit elevated cocaine self-administration (Caine et al., 2002; Nader et al., 2006), and thus has been proposed as a vulnerability marker for progression to addiction. In human studies it is usually unclear due to methodological limitations how much this may

be a cause and how much it may be an effect of drug use (Neale et al., 2006). Indeed, it is likely a combination of both (Simon et al., 2007; Caprioli et al., 2013; Jentsch et al., 2014).

Regarding evidence implicating high SS trait in *severity* of psychopathology in people with substance use disorders, one possible explanation is that these findings are all a legacy of earlier onset of drug use (Nees et al., 2012), i.e. during a period of heightened sensitivity to direct effects of substances of abuse on brain chemistry (Suri et al., 2015). For example, it has been found that rates of adult alcohol dependence can be reduced by 10% for each year that drinking is delayed in adolescence (Grant et al., 2001). Intriguingly, a recent study in mice found that binge-like cocaine administration during adolescence induced a higher sensitivity to rewarding effects of both cocaine and MDMA (ecstasy) selectively in high novelty-seeking animals (Mateos-Garcia et al., 2015). This finding suggests the existence of some kind of interactive effect between the sensitive period of adolescence and trait novelty and/or sensation-seeking.

However, there may also be a role for heightened trait SS in increased susceptibility to progression from initial experimentation to *compulsive* substance use. In support of this, the animal evidence discussed above suggests a role of high SS trait (modelled as novelty preference across several different behavioural paradigms) in progression from sporadic use to an addiction-like phenotype. Furthermore, as we have seen, evidence from NP and OSS models of SS also implicates a possible role of high trait SS in *susceptibility to relapse* – an integral feature of addiction psychopathology.

Thus it is likely that individual differences in SS play a significant role in disease progression (Jupp and Dalley, 2014), although further work needs to be conducted to extract out exactly which components are the best predictors of different aspects of disease progression. As drug addiction is a multi-stage and multi-faceted disease, associated with numerous distinct behavioural traits, it will be important for future research to identify which dimensions of sensation and/or novelty-seeking in humans are modelled in rodent paradigms that embody vulnerability markers for progression to and maintenance of the addicted state (Deroche-Gamonet and Piazza, 2014). This will be aided by development of similar operationalized paradigms for humans, which would be more directly comparable to animal findings than existing self-report measures.

1.3.2 High sensation-seeking and pathological gambling

High SS is often cited as a risk factor for pathological gambling (PG; e.g. Roberti, 2004), however, there are surprisingly inconsistent findings regarding the role of heightened SS in pathologically disordered gambling behaviour (Hammelstein, 2004). Laboratory studies have found medium to high effect sizes for SS scores on gambling and risky decision-making in healthy individuals, particularly when studied in more naturalistic settings such as mock or real casinos (Anderson and Brown, 1984; Roberti, 2004; Ashrafioun et al., 2012). High SS individuals may also be more likely to engage in gambling activities in the real world (McDaniel and Zuckerman, 2003). Several studies report significantly higher SS scores in

samples of pathological gamblers compared with controls (Blanco et al., 1996; Whiteside et al., 2005; Fortune and Goodie, 2009; Hodgins et al., 2012), however others have found either a non-specific relationship (Grall-Bronnec et al., 2011) or no difference in SS score between problem gamblers and healthy controls (Michalczuk et al., 2011; Clark et al., 2012; Lorains et al., 2014). This inconsistency may be due to heterogeneity within PG populations. Indeed there is some evidence that the role of heightened SS in PG may depend on the particular form of gambling engaged with (Coventry and Brown, 1993), with high SS trait evident only in a subset of individuals with PG behaviour (Carver and McCarty, 2013).

While there are links between brain systems associated with trait SS, risky decision-making, and PG – again, with transmission via D2-type dopamine receptors being commonly implicated (Comings et al., 1996) – it is currently unclear exactly what the nature of this relationship is. For example, a recent study found that rats more prone to an 'irrational' choice bias when choosing between risky reward options had lower striatal D2/D3 receptor density (Cocker et al., 2012). However, no evidence has so far been found for differences in striatal D2 receptor density in samples of human pathological gamblers compared to controls (Clark et al., 2012; Boileau et al., 2013). Some authors have argued that the high comorbidity between substance use disorders and PG (Petry et al., 2005), in addition to evidence for common genetic factors (Slutske et al., 2000), implies that the two disorders have overlapping aetiologies (Clark and Dagher, 2014). It is possible that the role of trait SS in PG may be less clear than that observed in substance addiction due to a lack of involvement of substances of

abuse that actively target brain systems that are associated with SS trait (Clark et al., 2013).

The relationship between high trait SS and vulnerability to develop behavioural addictions may be more evident in disorders where prodopaminergic (predominantly D2 agonist) therapies have been linked to development of *de novo* compulsive behaviours. These are most commonly PG but also include compulsive shopping, hypersexual behaviour, and addiction to dopaminergic medication; collectively known as impulsive control disorders or ICDs (American Psychiatric Association, 1994). This has been observed clinically in a variety of disorders treated with DA agonists (e.g. prolactinoma and restless legs syndrome), but has been most well studied in individuals with Parkinson's disease (PD), a disorder involving progressive loss of dopaminergic neurones (Weintraub et al., 2010; Claassen et al., 2011; Dang et al., 2011; Djamshidian et al., 2011; Martinkova et al., 2011).

PD patients have previously been reported to show relatively low self-reported SS scores (Evans et al., 2006; Poletti and Bonuccelli, 2012). Some researchers have developed this finding into the notion of the 'pre-Parkinsonian personality': a prodromal period of altered brain DA function, prior to the onset of signature motor symptoms, where individuals exhibit lowered sensation-seeking personality (Evans et al., 2006). However, PD patients with ICDs may exhibit *heightened* impulsivity and novelty-seeking questionnaire scores, compared with non-ICD PD controls (Voon et al., 2007). Although to date almost all studies of this relationship have been cross-sectional in design, one intriguing longitudinal

study has shown evidence for decreased novelty-seeking in *de novo* PD, with *increased* novelty-seeking relative to healthy controls observed post commencement of pro-dopaminergic medication (Bódi et al., 2009).

These findings may relate to increased reactivity of striatal DA observed in PD patients with ICDs. For example, greater radioligand displacement (interpreted as greater endogenous DA release) has been reported during gambling in PD patients with a diagnosis of PG (Steeves et al., 2009). Further, self-reported SS score has been found to be significantly positively correlated with striatal DA release to reward cues in PD patients with ICDs (O'Sullivan et al., 2011). Similar to high SS healthy individuals, there is evidence of reduced D2/D3 receptor tracer binding in the ventral striatum of PD patients with a diagnosis of PG compared to PD controls (Steeves et al., 2009 although see also O'Sullivan et al., 2011). This may be due to greater endogenous striatal DA levels in PD patients who go on to develop PG, as these individuals exhibit both reduced binding of DA transporter ligands in the ventral striatum (Cilia et al., 2010; Voon et al., 2014) and reduced concentration of midbrain dopamine autoreceptors (Ray et al., 2012).

These studies have recently been interpreted as providing converging evidence that both heightened striatal DA tone and increased DAergic response to reward cues constitute the underlying vulnerability in PD patients who develop ICDs such as PG after undergoing dopamine agonist treatment (Clark and Dagher, 2014). Strikingly, this is the same neurobiological signature that has been reported across several studies to be associated with high SS personality in the normal population.

1.3.3 Is high sensation-seeking always a bad thing? Stress resiliency and the role of environment

Although so far we have presented evidence that high trait SS may be associated with increased levels of dysfunctional behaviour, there is also preliminary evidence that, under certain circumstances, high SS may be functionally useful.

From a developmental perspective, a general increase in SS in all individuals with onset of puberty (Steinberg et al., 2008; Harden and Tucker-Drob, 2011) has been hypothesized to underpin an enhanced capacity to approach high-arousal, novel, or uncertain situations. This would promote general exploration and other 'independence-building' behaviours, in addition to underlying increases in potentially dangerous behavioural choices (Crone and Dahl, 2012; Spielberg et al., 2014). Thus it has been suggested that one possible adaptive function for higher trait SS in both adolescence and adulthood is to serve as a 'stress-buffer', allowing individuals to explore challenging and unpredictable environments laden with unknown risks (Smith et al., 1992).

In support of this hypothesis, higher SS status has been associated in humans with a general decrease in the tendency to view the world as 'threatening' (Zuckerman, 1994). There is a negative correlation between both participants' estimated probabilities of negative outcomes and their ratings of various real-world activities as being either risky or dangerous (Franken et al., 1992), and higher sensation-seekers show heightened thresholds for threat detection when viewing faces morphed between neutral and angry expressions (Mujica-Parodi et

al., 2014). Further, threatening images evoke potentiation of startle responses in low, but not high, SS individuals (Lissek and Powers, 2003), and high sensation seekers display relatively decreased fear-potentiated startle to predictable aversive stimuli (Lissek et al., 2005). Animals inbred for low locomotor response to novelty also display enhanced anxiety-like behaviour on various measures (Stead et al., 2006; although see **section 1.2.1** for a discussion of why this is perhaps somewhat unsurprising).

In support of a role of higher SS in coping with extreme stress in humans, several studies have reported that higher SS ex-prisoners of war report fewer symptoms of post-traumatic stress disorder (PTSD), and less severe psychiatric symptomatology in general, than low SS individuals (Solomon et al., 1995; Neria et al., 2000). SS scores were also significantly lower in those with compared to without PTSD in a sample of individuals with substance use disorders (Weiss et al., 2013) and, under some circumstances, high SS status has been associated with higher physiological pain tolerance (Bender et al., 2012). Evidence from the LRN model supports the idea that this may be due to increased stress resilience in high SS individuals. For example, inbred low response to novelty (bLR or 'low SS') adult rats who have undergone maternal separation stress when young show exaggerated stress responses in adulthood, while inbred high responders (bHR or 'high SS') animals are unaffected (Clinton et al., 2014). Exposure to chronic mild stress has been shown to result in increases in 'anhedonic' and anxiety-like behaviours in bLR animals, whereas stress-exposed bHR rats resemble non-stressed control animals on these measures (Stedenfeld et al., 2011).

This increase in stress tolerance may relate to differences in midbrain dopamine and D2 receptor function in high SS individuals (Cabib and Puglisi-Allegra, 2012). Recent optogenetic studies have demonstrated a causal role for phasic firing of midbrain DA neurones in resilient *vs* susceptible phenotypes to repeated social defeat stress in mice (Chaudhury et al., 2013). Further, D2 receptor function has been implicated in successful resilience to chronic mild stress, in that changes in D2 receptor gene expression post stress-exposure have been shown to differentiate between stress-resilient and stress-reactive animals (Żurawek et al., 2013; Faron-Górecka et al., 2014).

In some cases, it is possible that higher SS status itself may represent an active adaptation to chronic stress exposure. Possession of the *Taq1a* A1 allele (associated with lower rates of DA catabolism) plus a history of high intensity stress exposure (sexual abuse or overly strict parental disciplinary style) has been found to result in significantly higher sensation and novelty-seeking scores in adulthood, including in a longitudinal study (Keltikangas-Järvinen et al., 2009; Groleau et al., 2012). Similarly, a recent longitudinal study found that an association between childhood sexual abuse and higher self-reported sensation-seeking score was moderated by *DRD4* (dopamine D4 receptor) genotype (Harden et al., 2015).

It is important to bear in mind that the environment plays a significant role in determining the form that SS behaviours may take. Families at higher socioeconomic levels may be able provide socially acceptable outlets such as adventure sports, travel and other stimulatory extra-curricular activities,

whereas in many low socioeconomic environments the only readily available means of intense sensory experience may be higher risk, criminal or antisocial (Farley, 1981). Recently, it has been argued that the expression of problematic behaviours associated with high trait SS is likely to depend on a complex interplay between environmental constraints (e.g. availability of satisfying behaviours), and other cognitive factors, such as impulse control (Hammelstein, 2004). Indeed, in animal models home-cage environmental enrichment decreases both rate of responding for unconditioned visual stimuli (OSS, Cain et al., 2006) and self-administration of amphetamine (Bardo et al., 2001; Green et al., 2002), an effect which may depend in part on changes to DAergic transmission (Zhu et al., 2005).

Intriguingly, self-reported SS has been found to be somewhat *positively* related to IQ in samples of high school and college students (Zuckerman, 1994). Although the mechanism underlying this relationship is unclear, it is possible that a positive correlation between SS score and working memory performance during adolescence (Romer et al., 2011) may be due to a common relationship with striatal DA function (Cools et al., 2008). It has also been reported in one longitudinal study that high 'stimulation-seeking' at age three predicts significantly higher IQ and school achievement at age 11 (Raine et al., 2002). The authors argue that this is the result of young stimulation-seekers creating enriched environments for themselves, that in turn stimulate further cognitive development.

1.4 Interim summary

Sensation-seeking is an intriguing trait, which appears to vary considerably across individuals in both humans and other animals. A growing body of evidence, reviewed above, has allowed us to start to understand some of the neurobiological differences underlying this variation. A combination of high dopaminergic tone and a hyper-reactive striatal DA system appear to be potentially important contributors to higher SS trait – as reflected in an increased tendency to exhibit approach reactions towards intense and novel stimuli that may elicit aversive reactions in others (Zuckerman, 1985, 1990; Blanchard et al., 2009; Derringer et al., 2010; Gjedde et al., 2010; Shin et al., 2010; Marusich et al., 2011).

This neurobiological signature may constitute a vulnerability to the development of addictions when 'revealed' by the addition of drugs which increase striatal DA levels, both in the case of recreational substances (which tend to have a final common pathway in increasing ventral striatal DA levels) and prescription drugs that directly target D2-type receptors (abundant in striatal regions). In other circumstances, the relative under-activation of avoidance or withdrawal reactions towards intense stimuli may serve a protective role, e.g. in coping with situations of acute stress, which may have relevance for anxiety disorders such as PTSD (Solomon et al., 1995; Neria et al., 2000; Clinton et al., 2014).

The exact contribution of trait SS to the aetiology of these disorders is often difficult to parse out in human studies, and will be aided by development of

analogous paradigms to the animal literature – a strategy which has previously proved fruitful with respect to increasing our understanding of other kinds of impulsive behaviour (Winstanley, 2011; Jupp and Dalley, 2014).

The aim of this thesis was, firstly, to develop such a paradigm, and, secondly, use the novel task to directly test the neurobiological model described above, via a combination of behavioural, psychopharmacological, and functional imaging methods. In a parallel set of studies, we also investigated the effects of dopaminergic agents on risky decision-making, in order to gain further clarity on the relationship between self-reported sensation-seeking personality, D2ergic transmission, and risk-taking behaviour.

Chapter 2 An operational measure of sensation-seeking in humans

2.1 Introduction

One influential theoretical account proposes that the core basis for individual differences in sensation-seeking is in the differential activation of approach-withdrawal mechanisms in response to novel and intense stimuli (Zuckerman, 1990, see main **Introduction**).

However, a previous lack of behavioural paradigms analogous to those in the preclinical literature has meant that it has not been possible to test the approach-avoidance hypothesis directly in humans. Development of such an approach has previously proved highly fruitful with respect to other facets of impulsivity (Winstanley, 2011; Jupp and Dalley, 2014).

Here, we first tested a novel instrumental test of human sensation-seeking-like behaviour that involved the opportunity to self-administer mild (but non-painful) electric stimulation (MES) during performance of an economic decision-making task. This task was designed to be analogous to a recent operant sensation-seeking paradigm developed for rodents (Olsen and Winder, 2009). We predicted that: 1) Individuals high in trait sensation-seeking would assign a positive economic value to the opportunity to experience such an 'intense and unusual' sensory stimulus; 2) This preference would be reflected in an approach-like speeded relative response time for these stimuli.

2.2 Methods

2.2.1 Participants

Forty-seven healthy participants (28 female), mean age 24.3 (SD 3.55), were recruited via internet advertisements (for further demographic information see **Table 1**). This sample size was chosen to allow us to detect a moderate-strength relationship between task performance and self-reported sensation-seeking trait, on the basis of previous findings that correlations between behavioural and questionnaire measures of other facets of impulsive behaviour are modest in strength (correlation coefficients up to 0.40; e.g. Helmers et al., 1995; Mitchell, 1999). An *a priori* power calculation determined that a sample size of 44 would be necessary to detect a correlation coefficient of 0.40, at a conventional power of 80% and alpha of 0.05.

Exclusion criteria consisted of any current or past neurological or psychiatric illness, or head injury. All participants provided written informed consent and the study was approved by the University College London ethics committee. Two participants failed to meet criteria for points learning during the initial (acquisition phase) of the task, and so their data were excluded, yielding a final *N* of 45.

N (female)	45 (28)
Age (years)	24.3 (3.55)
Years of education	16.1 (3.1)
SSS-V-R total score	261 (46)
(range)	(162-352)
Alcohol (drinks per week)	3.7 (4.5)
Tobacco (cigarettes per week)	4.1 (10.2)
Other drug use (*N*):	
None	30
Marijuana (ever)	8
Marijuana (regularly)	5
Stimulant use (ever)	2
Gambling behaviour (*N*):	
None	39
Several times per year	5
Several times per month	1
Weekly or more	0

Table 1. Demographic information for participants. SS=sensation-seeking; SSS-V-R=Sensation-Seeking Scale version V (Revised). Other demographic scores refer to behaviour over the last 12 months. Unless otherwise specified, figures represent mean (SD).

2.2.2 Sensation-Seeking Task

Participants completed a novel 'sensation-seeking task' designed to probe the precise economic value (positive or negative) they assigned to the opportunity to receive an 'intense' sensory stimulus (mild electric stimulation or MES). In the first part of the task (*acquisition* phase) they simply learnt the points values associated with various different abstract visual stimuli (**conditioned stimuli**, or **CSs**). Eight different fractals were used as CSs, with two of them assigned to each of four possible points values (25, 50, 75, or 100 points). In every trial, fractals were presented as pairs, restricted to consist of either adjacent or equal points value stimuli, yielding ten different trial types (**Figure 3**).

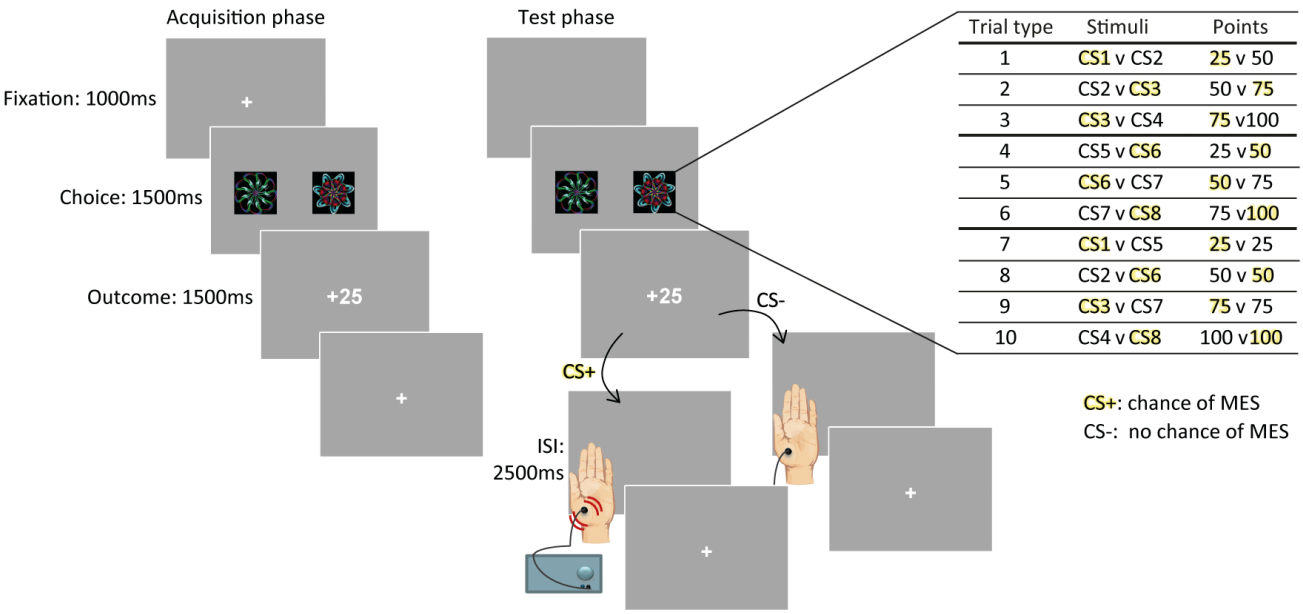

Figure 3. Novel 'sensation-seeking' task.

In the first part of the task (*acquisition phase*), participants were presented with a series of forced choice decisions between pairs of abstract fractal images. There were eight different fractal stimuli (conditioned stimuli, or CSs), with two different CSs assigned to each of four possible points values (25, 50, 75, or 100 points; with which choice option a particular fractal represented randomised for every participant). Choice pairs were restricted to consist of either adjacent or equal points value stimuli, yielding ten trial types. The acquisition phase of the task continued for a minimum of 80 trials until participants reached a criterion level of performance – namely 80% or above higher points value choices over the last ten trials where a higher points value choice was possible. After this learning stage was completed, participants progressed to the second part of the task (*test phase*).

For the test phase, participants were instructed that all stimuli were associated with the same points value as before, but that some of the stimuli were now associated with the *chance* of receiving a mild electric stimulus (MES) to their non-dominant hand (the magnitude of the MES was individually calibrated to be "stimulating but not painful" prior to starting the task). Specifically, half of the stimuli became designated as CS+s (*chance of MES*), and the other half CS-s (*no chance of MES*), in such a way that trials fell into one of three types: those where the CS+ was the lower points option, those where the CS+ was the higher points option, and, crucially, those where the CS+ and CS- stimuli were of equal points value. In order to increase the salience of the tactile stimulus, receipt of the electrical stimulation was probabilistic in both occurrence and timing. The probability of receiving the MES given selection of a CS+ stimulus was 0.75, with the onset of the MES occurring randomly during a 2500ms inter-stimulus interval (ISI), throughout which participants were presented with a blank screen.

The acquisition phase continued for a minimum of 80 trials until participants reached a criterion of choosing on 80% of trials the fractal associated with the higher points value, over the last ten trials where a higher points value choice was possible. After this learning stage was completed, participants progressed to the second part of the task (*test phase*).

In the test phase, half the choice stimuli became additionally associated with the *chance* of receiving non-painful, mild MES to the hand. These fractals will henceforth be referred to as **CS+** (for full details see **Figure 3**). The other fractals were not associated with electrical stimulation and so are referred to as **CS-**. For each points value, one of the associated fractals became **CS+** (*chance of MES*), while the other was **CS-** (*no chance of MES*). This yielded three types of trial: those where **CS+** was the lower points option, those where **CS+** was the higher points option, and, crucially, those where the **CS+** and **CS-** stimuli were of equal points value.

Participants thus continued to make choices between fractal pairs, with the only difference being that now half of the choice options were associated with the chance of receiving the MES – including, importantly, on trials where both fractals were of the same points value. The key experimental question was whether some participants' choices would be biased towards selecting the **CS+** stimuli, when it was of equal points value to, or even less than, the **CS-**. The degree of bias in participants' choice towards or away from **CS**+ stimuli, with respect to the relative points value of the **CS+** option, thus allowed precise calculation of the economic *value* (positive or negative) each participant assigned to the

opportunity to receive the additional intense sensory stimulus (see **section 2.2.5**).

Participants completed 100 test phase trials (ten per trial type), and were told they would be paid a cash bonus at the end which depended on the total number of points accrued. To increase the salience of the tactile stimulus, receipt of MES was probabilistic, in both occurrence and timing. The probability of receiving the MES given selection of a **CS+** stimulus was 0.75, with the onset of MES occurring randomly during a 2500ms inter-stimulus interval (ISI).

Prior to initiation of the task, participants rated their preference for each of the fractals to be used in the paradigm on a computerised VAS (ranging '*like*' – '*dislike*'). This measure was repeated for a second time following completion of the acquisition phase (i.e. after learning the points value associated with each CS), and for a third time at the end of the experiment (i.e. following introduction of the MESs).

2.2.3 Apparatus

Electrical stimulation was generated using a Digitimer DS7A constant current stimulator (Digitimer Ltd., Hertfordshire, UK), with output triggered remotely from a desktop computer using Matlab version R2011b (Mathworks, Inc., Sherborn, MA) via parallel port. Pulse duration was 2000μs, and the mean current amplitude was 2.9mA (SD 1.9, range 1.0-5.5mA). Stimulation was

delivered to participants via a pair of disposable Ag/AgCl EEG-EMG electrodes with 15x20mm self-adhesive pads (Spes Medica, Italy), attached approximately 1cm apart on the thenar eminence of the non-dominant hand.

2.2.4 Design

Following consent and standardised task instructions (see **Appendix 1**), the amplitude of the electrical stimulation was calibrated individually for each participant via a standardised work-up procedure. Specifically, participants received a series of single stimulation pulses, starting at a very low amplitude (0.5mA; generally reported by participants as being only just detectable) and gradually increasing in current strength until the stimulation was rated as 6 out of 10 on a visual analogue scale (VAS) ranging from 0 ('*just detectable*') to 10 ('*painful or unpleasant*') – a level at which participants endorsed a description of the sensation as being "stimulating but *not painful*". This procedure was repeated twice for each participant to ensure consistency.

After the task, participants completed the revised version of the Sensation-Seeking Scale form V (the SSS-V-R; Zuckerman, 1994; Gray and Wilson, 2007). The SSS-V-R is scored on a 7 point Likert scale ranging from 1 (completely disagree) to 7 (completely agree) and comprises of 61 items (for sample items see **section 1.1.1**), thus scores may range from 61 to 427. A measure of hedonic tone, the Snaith-Hamilton Anhedonia Scale (Snaith et al., 1995); and the trait scale of the State-Trait Anxiety Inventory (Spielberger et al., 1970) were also

collected. The latter two self-report measures were included in order to test the possibility that individual differences in MES preference may be related to trait anxiety or current state (an)hedonia rather than being driven by sensation-seeking personality *per se*. Demographic information regarding years of education, cigarette and alcohol consumption, recreational drug use, and frequency of engagement in gambling-related activities was also collected.

2.2.5 Computational modelling analysis

For test phase data, it was assumed that a choice between two **CSs**, A and B (where A is the **CS+** stimuli and B is the **CS-**), could be represented as:

$$V_A = R_A + \theta$$

$$V_B = R_B \qquad \textbf{(Equation 1)}$$

where

- R_X is the points value of stimulus X
- θ is the additional value (in points) assigned to the opportunity to receive the MES (positive or negative)
- V_X represents the overall value of each option.

This model was then fit across all test phase choice data from each participant via a sigmoidal choice (softmax) function:

$$P(\text{choose A}) = 1 / (1 + \exp(-\beta*(V_A-V_B))) \quad \textbf{(Equation 2)}$$

Values of the free parameters θ and β (the softmax temperature parameter, a measure of choice stochasticity) were fit to the data on a subject-by-subject basis using log likelihood maximisation.

Unless otherwise specified, all reported statistical tests were two-tailed, with an alpha of 0.05.

2.3 Results

2.3.1 Individual differences in preference for additional intense sensory stimulation

Overall, participants chose the MES-associated stimulus (**CS+**) on 20.4% (SD 17.6) of the trials where these represented the *lower points option*, 68.9% (24.8) of the trials where they were *the higher points option*, and 45.2% (19.9) of trials where **CS+** and **CS-** stimuli were *equal* in points value. There was a significant effect of trial type on proportionate choice of **CS+** stimuli ($F(2,88)=157.29$, $p<0.001$). Post-hoc *t*-tests revealed that overall participants chose the **CS+** option significantly less frequently on lower points trials than equal points trials, and significantly more often on higher points trials than equal points trials ($t_{44}=-11.997$, $p<0.001$; $t_{44}=-8.102$, $p<0.001$, respectively).

Importantly, there was substantial variation in preference for the MES-associated option on trials where **CS+** and **CS-** options were *equal* in points value. Mean proportionate choice of **CS+** stimuli ranged from 7.5% to 92.5% (relative **CS+** value of 0, **Figure 4A**). An estimate of significantly biased choice on these trials can be made by sampling the binomial distribution – for 40 trials and an alpha of 0.05 this threshold is approximately 26/40 (0.65) for significantly high choice and 13/40 (0.35) for significantly low choice. Based on these thresholds, 8/45 (or 18%) of participants chose a significantly high proportion of **CS+** stimuli – in other words, significantly sought the MES – and 13/45 (29%) of participants significantly avoided the **CS+** options.

Consistently high choice of MES-associated stimuli was observed in a subset of participants – even on trial types where the **CS+** was the *lower* points value option, i.e. involved sacrifice of economic value (relative **CS+** value of -25, **Figure 4A**).

In order to test whether participants' choice of the MES-associated stimuli varied significantly over the course of the task (i.e. whether preference changed with decreasing stimulus novelty), test phase trials were binned into four sections. A repeated-measures ANOVA with the within-subjects factor of time (four levels) found no evidence for a main effect of time-on-task on proportionate choice of **CS+** stimuli across all subjects (p>0.1). Overall choice of **CS+** stimuli was also unrelated to number of trials taken to reach criterion performance, or proportion of correct responses (higher points value choice on trials where this was possible) during the acquisition phase (p>0.1), suggesting that preference for

MES-associated stimuli was not associated with the learning of the points values during the first part of the task. MES preference was also not related to current amplitude (p>0.1).

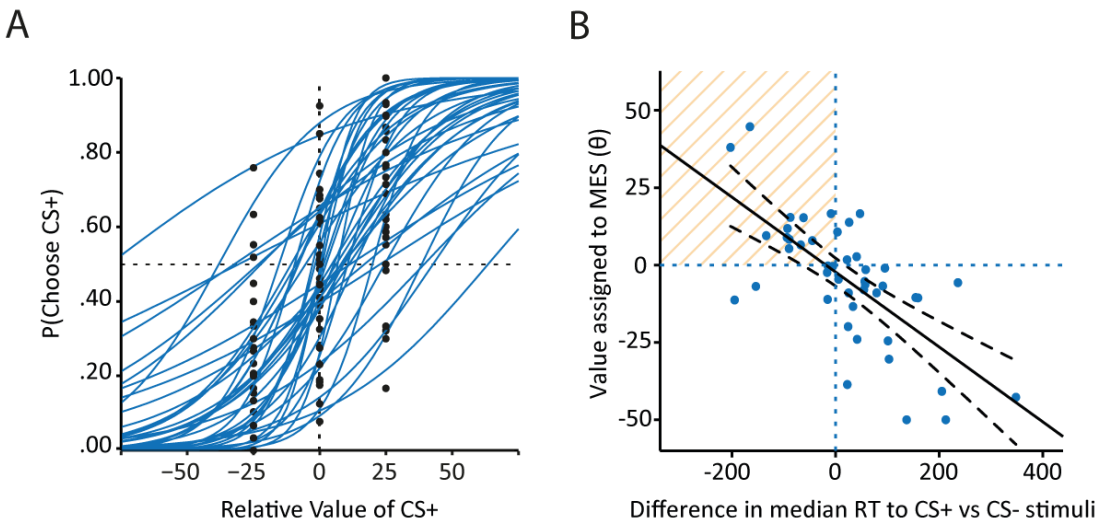

Figure 4. Interindividual variation in task performance.

A Individual psychometric functions for probability of choosing the CS+ (mild electric stimulation or MES-associated) option as a function of its relative points (monetary) value, generated for each participant from choice data across all trial types (black circles indicate actual proportionate choice for each trial type). The left/right translation of each function represents the influence of *MES value* (or θ) on choice, with the gradient of the function determined by the softmax temperature parameter β (a measure of the stochasticity of participants' choice). A *leftward* shift in the function reflects a *positive* effect of opportunity for intense tactile stimulation on choice – i.e. greater choice of the MES-associated options than would be expected from points-based choice alone.

B The value an individual assigned to the opportunity to receive the MES (θ) strongly predicted their difference in choice reaction times to CS+ vs CS- stimuli (median RT_{CS+} – median RT_{CS-}; r =-0.690, p<0.001). The opportunity for extra sensory stimulation *slowed* choice of these options in participants for whom it was *aversive* (low proportionate choice of the CS+; bottom right quadrant), but *speeded* choice in participants for whom it was *appetitive* (high choice of the CS+; top left quadrant, orange shading). Black dashed lines indicate 95% confidence intervals.

Figure 4A shows individual psychometric curves for probability of choosing the MES-associated option (**CS+**) as a function of its relative points (monetary) value, generated by fitting the model to choice data across all trial types for each participant. The computational modelling parameter describing the value (in points) that participants assigned to opportunity to receive the MES (θ) provided a good account of task performance, in that calculated values of θ were strongly associated with proportionate choice of the MES-associated option (**CS+**) on trials where the two options were equal in points value (r=0.894, p<0.001). This relationship held even when these type of trials were excluded from the dataset used to derive θ (r=0.799, p<0.001).

Bayesian model comparison was used to compare the overall likelihood of the simple model (SM) described above (where θ is unconstrained in value) to both a reduced model (RM) where participants chose purely according to the points values of the different stimuli (i.e. θ=0), and a stricter model (StrM), where the addition of the MES was only allowed to have a negative impact upon the value of the CS (i.e. θ≤0). Across all participants, the simple model including a MES value parameter provided a substantially better account of the data then the reduced model (points only choice), and a marginally better account than the stricter model where θ was constrained to be negative in value only (SM>RM: Bayes factor K = 27.9, strength of evidence "strong"; SM>StrM: K = 2.06, strength of evidence "anecdotal"; Jeffreys, 1961; Wetzels et al., 2011).

2.3.2 Relationship between economic value assigned to opportunity to receive intense sensory stimulation and reaction time for MES vs non MES-associated stimuli.

Individual θ values were strongly negatively correlated with difference in choice reaction time (RT) for **CS+** vs **CS-** stimuli (r=-0.690, p<0.001; **Figure 4B**). Specifically, participants who chose a greater proportion of MES-associated stimuli were faster to choose these stimuli (suggestive of *conditioned approach*). In contrast, participants who tended to avoid **CS+** stimuli were slower to choose them (suggestive of *conditioned suppression*) (Pearce, 1997). This was not a time-on-task effect (e.g. due to a tendency to decrease both mean reaction time and choice of the **CS+** over the course of the task) as this relationship remained strongly significant when considering trials from only the latter half of the test phase (first half of trials r=-0.692, second half of trials r=-0.625, both p<0.001).

2.3.3 Relationship between task performance and self-report measures.

Total scores on the SSS-V-R demonstrated excellent internal reliability (Cronbach's alpha=0.935). Individual θ values were significantly positively related to total self-reported sensation-seeking, such that participants who reported higher trait sensation-seeking assigned a greater value to opportunity to receive the mild electric stimulation (r=0.325, p=0.043; **Figure 5A**).

Theta value was unrelated to trait anxiety, self-reported hedonic tone, current amplitude, or years of education (all $p>0.1$). Non-parametric tests were used to relate task performance to self-reported alcohol and tobacco use, as these data were substantially positively skewed. Independent-samples median tests revealed that individuals who assigned a positive value to the opportunity to receive the MES (i.e. $\theta>0$, $N=17$) smoked significantly more cigarettes per week (Fisher's $p=0.006$) and showed a nonsignificant trend towards consuming more alcoholic drinks per week ($p=0.098$) than individuals who tended to avoid the MES (i.e. $\theta<0$, $N=28$) (mean cigarettes per week 6.7±10.4 *vs* 2.5±9.9; mean drinks per week 4.2±3.9 *vs* 3.4±4.9). There was no significant difference in mean θ value between individuals who did *vs* didn't ($N=15$ *vs* $N=30$, **Table 1**) report any recreational substance use other than alcohol or tobacco over the past 12 months (independent samples *t*-test, $p>0.1$). There was no difference in mean θ value between male and female participants (independent samples *t*-test, $p>0.1$).

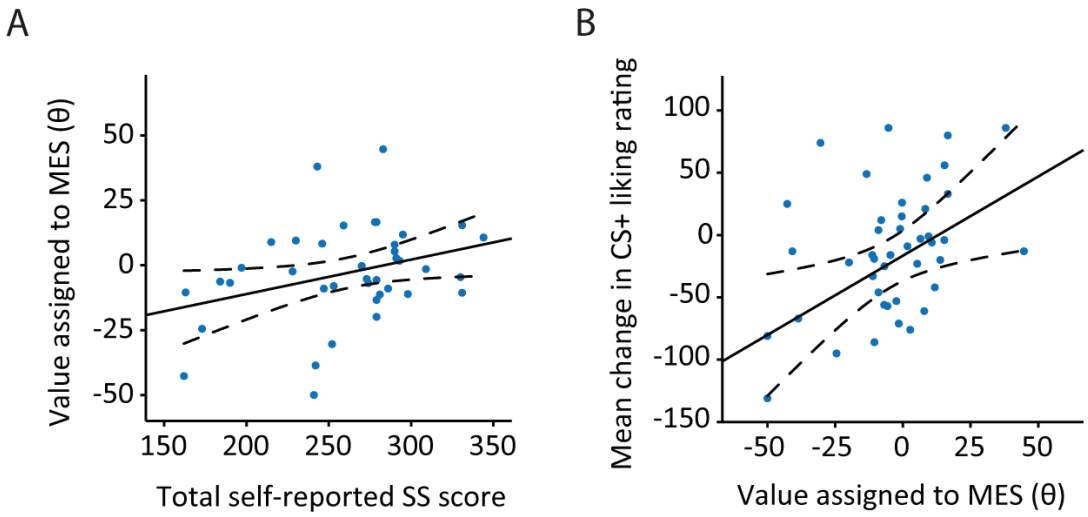

Figure 5. Relationship between task performance and self-report measures.

A Total self-reported sensation-seeking score was significantly positively related to the value participants assigned to opportunity to receive mild electric stimulation or MES (r=0.325, p<0.05).

B There was a positive relationship between value assigned to receipt of the intense sensory stimulation (θ) and mean change in VAS 'liking' rating of MES-associated (CS+) stimuli following the introduction of the additional electrical stimulation (r=0.368, p<0.05). Dashed lines indicate 95% confidence intervals.

MES value (θ) was also significantly positively related to mean change in VAS 'liking' rating for CS+ stimuli following introduction of the mild electric stimuli (i.e. between rating sessions 2 and 3; r=0.368, p=0.013; **Figure 5B**). Participants who assigned positive MES values tended to increase their liking rating of MES-associated stimuli, whilst participants with negative values tended to decrease their ratings.

Values of the model parameter indexing choice stochasticity (β; a measure of the extent to which participants' choice was influenced by the difference in value between the two options) were unrelated to both self-reported SS trait and θ values (p>0.1) – suggesting that higher sensation-seeking or MES-seeking individuals were not any less value-driven in their choice behaviour than their lower sensation-seeking counterparts.

2.4 Discussion

In this study, we examined how the opportunity to experience an intense sensory stimulus (mild electric stimulation, or MES) influenced behaviour during a simple economic decision-making task. Above chance choice of stimuli associated with intense tactile stimulation occurred reliably in some participants, even when this choice involved the sacrifice of monetary gain. This finding is consistent with the intense sensory stimulation being considered to be appetitive in these individuals. In support of this interpretation, participants who chose a greater proportion of MES-associated stimuli had higher self-reported sensation-seeking scores, increased their 'liking' ratings of these stimuli following the introduction of the MESs, and assigned a positive economic value to the opportunity to receive the additional sensory stimulation in a well-fitting computational model of task performance.

Importantly, there was a highly significant relationship between preference for the intense sensory stimulus and choice reaction times – consistent with the notion that the MES had motivational significance to participants. In both samples, participants who chose a greater proportion of MES-associated stimuli showed a relative speeding of their responses when choosing these stimuli, with the opposite effect observed in people who tended to avoid them. In conjunction with previous observations that individuals generally show speeded response times for appetitive stimuli, but are slower to approach aversive stimuli (Crockett et al., 2009; Wright et al., 2012), this suggests that the opportunity for intense

sensory stimulation influenced participants' choice via an approach–avoidance-like mechanism.

The results presented here are in line with broader background of evidence that indicates that whilst a particular stimulus may evoke an appetitive approach reaction in higher sensation-seekers, a stimulus of similar intensity may be aversive and elicit a withdrawal or avoidance-type reaction in lower sensation-seeking individuals. For example, sensation-seeking score has been found to be negatively correlated with rise in salivary cortisol level during a risk-taking task (Freeman & Beer, 2010), and high sensation-seekers showed both decreased sensitivity to punishment and increased sensitivity to rewarding outcomes, compared with a low sensation-seeking group, during a test of risky decision-making (Kruschwitz et al., 2012). Conversely, low sensation-seekers have been found to exhibit greater affective startle potentiation, particularly during anticipation of aversive stimuli (Lissek and Powers, 2003).

Both fMRI and EEG measures have also demonstrated different timescales and patterns of regional brain activity to high-arousal emotional or novel stimuli when participants are divided into low and high SS groups on the basis of self-report scores (Joseph et al., 2009; Zheng et al., 2011; Lawson et al., 2012), although the meaning of these differences is somewhat ambiguous. In consequence, these results provide the first direct evidence of approach-avoidance processes at play *during performance* of sensation-seeking behaviour in humans.

A potential neurobiological mechanism underlying our findings is in individual differences in brain dopamine function. Trait sensation-seeking has been related to variation in dopaminergic neurotransmission in both humans and animals, particularly in striatal regions (Hamidovic et al., 2009; Olsen and Winder, 2009; Gjedde et al., 2010; Shin et al., 2010). Inconsequential but 'intense' or physically salient sensory stimuli have been shown to evoke robust responses in midbrain dopamine neurones in a variety of animal models (Freeman & Bunney, 1987; Horvitz, 2000; Schultz, 2010), and it has been argued that dopaminergic transmission in the ventral striatum may govern the vigour of approach-type behaviours in response to salient stimuli (Robbins and Everitt, 2007; Ikemoto, 2007). Individual differences in the efficacy of dopaminergic neurotransmission in this pathway might therefore contribute to interindividual variation in responsivity to these kinds of salient stimuli, constituting a quantitative trait of novelty/intensity preference.

However, to date, there has been no way to test this hypothesis directly in humans. A strong advantage of our novel paradigm is that, unlike self-report based measures, it allows for direct comparison to causal investigations of sensation-seeking–like behaviour in preclinical models. An important direction for future work will therefore be to investigate whether behaviour on our task is similarly under the influence of striatal dopamine function (Olsen and Winder, 2009; Shin et al., 2010) (see **Chapter 3; Chapter 4**).

This study has some limitations. Firstly, as sensation-seeking behaviours in the real world can take many different forms, it might appear surprising that use of a

single, tactile sensory stimulus (mild electric stimulation) is able to sufficiently capture sensation-seeking behaviour in all individuals. However, our findings are consistent with a previous study reporting distinct physiological response profiles to mild electric shock in low and high self-reported sensation-seekers (De Pascalis et al., 2007). We would not seek to claim that performance on our task captures *all* of sensation-seeking personality, as this is a complex multidimensional trait, but it may tap operational sensation-seeking-like behaviour in at least a subset of high sensation-seeking individuals – thereby allowing us to probe underlying neural mechanisms in the laboratory (e.g. with pharmacological manipulations). In analogous fashion, there is some evidence that apparently dissimilar animal operationalisations of 'sensation-seeking' behaviour may tap at least partially overlapping neural circuitry (e.g. Parkitna et al., 2013).

Crucially, in both our studies choice of MES-associated stimuli was found to correlate selectively with total self-reported sensation-seeking scores, which probe multiple classes of sensation-seeking–type behaviours. Although this relationships was of only moderate strength, it should be noted that this finding is at the higher end of the range of those generally found between behavioural and questionnaire measures of impulsive behaviour (Helmers et al., 1995; Mitchell, 1999). We also found some evidence of greater recreational substance consumption amongst individuals who assigned a positive value towards opportunity to experience the MES, indicating that task performance may relate to real-life engagement in sensation-seeking behaviours. Our results are therefore consistent with a conceptualisation of SS in which a common drive for

intense or unusual sensory stimulation generalises across different sensory modalities, though this needs to be tested in future work.

In summary, the novel behavioural paradigm introduced here appears to tap a dimension of willingness to self-administer intense sensory stimulation. For participants who choose to approach rather than avoid this kind of stimulation, we propose that it is appetitive, or intrinsically rewarding. These findings constitute the first direct evidence of sensation-seeking behaviour being driven by an approach-avoidance-like mechanism in humans, and may aid investigation not only of the neural mechanisms underlying this core personality trait, but also various psychopathologies for which more extreme sensation-seeking scores constitute a risk or vulnerability factor.

Chapter 3 Dopamine regulates approach-avoidance in human sensation-seeking behaviour

3.1 Introduction

Investigations of animal models of sensation-seeking have implicated variation in striatal dopamine function – particularly at 'D2 type' (D2/D3/D4) dopamine receptors – as playing a pivotal role in mediating individual preferences for novel or sensory stimulation-inducing choice options (Bardo et al., 1996; Blanchard et al., 2009; Shin et al., 2010). As the efficacy of striatal dopaminergic transmission is considered to be involved in the vigour of approach behaviours in response to salient stimuli (Ikemoto, 2007; Robbins and Everitt, 2007), one theoretical account proposes that the core basis for individual differences in sensation-seeking is in the differential activation of dopaminergic approach-withdrawal mechanisms in response to novel and intense stimuli (Zuckerman, 1990).

Consistent with this view, genetic and PET evidence has implicated differences in function at D2-type receptors mediating individual differences in human sensation-seeking (e.g. Hamidovic et al., 2009; Gjedde et al., 2010). Previously, however, a lack of behavioural paradigms analogous to those in the preclinical literature has meant that it has not been possible to test the approach-avoidance hypothesis directly in humans.

Here, we used a double-blind, placebo-controlled, within-subjects design to investigate the effects of the D2 dopamine receptor antagonist haloperidol on performance of a novel operational measure of sensation-seeking in humans (see **Chapter 2**). We predicted that 'behavioural sensation-seeking' would be

disrupted by antagonism at D2 receptors, depending on baseline sensation-seeking performance (Norbury et al., 2013).

3.2 Methods

3.2.1 Participants

Participants were 30 healthy males, mean age 22.3 (SD 2.74; **Table 2**). Potential effects of haloperidol in female volunteers who might be pregnant precluded use of the drug in women in this study. Sample size (*N*=30) was based on the strength of the MES value/RT effect relationship we observed in **Chapter 2**. It was calculated that a sample of 29 participants should allow us to replicate (and detect any effects of haloperidol on) a true effect size of *r*=0.50, at a power of 80% and an alpha of 0.05. Exclusion criteria consisted of any current major illness, current or historic incident of psychiatric illness, and/or history of head injury. All subjects gave informed written consent and the study was approved by the University College London ethics committee.

One participant was unable to attend for a final test session and so their data were excluded from the analysis. A further participant failed to reach criterion level performance in the acquisition stage of the task on both test sessions, and so his data were also excluded, yielding a final *N* of 28.

N (female)	28 (0)
Age (years)	22.3 (2.74)
Raven's 12-APM score	9.1 (2.5)
UPPS SS score	23.2 (5.8)
(range)	(18-47)
Alcohol (drinks per week)	5.9 (8.7)
Tobacco (cigarettes per week)	8.4 (18.3)
Other drug use (*N*):	
None	18
Marijuana (ever)	5
Marijuana (regularly)	1
Stimulant use (ever)	4
Gambling behaviour (*N*):	
None	17
Several times per year	3
Several times per month	7
Weekly or more	1

Table 2. Demographic information for participants.

SS=sensation-seeking; Raven's 12-APM=Raven's Advanced Progressive Matrices non-verbal IQ test (12-item version); UPPS SS=UPPS impulsivity scale sensation-seeking subscale score. Other demographic scores refer to behaviour over the last 12 months. Unless otherwise specified, figures represent mean (SD).

3.2.2 Design

The study was carried out according to a within-subjects, double-blind, placebo-controlled design. On the first session, participants gave informed consent and completed the sensation-seeking task, in order to reduce the impact of any practice effects on performance across the subsequent two sessions (under placebo or drug). They then completed the UPPS impulsivity questionnaire (Whiteside and Lynam, 2001) which has subscales of sensation-seeking and three other factor analysis-derived impulsivity facets. This measure was chosen in order to evaluate the selectivity of the relationship between task performance and sensation-seeking, as compared to other kinds of impulsivity.

The sensation-seeking subscale of the UPPS is predominantly derived from items of the SSS-V, and therefore scores on the two measures intercorrelate highly (*ibid*). It includes SSS-V items referencing specific physical activities, such as "I would enjoy the sensation of skiing very fast down a high mountain slope/waterskiing/parachute jumping", as well as more general statements, such as "I generally seek new and exciting experiences and sensations". There are 12 sensation-seeking items, scored on a 4 point Likert scale (ranging agree strongly to disagree strongly), thus possible scores on this subscale range from 12-48. A standardised non-verbal measure of mental ability was also administered (Raven's 12-item Advanced Progressive Matrices; Pearson Education, 2010).

On the second and third sessions, participants arrived in the morning and were administered *either* 2.5mg haloperidol or a placebo (drug and placebo were

indistinguishable). A dose of 2.5mg haloperidol was chosen, in order to be greater than that given in a previous study where inconsistent drug effects were observed (2mg; Frank and O'Reilly, 2006), but less than that used in other behavioural studies where significant negative effects of haloperidol on mood or affect were detected (3mg; Zack and Poulos, 2007; Liem-Moolenaar et al., 2010). Testing commenced 2.5 hours after ingestion of the tablet, in order to allow drug plasma levels to reach maximum concentration (Midha et al., 1989; Nordström et al., 1992).

Following this uptake period, participants completed VAS measures of mood, affect, potential physical side effects and knowledge of the drug/placebo manipulation, and performed the sensation-seeking task described in **Chapter 2**. The Addiction Research Centre Inventory of psychoactive drug effects (ARCI; (Martin et al., 1971) was also administered, as this previously has been shown to be sensitive to haloperidol (Ramaekers et al., 1999). Participants further completed one of two equivalent forms of the letter-digit substitution test (LDST; van der Elst et al., 2006) – a simple pencil-and-paper test of general psychomotor and cognitive performance. Arterial heart rate and blood pressure were monitored pre and post-drug administration.

The sensation-seeking task was as described in **Chapter 2** (**section 2.2.2**). For this study, participants completed an additional set of VAS ratings at the end of the task to test learning of **CS+/CS-** (MES-associated *vs* non MES-associated) contingencies. For each **CS**, participants rated how strongly they believed choosing that stimulus had been associated or not with the chance of receiving

electrical stimulation ('*no chance of shock*' – '*chance of shock*'). The individualised work-up procedure was repeated on every session, to ensure that subjective intensity (as opposed to actual current amplitude) was matched across sessions. Drug/placebo order was counterbalanced across subjects, with a minimum of a one-week washout period between the two test sessions (the mean time between visits was 18 days).

3.2.3 Analysis

Computational modelling analysis of the sensation-seeking task was as described in **Chapter 2** (**section 2.2.5**). A repeated-measures ANOVA with the within-subjects factor of drug (haloperidol *vs* placebo), and the between-subjects factor of drug order (first *vs* second test session) was used to analyse key dependent variables from test session data. Specifically, these were participant-determined current amplitude, modelling parameters describing MES value (θ) and choice stochasticity (β), mean choice reaction time, and individual reaction time effect (median RT_{CS+} – median RT_{CS-}). All reported simple effects analyses are via pairwise comparison, with the Bonferroni adjustment for multiple comparisons.

Measures of general and subjective drug effects (VAS, ARCI, LDST scores and cardiovascular measures) were compared between test sessions via paired-sample *t*-tests. All reported statistical tests were two-tailed, with an alpha of 0.05.

3.3 Results

3.3.1 Replication of previous findings

The main findings from our previous study of behaviour on the novel sensation-seeking task (see **Chapter 2**; **section 2.3**) were replicated in the baseline session data from this study. Specifically, the model parameter representing value assigned to opportunity to receive the MES (θ) was significantly negatively correlated with difference in choice reaction time for CS+ *vs* CS- stimuli (median RT_{CS+} – median RT_{CS-}; r=-0.593, p=0.001; **Figure 6A**) and significantly positively correlated with self-reported sensation-seeking personality (UPPS sensation-seeking subscale score; r=0.376, p=0.048; **Figure 6B**; UPPS subscale scores demonstrated excellent internal reliability in this sample, Cronbach's alpha=0.925).

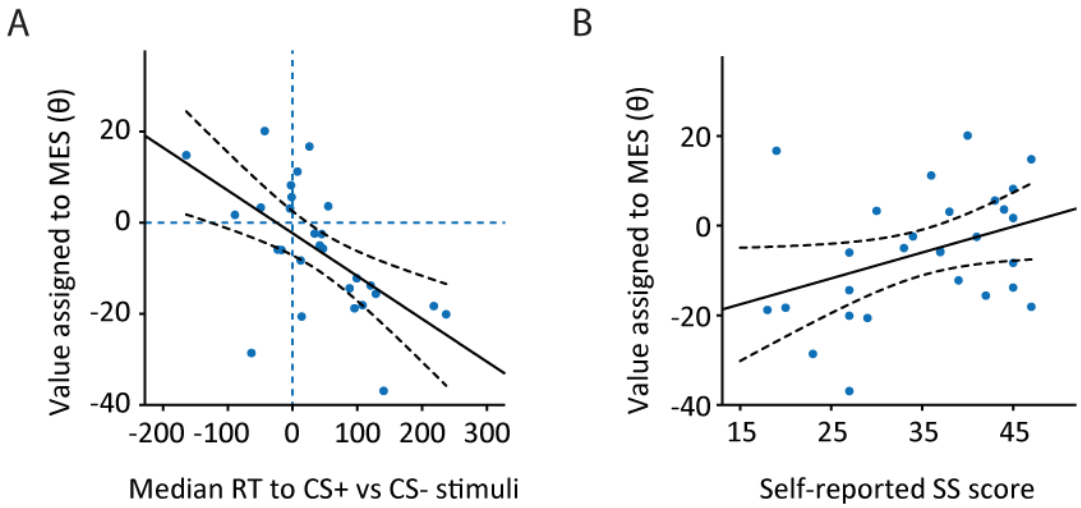

Figure 6. Baseline session data.

A Relationship between value assigned to opportunity to experience the mild electric shock or MES (θ) and individual difference in choice reaction time for MES-associated (CS+) *vs* non MES-associated (CS-) stimuli (r=-0.593, p=0.001).

B Relationship between value assigned to opportunity to experience the MES (θ) and self-reported sensation-seeking (SS) personality (UPPS SS subscale score; r=0.376, p=0.048). Dotted lines represent 95% confidence intervals.

3.3.2 Baseline-dependent effects of haloperidol on behavioural sensation-seeking

When considering data from the two test (drug/placebo) sessions, overall, participants again chose the shock-associated stimulus (**CS+**) significantly more often on *higher points* than *equal points* trials, and on *equal* compared with *lower* points trials, on both placebo and drug sessions (main effect of trial type; $F(2,54)=138.54$, $\eta_p^2=0.837$, $p<0.001$; difference between types all $p<0.001$; mean

(± SD) choice on placebo was 0.806 ± 0.19, 0.398 ± 0.17, 0.126 ± 0.13 respectively for these trial types; while on haloperidol 0.744 ± 0.19, 0.399 ± 0.15, 0.158 ± 0.15).

There were no significant overall effects of haloperidol treatment on current amplitude, points value assigned to the MES (θ), choice stochasticity (β), mean reaction time or relative reaction time for MES *vs* non MES-associated stimuli (all $p>0.1$). Drug order (active preparation on first *vs* second test session) was not a significant between-subjects factor for any of the dependent variables ($p>0.1$), and there was no overall drug*drug order interaction ($p>0.1$). Therefore drug order was discarded from the model for subsequent analyses, in order to maximise sensitivity.

The strong relationship between the points value participants assigned to receipt of the MES and relative choice reaction time for MES-associated *vs* non MES-associated stimuli observed in our previous study (**Chapter 2**; **section 2.3**) was replicated in the second sample under placebo conditions ($r=-0.602$, $p=0.001$), but, intriguingly, not under haloperidol ($r=-0.199$, $p>0.1$; **Figure 7**).

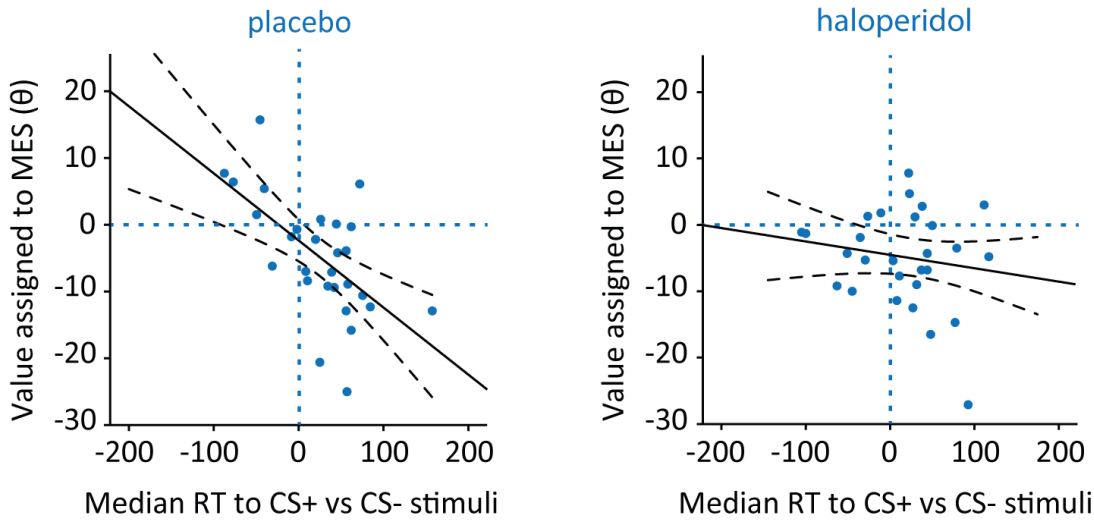

Figure 7. Effects of haloperidol on the value assigned to intense sensory stimulation (I). The value assigned to intense sensory stimulation (mild electric stimulation or MES) was significantly related to relative choice reaction time for MES *vs* non MES-associated stimuli on placebo (r=-0.602, p=0.001), but not under haloperidol (p>0.1; significant decrease in regression coefficient, p<0.05). Dashed lines indicate 95% confidence intervals.

A post-hoc analysis revealed that there was indeed a significant attenuation of this relationship under haloperidol (Fisher r-to-Z transformed Pearson-Filon test for decrease in correlation coefficient; Z=-1.735, p=0.041, one-tailed; Raghunathan et al., 1996). Thus, haloperidol treatment appeared to abolish the approach-avoidance effect, with respect to relative preference for the intense sensory stimulus. Similarly, although self-reported sensation-seeking score was significantly, and *selectively*, positively correlated with MES value (θ) on placebo

(r=0.391, p=0.040; all other UPPS impulsivity subscale scores unrelated to MES preference, p>0.1), this was not the case under haloperidol (r=-0.127, p>0.1; Steiger's Z for significant difference in correlation coefficient between drug conditions=2.25, p=0.024; Steiger, 1980).

Based on the above finding, in conjunction with our previous observation that the effects of a D2ergic drug may depend on baseline sensation-seeking (Norbury et al., 2013), a further analysis was conducted in order to check for baseline-dependent drug effects that may have been masked in the group-level analysis. In order to discover what was driving the attenuation of the RT effect under drug, participants were grouped according to whether they showed *conditioned approach* (speeded reaction time to **CS+** *vs* **CS-** stimuli, i.e. individual RT effect <0, N=8) or *conditioned suppression* (slowed RT to **CS+** *vs* **CS-** stimuli, i.e. individual RT effect >0, N=20) of their responses towards the intense sensory stimulation under placebo conditions.

When this 'approach' or 'avoid' grouping was added to the model as a between-subjects factor, there was a significant interaction between drug treatment and group on *value* assigned to the MES (significant drug*group interaction on θ value; $F(1,26)=10.64$, $\eta_p^2=0.290$, p=0.003; interaction with β p>0.1). Simple effects analysis revealed a significant *decrease* in MES value in the *approach* group on haloperidol *vs* placebo ($F(1,26)=7.97$, $\eta_p^2=0.235$, p=0.009). By contrast, there was no effect of drug on MES value in the avoidance group (p>0.1; **Figure 8**). Thus, haloperidol appeared to selectively attenuate MES value in individuals

who exhibited approach behaviour towards the intense sensory stimulus under nondrug conditions.

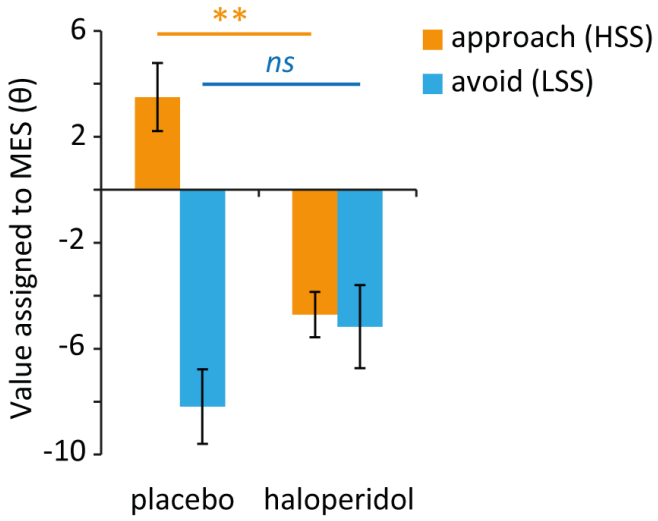

Figure 8. Effects of haloperidol on the value assigned to intense sensory stimulation (II). If subjects were divided into those who approached (showed speeded relative reaction times towards, *N*=8) and those who avoided (showed slowed relative reaction times towards, *N*=20) the opportunity for the intense sensory stimulation under placebo, there was found to be a significant interaction between sensation-seeking group and effect of drug ($p<0.01$). Haloperidol decreased the economic value assigned to the MES *only* in those participants who exhibited approach reactions towards MES-associated stimuli under normal conditions ('high sensation-seekers' or HSS; *cf* 'low sensation-seekers' or LSS). Error bars represent SEM. **$p=0.01$, *ns* $p>0.10$, drug vs placebo.

Approach and avoid groups did not differ in age, weight, estimated IQ or self-determined current intensity (independent samples *t*-tests, all $p>0.1$), but did differ in UPPS sensation-seeking score ($t_{26}=2.261$, $p=0.032$, significantly higher mean score in the 'approach' group; 40.9±8.1 *vs* 32.9±8.5). Similarly to in our previous study (**Chapter 2**; **section 2.3**), independent-samples median tests revealed that individuals in the approach group smoked significantly more cigarettes per week than the avoid group (Fisher's $p=0.022$), and showed a non-significant trend towards greater weekly alcohol consumption ($p=0.096$; mean cigarettes per week 20±25 *vs* 3.9±13; mean drinks per week 12±13 *vs* 3.5±3.9).

The effect of haloperidol on θ value (difference in value between drug and placebo sessions) was unrelated to age, weight, estimated IQ, drug effect on overall mood or alertness visual analogue scale VAS ratings, drug effect on the 'sedation' or 'dysphoria' scales of the Addiction Research Centre Inventory (ARCI), or drug effect on general psychomotor function (LDST score; all $p>0.1$). There was also no significant relationship between effect of drug on θ value and number of alcoholic drinks consumed or cigarettes smoked in an average week (Spearman's $\rho<0.25$, $p>0.1$). Subjects who had/hadn't ($N=10$ *vs* $N=18$, **Table 2**) engaged in any recreational drug use other than alcohol or tobacco over the last 12 months did not differ in the effect of haloperidol on θ value (independent samples *t*-test, $p>0.1$).

3.3.3 Subjective and general psychomotor drug effects

The above findings could not be explained by generic effects of drug treatment. Overall, there were no significant effects of haloperidol on VAS ratings of mood, affect, or potential physical side effects (16 scales, all $p>0.1$; for details see **Table 3**). There was also no effect of haloperidol on any ARCI subscale score (MBG 'euphoria', PCAG 'sedation', LSD 'dysphoric and psychotomimetic effects', BG and A 'stimulant-like effects' scales all $p>0.1$), or cardiovascular measures (blood pressure and heart rate, $p>0.1$). There was no effect of drug treatment upon participant ratings of whether they believed they were on the drug or placebo session ($p>0.1$). Finally, there was no effect of haloperidol on general psychomotor function as indexed by LDST performance ($p>0.1$).

	Placebo	Haloperidol	*p*
VAS ratings			
'Alert','Drowsy'	-162 (168)	-127 (203)	0.451
'Calm','Excited'	-179 (168)	-151 (165)	0.333
'Strong','Feeble'	-122 (165)	-139 (162)	0.668
'Clear-headed','Fuzzy'	-197 (162)	-146 (210)	0.228
'Well-coordinated','Clumsy'	-182 (159)	-132 (204)	0.225
'Tired','Energetic'	70 (143)	47 (206)	0.628
'Tense','Relaxed'	186 (134)	154 (149)	0.311
'Good mood','Bad mood'	-221 (130)	-181 (134)	0.243
'Withdrawn','Sociable'	97 (167)	90 (148)	0.848
'No headache','Headache'	-313 (140)	-272 (157)	0.252
'No stomach ache','Stomach ache'	-353 (104)	-328 (127)	0.333
'No nausea','Nauseous'	-358 (93)	-351 (82)	0.525
'No dizziness','Dizzy'	-306 (187)	-256 (202)	0.338
'Normal vision','Blurred vision'	-301 (184)	-297 (181)	0.925
'No muscle pain','Muscle pain'	-322 (147)	-320 (151)	0.950
'No muscle twitches','Muscle twitches'	-337 (134)	-359 (76)	0.235
'I think I'm on the drug','I think I'm on placebo'	135 (238)	91 (236)	0.571
ARCI			
MBG	4.4 (3.5)	4.6 (4.1)	0.839
PCAG	0.1 (3.2)	0.3 (3.0)	0.897
LSD	-1.3 (1.7)	-0.8 (2.0)	0.343
BG	-0.1 (2.3)	-0.3 (2.2)	0.696
A	2.5 (1.8)	2.4 (1.9)	0.776
LDST	43.4 (8.0)	43.9 (7.1)	0.605
Cardiovascular measures			
HR	65.9 (11.9)	69.2 (7.6)	0.961
BP (systolic)	120 (14.2)	120 (15.0)	0.352
BP (diastolic)	68.0 (12.9)	65.7 (11.0)	0.139

Table 3. Details of subjective and general measures of drug effects, on haloperidol *vs* placebo. *VAS* = visual analogue scale (rating on a linear scale ranging from -400 (first descriptor) to +400 (second descriptor), scales are based on Herbert et al., 1976 and potential side-effects of haloperidol); *ARCI* = Addiction Research Centre Inventory: *MBG* (morphinebenzedrine group, a measure of euphoria), *PCAG* (pentobarbital-chlorpromazine-alcohol group, a measure of sedation), *LSD* (lysergic acid dyethylamide scale, a measure of dysphoric and psychotomimetic changes), *BG* (benzedrine group, a stimulant-sensitive scale), *A* (amphetamine, an empirically-derived scale sensitive to the effects of d-amphetamine); *LDST* = Letter Digit Substitution Test (number of symbols transcribed in 60s); *HR*= heart rate; *BP*=blood pressure. Values represent mean (SD). *P* values reported are from paired samples *t*-tests, drug *vs* placebo session.

3.3.4 Effects of drug on learning

Finally, we examined the hypothesis that the observed effects of haloperidol could be due to differences in learning between drug and placebo sessions. We found no effect of haloperidol on number of trials required to reach criterion performance in the first phase of the task (p>0.1). Participants' mean 'shock knowledge' ratings for **CS+** and **CS-** stimuli (ratings on a VAS ranging from '*chance of shock*' (+300) to '*no chance of shock*' (-300)) were entered into a repeated-measures model with the within-subjects factors of drug (haloperidol *vs* placebo) and CS type (**CS+** *vs* **CS-**), revealing a significant main effect of CS type ($F(1,27)=74.56$, $\eta_p^2=0.734$, $p<0.001$; mean (± SEM) rating of **CS+** stimuli 146 ± 18.2, mean rating of **CS-** stimuli -150 ± 19.1), but no effect of drug treatment (p>0.1) or drug*CS type interaction (p>0.1) on explicit knowledge of MES

associations. When approach' *vs* 'avoid' group was added to the model as a between-subjects factor, there was no difference between groups in the effect of drug on shock knowledge ratings (drug*group, $p>0.1$), or the effect of drug depending on CS type (drug*CS type*group, $p=0.09$).

3.3.5 Paradigm reliability

In order to estimate the test-retest reliability of our paradigm, an intra-class correlation coefficient (ICC) was calculated for values of θ derived from baseline and placebo session data for each participant (as per Shrout and Fleiss, 1979; McGraw and Wong, 1996). This estimate can be considered as a lower bound on the consistency index of the paradigm, as there are salient differences between measurements in potential placebo (non-active product administration) and order (placebo taken on the second *vs* third session) effects.

Using a two-way mixed model testing for consistency across the two sessions, the ICC for the average of the two measures (baseline and placebo sessions) was found to be 0.435. An ICC>0.4 is generally considered to represent fair-to-good reliability (nearly half of measurement variance attributable to consensus score variation; Landis and Koch, 1977; Shrout, 1998). A second analysis investigated the concordance of θ values across drug and placebo test sessions within individuals who exhibited an 'avoidance' reaction-time effect to MES (mild electrical stimulus)-associated stimuli on the placebo session, i.e. those who did not show a significant effect of drug on θ value (**see section 3.3.2**). This revealed

an average ICC across sessions of 0.542, providing further evidence of the reliability of our novel approach to measuring sensation-seeking across test sessions.

3.4 Discussion

In this study, we examined how performance on our novel behavioural index of sensation-seeking was affected by administration of the D2 dopamine receptor antagonist haloperidol. On both baseline and placebo sessions we replicated our previous finding of a significant positive relationship between task performance (summary statistic representing value of the mild electric stimulation, θ) and self-reported sensation-seeking. On both drug-free sessions, there was also a strong relationship between preference for the intense sensory stimulus and relative choice reaction times – suggesting that the opportunity for intense sensory stimulation influenced participants' choice via an approach–avoidance-like mechanism (Crockett et al., 2009; Wright et al., 2012). Critically, this effect was not evident under the influence of a D2 receptor antagonist. This was due to a selective decrease in the economic value assigned to receipt of the intense sensory stimulus in participants who exhibited speeded relative reaction times towards (or displayed approach reactions to) the MES under placebo conditions (behavioural 'high sensation-seekers').

The results presented here are in line with broader background of evidence from both humans and animals that relates trait sensation-seeking to variation in dopaminergic neurotransmission, particularly in striatal regions (Hamidovic et al., 2009; Olsen and Winder, 2009; Shin et al., 2010; Gjedde et al., 2010; Norbury et al., 2013). A combination of evidence from genetic and PET radioligand displacement studies suggests that individuals higher in sensation-seeking personality may have both higher endogenous dopamine levels and greater

dopaminergic responses to cues of upcoming reward in the striatum (Riccardi et al., 2006; Gjedde et al., 2010; O'Sullivan et al., 2011). According to one influential model of the role of dopamine in striatal function (Frank, 2005), in the normal state this may contribute to increased inhibition of 'NoGo' (action inhibition) pathway neurons via increased stimulation of inhibitory post-synaptic D2 receptors. This in turn would result in greater overall thalamic disinhibition or 'Go' bias (favouring action expression) in high sensation-seekers – particularly in the presence of reward cues.

Haloperidol is a 'silent' D2 receptor antagonist (blocks endogenous dopamine signalling via D2 receptors; Cosi et al., 2006), and D2 antagonists have previously been shown to preferentially affect striatal function (Kuroki et al., 1999; Honey et al., 2003). Therefore, it is possible that under haloperidol the responses of higher sensation-seekers may be 'normalised' (increase in resemblance to lower sensation-seekers) by allowing increased 'NoGo' pathway output. This would explain our finding of a selective decrease in appetitive reactions to the intense sensory stimulation in the higher sensation-seeking ('approach' group) individuals.

Our finding of a significant effect of haloperidol on choice, in the absence of any influence on learning, is consistent with recent work suggesting that that D2 antagonists may have strong effects on choice of rewarding-predicting stimuli whilst leaving learning intact (Eisenegger et al., 2014). However, it is important to note that the putative mechanism suggested above assumes a predominantly post-synaptic effect of haloperidol (see Frank and O'Reilly, 2006). Despite our

attempt to ensure significant post-synaptic receptor binding by use of a greater dose than the previously cited study (where mixed pre- and post-synaptic D2ergic effects were thought to be observed), we can provide no direct evidence of this. Further, inferences regarding the brain regions involved in our findings are speculative and would need to be tested in further work, for example involving functional imaging.

This study has some limitations. As our main result is based on a significant decrease in value in one (previously higher mean value) subgroup, an alternative explanation of our findings is that this simply represents a regression to the mean effect. However, against this interpretation, we found evidence of fair-to-good reliability of θ values generated from the same participants across multiple sessions of our novel paradigm. Furthermore, the sub-grouping is based on individual difference in relative choice RTs rather than θ values per se (although the two are significantly correlated). We also used our estimate of RT effect from the second or third testing session (placebo session) to group participants – a strategy which has previously been argued to help guard against regression to the mean effects (Barnett et al., 2005). Taken together, we would contend that these factors argue against a purely trivial effect of haloperidol on MES value in the approach or 'high sensation-seeking' individuals.

Additionally, although haloperidol is considered to be a selective D2 receptor antagonist (it binds over 15 times more strongly to D2 than D1 receptors in rat and human cloned cells; (Arnt and Skarsfeldt, 1998), it has also been shown to have modest affinity for the α-1 adrenoreceptor and the serotonin 2A receptor in

post-mortem human brains (Richelson and Souder, 2000). Therefore we cannot be completely certain about the mechanism underlying our drug effects. However, as haloperidol has previously been reported to induce high levels of brain D2 receptor occupancy at relatively low oral doses (60–70% at 3 mg and 53%–74% at 2mg; Nordström et al., 1992, Kapur et al., 1997), we are confident that dose used in our study (2.5mg) was sufficient to antagonize central D2 receptors in our participants.

A further potential limitation is the possibility that the behavioural effects we observed are due to some general effect of haloperidol treatment, e.g. increased negative affect in some participants. However against this interpretation the effect of drug on MES value was unrelated to differences in mood, affect, sedation or dysphoria ratings, or our measure of general psychomotor function, between drug and placebo sessions.

In summary, here we have used a novel paradigm to demonstrate for the first time directly in humans that appetitive responses towards 'intense and unusual' sensory stimulation involve the dopamine D2 receptor system. These findings may aid investigation of various psychopathologies for which more extreme sensation-seeking scores constitute a vulnerability factor.

Chapter 4 The opportunity to experience intense sensory stimulation activates neural 'reward' circuitry in behaviourally-defined high sensation-seekers

4.1 Introduction

Previous studies have identified significant differences in regional brain activity between high and low self-reported sensation-seeking individuals during passive viewing of 'high arousal' and emotional stimuli (Joseph et al., 2009; Straube et al., 2010), reward anticipation (Abler et al., 2006), and risky choice (Freeman and Beer, 2010; Kruschwitz et al., 2012) – with differences in activity in the orbitofrontal cortex (OFC), ventral striatum (vS), and insula being commonly implicated.

These studies have been limited to investigating cognitive-behavioural processes *related* to sensation-seeking trait, due to a lack of paradigms interrogating sensation-seeking-like behaviour itself in the laboratory. In this study, we used our novel behavioural task of sensation-seeking, in conjunction with functional magnetic resonance imaging (fMRI), to probe individual differences in regional brain activity *during performance* of sensation-seeking behaviour.

This approach allowed us to address directly for the first time in human volunteers whether the opportunity to experience intense sensory stimulation activates brain regions that have come to be considered part of 'reward' circuitry (Haber and Knutson, 2009) in individuals for whom such stimulation appears to be appetitive. Specifically, we tested the hypothesis that choosing options associated with intense sensory stimulation (sensory reward) and higher economic value (monetary reward) would activate common neural circuitry,

selectively in individuals who sought out the intense sensory stimulus (in this case, mild electric stimulation, MES).

Based on studies cited above, in conjunction with previous work indicating a role for the vS and OFC/ventromedial prefrontal cortex (vmPFC) in representing the expected value of choice options (e.g. Knutson et al., 2001; Abler et al., 2006; Levy and Glimcher, 2012), we hypothesized that these regions may encode common responses to MES-associated stimuli and economic reward in behavioural *high sensation-seekers*.

Conversely, we hypothesized that behavioural *low sensation-seekers* may experience (anticipation of) the MES as more aversive and/or salient. Thus, we predicted that a brain region that has consistently been implicated in responding to aversive stimuli, the insula, would exhibit increased activity when choosing MES-associated options in these individuals (Büchel et al., 1998; Nitschke et al., 2006; Menon and Uddin, 2010).

4.2 Methods

4.2.1 Participants

Twenty-seven right-handed healthy participants (18 female), mean age 22.6 (SD 2.9), were recruited from a pool of volunteers who had completed the sensation-seeking task at an initial prescreening session (*N*=94, 60 female, mean age 22.8 ± 3.2), in order to ensure sufficient variation in task performance at the imaging stage. (For further demographic information see **Table 4**.) Exclusion criteria consisted of any current or past neurological or psychiatric illness, or head injury. All participants provided written informed consent and the study was approved by the University College London ethics committee. Data from one participant had to be discarded due to technical difficulties on the scan day, yielding a final *N* of 26.

N (female)	26 (17)
Age (years)	22.6 (2.9)
Raven's 12-APM score	9 (1.9)
SSS-V-R total score	286 (35)
(range)	(215–337)
Alcohol (drinks per week)	4.5 (5.8)
Tobacco (cigarettes per week)	3.4 (13.6)
Other drug use (*N*):	
None	21
Marijuana (ever)	2
Marijuana (regularly)	0
Stimulant use (ever)	3
Gambling behaviour (*N*):	
None	24
Several times per year	1
Several times per month	1
Weekly or more	0

Table 4. Demographic information for imaging study participants. SS=sensation-seeking; Raven's 12-APM=Raven's Advanced Progressive Matrices non-verbal IQ test (12-item version); SSS-V-R=Sensation-Seeking Scale version V (Revised). Other demographic scores refer to behaviour over the last 12 months. Unless otherwise specified, figures represent mean (SD) for each group.

4.2.2 Design

During the prescreening session, participants completed a baseline measure of the sensation-seeking task (as described in **Chapter 2**) and were screened for functional imaging counterindications. Volunteers then completed a range of self-report measures: the revised form of the Sensation-Seeking-Scale version V (SSS-V-R; Zuckerman, 1994; Gray and Wilson, 2007), the trait scale from the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970), and the sensitivity to sensory stimuli subscale of the Adult Sensory Questionnaire (ASQ; Kinnealey et al., 1994). Information about cigarette and alcohol consumption, recreational drug use, and frequency of engagement in gambling-related activities was also collected. Where appropriate (alcohol or recreational drug use >0), participants then completed the Alcohol Use Disorder Identification and Drug Abuse Screening Tests (Skinner, 1982; Saunders et al., 1993). Finally, a standardised measure of non-verbal IQ was administered (Raven's 12-item Advanced Progressive Matrices; Pearson Education, 2010).

Participants were then selected based on performance on the sensation-seeking task, in an attempt to achieve a balanced sample of high and low behavioural sensation-seekers for the imaging stage of the study. Additional exclusion criteria at this stage consisted of unsuitability for functional imaging (non-removable metal or claustrophobia), STAI trait score indicative of a current anxiety disorder, DAST score indicative of a past or present substance use disorder, or self-reported recreational drug use within the last month.

4.2.3 Sensation-seeking task

On the scan day, participants completed a slightly modified version of the sensation-seeking task, designed to minimise the amount of learning occurring during the scanning stage.

During a period of pre-scan training, participants first learnt the points values associated with each fractal image (CS). This was achieved using a more stringent version of the 'acquisition phase' of the sensation-seeking task (**Figure 3**, **Chapter 2**), whereby each CS was pitted against each other in a tournament design (each of eight CSs was pitted against each other four times, yielding 112 trials in total). Participants were also exposed to the CS-MES contingencies prior to entering the scanner. Specifically, they completed 10 of each 'equal points' trial type (inset, **Figure 3**), where one of each choice pair was associated with a chance of receiving the MES (P=0.75, the CS+), and the other was associated with no chance of receiving the MES (P=0, the CS-) (40 trials in total).

Participants further completed visual analogue scale (VAS) 'liking' ratings of each CS at three stages: prior to starting the task, after learning the CS-points value associations, and after exposure to the CS-MES contingencies (on a scale ranging '*like*' to '*dislike*'). As in **Chapter 2,** they also completed 'shock knowledge' ratings of each CS at the end of the pre-scan block, on a VAS ranging '*chance of shock*' to '*no chance of shock*'. Finally, they additionally rated how they felt about the MES *itself*, on a VAS ranging '*like*' to '*dislike*'.

Participants then proceeded to the in-scanner phase. Firstly, all individuals repeated the shock amplitude work-up procedure (see **Chapter 2, section 2.2.4**), in order to attempt to match subjective intensity of the mild electric stimulation across contexts and apparatus setups (see below). Once inside the scanner, participants completed three blocks of 100 test phase trials (all trial types, **Figure 3**). In order to increase the frequency of crucial 'equal points' trials inside the scanner, for each 100 trial block, they completed 13 of each type of equal points trial (52 trials total), and 8 of each type of unequal points trial (48 trials total).

4.2.4 Apparatus

Apparatus for the prescreen and pre-scanner testing was exactly as described in **Chapter 2** (**section 2.2.3**).

For the functional imaging stage, participants wore disposable, radiotranslucent, pre-gelled electrodes (Ag/AgCl laminated, carbon composition contact; Biopac Systems Inc., CA) on the thenar eminence of their left hand. Electrodes were attached to a Digitimer DS7A constant current stimulator (as before) via a radiotranslucent carbon fibre clip lead (Biopac). Stimulator output was controlled via optic fibre projection from a stimulus PC in the scanner control room. Visual stimuli were displayed via back projection on to a head-set mirror worn by participants inside the scanner. Visual stimulus presentation and MES delivery were controlled via Cogent2000 v1.30, run in Matlab.

4.2.5 Behavioural analysis

For the prescreening session, behavioural data were analysed using the model described in **Chapter 2** (**Equation 1**).

For the analysis of behaviour inside the scanner, a trial-by-trial model of task behaviour was also implemented, in order to regress model terms against trial-by-trial fluctuations in blood oxygenation level- dependent (BOLD) signal (see Pessiglione et al., 2006; Daw, 2011). Choice data from the pre-scan 'test' phase (first exposure to CS-MES pairings) were included in the model, in order to fully account for experience of CS-MES contingencies at the start of the first scanner trial. (Data from the pre-scan 'acquisition' (points learning) phase were not included, therefore it was assumed that points values of CSs were fully learnt by this stage.)

For the modelled data (pre-scan test phase and all in-scanner trials), it was assumed that the value of each CS (V_{CS}) on each trial (t) could be represented as:

$$V_{CS,t} = R_{CS} + SA_{CS,t} * \theta \qquad \textbf{(Equation 3)}$$

Where R_{CS} represents points value of each CS, θ again represents the additional value (positive or negative) participants assign to opportunity to receive the MES, and SA_{CS} represents modelled internal probability of receiving a shock, given choice of that CS (shock associative value of each CS) on each trial.

Following the outcome of trial *t*, the shock associative value of each CS (SA_{CS}) was updated according to the actual trial outcome (shock *vs* no shock received) and a simple Rescorla-Wagner learning rule:

$$SA_{CS,t+1} = SA_{CS,t} + \alpha(S - SA_{CS,t}) \quad \textbf{(Equation 4)}$$

Simply, after the outcome of each trial *t*, the shock associative value of the chosen CS is updated to new value, which is equal to the sum of the previous SA value for that CS ($SA_{CS,t}$), plus a prediction error term multiplied by a learning rate (α). The prediction error term represents the difference between the expected sensory outcome (previous probability estimate for receipt of the MES, given choice of that CS, i.e. $SA_{CS,t}$) and the actual sensory outcome (S; with a value of 1 for shock or 0 for no shock received).

This model was then fit across choice data from each participant via a sigmoidal link (softmax) function:

$$P(\text{choose CS+}) = 1 / (1 + \exp(-\beta*(V_{CS+} - V_{CS-}))) \quad \textbf{(Equation 2)}$$

Values of the free parameters (θ, α, and the softmax parameter β), were then estimated for each participant using maximum likelihood estimation (MLE). To decrease the likelihood of outliers, we implemented an additional stage of maximum a posteriori (MAP) likelihood estimation on parameter estimates (Daw, 2011). MAP represents a hierarchical Bayesian approach to parameter estimation, such that the group of parameter estimates derived at the first stage (MLE step) are subsequently used to estimate the true population distribution of

parameter values (in this case, assumed to be Gaussian). This distribution then becomes the prior likely distribution of parameters, for use in a second round of inference using maximum a posteriori.

Computational modelling of choice data was implemented in Matlab r2015a (Mathworks, Inc., Sherborn, MA), and used a sequential quadratic programming solver to infer the optimal parameters for each individual (Matlab function fmincon). Other statistical analyses were carried out in SPSS Statistics 19.0 (IBM Corp., Armonk, NY). Associations of model parameters with non-normally distributed self-report data were tested using non-parametric statistical tests. All reported statistical tests relating to behavioural performance and self-report variables were two-tailed, with an alpha of 0.05.

4.2.6 MRI data acquisition and analysis

4.2.6.1 Acquisition parameters

Functional imaging data were collected using a 3T Magnetom TIM Trio scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 32-channel head coil. To correct for inhomogeneities in the static magnetic field, field maps were first acquired using a double-echo FLASH (gradient echo) sequence (short TE=10ms, long TE=12.46ms, 64 x 2mm slices, 3x3mm^2 resolution). Three functional scanning sessions, consisting of six dummy volumes and 188 functional volumes were then acquired using a T2* weighted gradient echo-planar imaging (EPI)

sequence optimised for OFC signal (voxel size =3x3x3mm^3, volume repetition time =3.36s, echo time =30ms, matrix size =64x74, tilt=-30^0, Z-shim =1.4, slices per volume =48, whole brain coverage; Weiskopf et al., 2006). A T1-weighted MDEFT structural scan was also acquired at the end of the session (see Deichmann et al., 2004).

4.2.6.2 Preprocessing

MRI data were analysed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK), run in Matlab. The first six (dummy) volumes of each functional session were discarded to allow for T1 equilibration. Due to inhomogeneity in signal intensity associated with use of a 32-channel head coil and an OFC signal-optimising acquisition sequence, functional images were first bias-corrected for overall signal intensity. Specifically, intensity profiles were flattened across images with the bias correction procedure used by the Segmentation toolbox in SPM. Functional images were next realigned to the first functional volume of each session and unwarped using a field map created by the SPM FieldMap toolbox for phase correction. Where resulting movement plots indicated scan-to-scan translations greater than half a voxel (1.5mm), or rotations greater than 1^0, corresponding functional scans were manually checked for presence of any corrupting movement artefacts (no such artefacts were detected in our dataset). Subsequently, all functional images underwent correction for slice-timing acquisition (as per Sladky et al., 2011), using the Slice timing toolbox.

The MDEFT anatomical scan was coregistered to the mean unwarped functional image. All images were then reoriented manually to ensure that that the anterior commissure lay at coordinates [0,0,0]. Functional images were spatially normalized to the Montreal Neurological Institute (MNI) EPI template using 7th degree B-spline interpolation, then smoothed using a 4mm^3 full-width at half maximum (FWHM) Gaussian kernel. After estimating first-level models, the resulting contrast images were smoothed again using a 7mm FWHM kernel, so that the final images were smoothed to around 8mm.

4.2.6.3 Statistical analysis

For each participant, general linear models (GLMs) were used to model BOLD signal during performance of the sensation-seeking task, in an event-related manner. The first level models included the following regressors (and associated durations), convolved with the SPM synthetic hemodynamic response function:

(1) Categorical analysis. This analysis was carried out in order to examine differences in brain activity when choosing MES-associated and non MES-associated stimuli, in MES-seekers *vs* MES-avoiders. Each trial was modelled as a compound event during the decision period, time-locked to cue onset (duration 1.5s), with points value of the chosen CS, and whether a CS+ or CS- was chosen on each trial (+1 or -1, respectively) as parametric modulators. Additional regressors representing shock receipt (stick function with duration 0s at actual

time of shock delivery) and omission trials (if any, duration 1.5s from time of trial onset) were also added to the model.

(2) "Model-based" trial-by-trial analysis. This analysis was carried out in order to test the hypothesis that the trial-by-trial variation in the modelled internal probability or shock-associative value of CSs (SA_{CS}) would be coded in the same way as variation in economic value, selectively in behavioural high sensation-seekers. As in the 'model-free' analysis, each trial was modelled as a compound event during the decision period, time-locked trial to cue onset (duration 1.5s), with the points value of the chosen CS, and modelled shock associative value of the chosen CS as parametric modulators. Additional regressors representing shock receipt and omission trials were also added to the model as for the first analysis.

(3) "Model-based" sensory prediction error analysis. This third analysis was carried out in order to test the hypothesis is that sensory prediction errors (SPEs) should be oppositely signed in MES-seeking *vs* MES-avoiding individuals. Specifically, we wanted to test the idea that MES receipt (S=1) represents a *better than expected* outcome for high behavioural sensation-seekers, but *worse than expected* outcome for low sensation-seekers. Trials were therefore modelled with onsets at start of the ISI period (duration 2.5s), with parametric modulators of the points value just received, whether a CS+ or CS- was chosen, and the SPE for that trial, calculated according to **Equation 4** (i.e. $SPE_t = S - SA_{CS,t-1}$; where S is 1 when a shock was delivered and 0 otherwise, and $SA_{CS,t-1}$ is the shock associative value of the chosen CS at the time of choice). Additional regressors representing

shock receipt and omission trials were also added to the model as for the first analysis.

All analyses were corrected for serially correlated errors by fitting a first-order autoregressive process (AR(1)), and a high-pass filter (1/128s) was used to attenuate linear scanner drift in low frequency components. Six movement parameters generated during preprocessing (image realignment) were also included in each model as regressors of no interest.

First-level contrasts were created through linear combinations of the resulting beta images. These contrast images were analyzed at the group level with one-sample *t*-tests, with individual θ values added as a covariate (for the 'model-free' analysis, θ was calculated according to **Equation 1**; for 'trial-by-trial' and SPE analyses, θ was calculated according to **Equation 3**). A cluster-forming threshold of $p<0.001$ (uncorrected) was applied to statistical tests at the group level, followed by cluster-level family-wise error (FWE) correction at $p<0.05$. Small-volume correction (SVC) was used in *a priori* regions of interest (ROIs).

ROIs were chosen on the basis of previous functional imaging studies examining differences in neural processing between high and low self-reported sensation-seekers during decision-making and emotional processing tasks (Abler et al., 2006; Joseph et al., 2009; Freeman and Beer, 2010; Straube et al., 2010; Kruschwitz et al., 2012; see **Introduction**). The vmPFC ROI was defined using the MNI coordinates [x, y, z] and extent estimate generated from a metaanalysis of neural valuation processes (right: [4.27, 35.18, 11.82], left: [-7.29, 38, -10.57],

spheres with 12mm radii; Levy and Glimcher, 2012). The vS ROI was also defined using estimates from the functional imaging literature ('nucleus accumbens': [±9, 9, -8] plus 'ventral caudate': [±10, 15, 0], spheres with 6mm radii; as per Di Martino et al., 2008; Engelmann et al., 2015). The insula ROI was defined anatomically using the automated anatomical labelling (aal) atlas (Tzourio-Mazoyer et al., 2002) in the WFU PickAtlas toolbox (Wake Forest University School of Medicine, North Carolina, USA).

4.3 Results

4.3.1 Behavioural prescreen data

4.3.1.1 Replication of previous findings

Data from this sample (*N*=94) provided a further replication of the two key behavioural findings from previous studies. Specifically, there was a significant positive relationship between self-reported sensation-seeking personality (SSS-V-R total score) and the value assigned to opportunity to receive the MES (θ), with higher value in individuals with higher trait sensation-seeking (r=0.230, p=0.027; Cronbach's alpha for internal reliability of SSS-V-R total score was 0.873). There was also a significant negative relationship between θ value and relative reaction time for MES-associated *vs* non MES-associated stimuli (median RT_{CS+} – median RT_{CS-}), with individuals who assigned a higher value responding

faster for MES-associated stimuli, and individuals who assigned a lower value responding slower for MES-associated stimuli (r=-0.397, p<0.001).

We also replicated our finding from the first study (see **Chapter 2, section 2.3.3**) of a positive relationship between mean change in 'liking' rating of CS+s following introduction of the MES stimuli (r=0.222, p=0.032). Specifically, individuals who assigned a positive value to opportunity to receive the MES tended to increase their liking ratings of MES-associated CSs following introduction of the shocks, whereas individuals who assigned a negative value tended to decrease their liking ratings of these CSs following this stage. Finally, data from our new additional measure of how participants felt about the MES stimulation *itself* supported the idea that the MES was seemingly appetitive for some individuals, as there was a significant positive relationship between θ value and MES liking rating (r=0.264, p=0.010).

4.3.1.2 Relationship to other self-report measures

Estimated theta value was not found to correlate with age, estimated IQ, trait anxiety, or self-determined current amplitude of the MES (all p>0.1). There was a significant negative relationship between θ value and ASQ 'sensory sensitivity' ratings (r=-0.239, p=0.024): such that participants who assigned a higher value to opportunity to receive the MES tended to report lower levels of 'sensory sensitivity' (sensitivity to sounds/smells/lights/textures etc. which do not appear to bother other people).

There was no association between θ value and scores on the alcohol or drug abuse screening disorders tests (p>0.1). A non-significant positive trend was found towards an association between θ and self-reported number of alcoholic drinks consumed per week (Spearman's ρ=0.174, p=0.093). No association was found between θ value and self-reported tobacco consumption (p>0.1; although there was a low frequency of smoking overall in this sample).

4.3.2 Scan day behaviour

4.3.2.1 Pre-scan behaviour

Data from the prescan acquisition (points learning) phase (N=26) were entered into a repeated-measures ANOVA to test whether points value of the CSs (four levels; 25, 50, 75, and 100) was reflected in their overall proportionate choice. There was a significant main effect of points value on proportionate choice of CSs (F(3,75)=92.946, η_p^2=0.788, p<0.001), indicating participants were indeed aware of the points value of each CS. Simple effects analysis by pairwise comparison revealed a significant difference in choice between each respective points level (all p<0.001; **Figure 9A**). If behavioural sensation-seeking group (θ>0, N=8 *vs* θ<0, N=18) was included as a between-subjects factor in the model, there was no significant interaction between factors of sensation-seeking group and points value (p>0.1), suggesting that there was no difference in learning of CS-points associations (as expressed in terms of choice behaviour) between groups.

Learning of CS-MES association was next probed using a repeated measures model of 'shock knowledge' VAS ratings of each CS (ratings on a VAS ranging from '*no chance of shock*' [-300] to '*chance of shock*' [+300]). There was a significant difference in mean VAS ratings for CS+ (MES-associated) compared with CS- (non MES-associated) stimuli (significant main effect of CS type: $F(1,25)=24.202$, $\eta_p^2=0.492$, $p<0.001$; **Figure 9B**). Again there was no interaction between the factors of CS type and behavioural sensation-seeking group ($p>0.1$), suggesting that there was no difference in explicit knowledge about CS-MES associations between individuals who sought out *vs* individuals who tended to avoid MES-associated stimuli.

As with the prescreen session, we also examined whether there were associations between behavioural sensation-seeking and 'liking' ratings of both the CS and MES itself in the prescan data. Again, there was a significant positive association between change in VAS liking rating of MES-associated CSs following introduction of the mild electric shocks (a measure of *implicit* MES liking) and the value assigned to opportunity to receive the MES calculated from behavioural data (i.e. θ): with individuals who assigned a higher value tending to increase their liking rating, and individuals who assigned a lower value tending to decrease liking ratings ($r=0.489$, $p=0.011$; **Figure 9C**). There was no significant relationship between theta value and *explicit* MES 'liking' rating in this sample ($r=0.245$, $p>0.1$; although considering the strength of the significant relationship observed in the larger group, this may be underpowered).

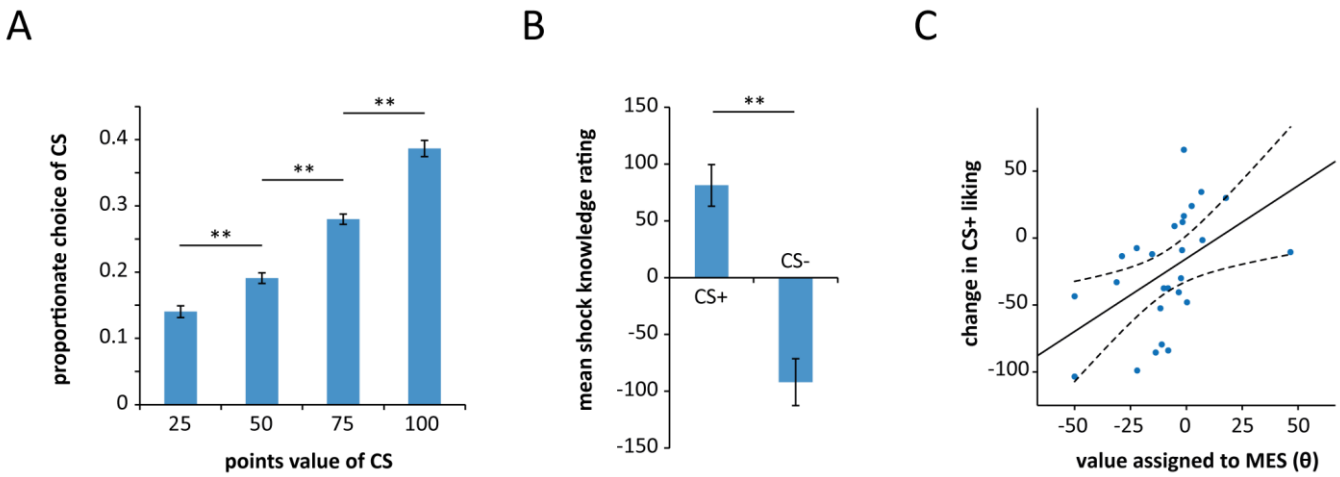

Figure 9. Summary of pre-scan training trials.

A Proportionate choice of conditioned stimuli (CSs) according to their points value, averaged across all acquisition phase (points learning) trials.

B Mean 'shock knowledge' ratings (ratings on a visual analogue scale (VAS) ranging from '*no chance of shock*' at -300 to '*chance of shock*' at +300) for CS+ (MES-associated) and CS- (non MES-associated) stimuli.

C Relationship between mean change in VAS 'liking' rating of CS+s following introduction of the mild electric stimuli (prior to entering the scanner), and MES value (θ) calculated from all scanner trials.

Error bars represent SEM, dotted lines represent 95% confidence intervals, N=26. **p<0.001

4.3.2.2 In-scanner behaviour

When considering data from inside the scanner, there was a significant positive relationship between θ value (calculated according to **Equation 1**) and self-reported sensation-seeking (r=0.391, p=0.048; **Figure 10A**), with higher self-reported sensation-seekers assigning greater economic value to opportunity to experience the MES (Cronbach's alpha for internal reliability of total sensation-seeking score in this subsample was 0.874). There was also a significant negative relationship between relative reaction time for MES-associated (CS+) *vs* non MES-associated (CS-) stimuli and θ value (r=-0.543, p=0.004; **Figure 10B**); with individuals who assigned a high value showing a relative speeding of responses for CS+ stimuli, and individuals who assigned a lower value showing a relative slowing of responses for CS+ stimuli.

In order to test for possible effects of increasing task length at the functional imaging stage (3*100 trial blocks, as compared with 1*100 trial block in previous behavioural testing), θ estimates derived from behaviour from each block separately for each participant were entered into a repeated-measures model with the within-subjects factor of block. There was no overall effect of block number on θ values (p>0.1), suggesting no overall tendency across participants to e.g. decrease choice of MES-associated stimuli over the course of the task . If behavioural sensation-seeking group (θ > or < 0, across all trials) was added to the model as a between-subjects factor, this finding did not differ between high and low sensation-seekers (block*SS group interaction, p>0.1; **Figure 10C**).

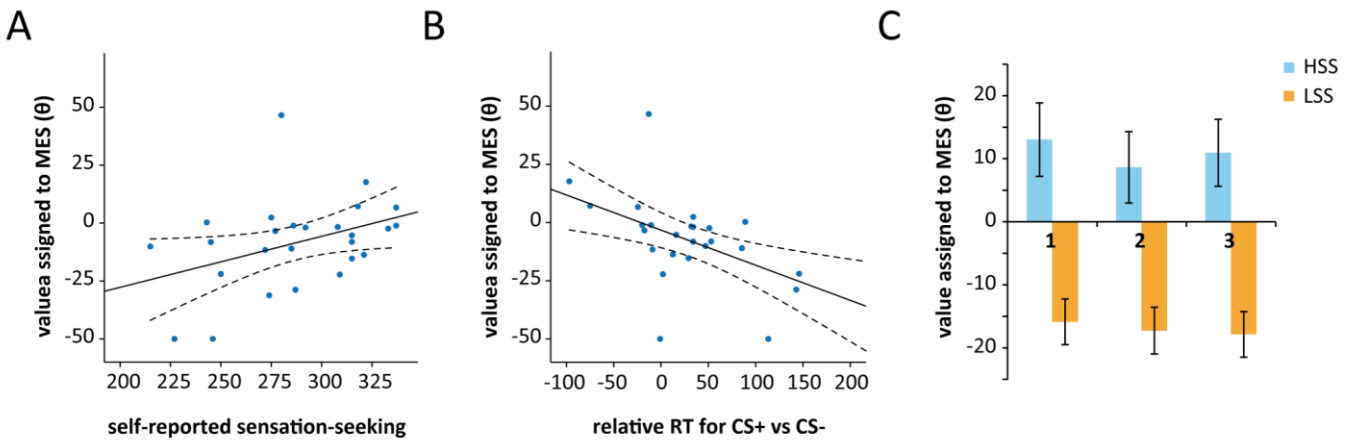

Figure 10. Summary of in-scanner behaviour.

A Relationship between value assigned to opportunity to experience the mild electric stimulus (MES) and self-reported sensation-seeking score (SSS-V-R total score; r=0.391, p=0.048).

B Relationship between MES value (i.e. θ) and relative choice reaction time for MES-associated (CS+) *vs* non MES-associated (CS-) stimuli (reaction time effect calculated as median RT_{CS+} – median RT_{CS-}; r=-0.543, p=0.004).

C Change in θ values across blocks inside the scanner, illustrated separately for high behavioural sensation-seeking (HSS, overall θ>0, N=8) and low behavioural sensation-seeking (LSS, overall θ<0, N=18) individuals. Dotted lines represent 95% confidence intervals. Error bars represent SEM.

There was a tendency for the value participants assigned to the opportunity to experience the MES to decrease between prescreening and scanning sessions (at recruitment: θ>0, N=19, θ<0, N=7; from scan day data: θ>0, N=8, θ<0, N=18). Formally, if θ estimates were contrasted between prescreen and scan-day sessions, there was a significant decrease in mean θ value across all subjects for trials completed inside the scanner (main effect of session: $F(1,25)=12.164$, $\eta_p^2=0.327$, $p=0.002$; mean θ on prescreen = 3.9 ± 14, mean θ from scan trials = -8.4 ± 19). In accordance with this, across-session reliability of theta estimates (as measured by intra-class correlation coefficient, or ICC; Shrout and Fleiss, 1979; McGraw and Wong, 1996) was found to be good for relative (rank) agreement, (two-way mixed model, average measures ICC=0.618), but slightly lower for absolute agreement (ICC=0.531).

This might reflect an effect of the unusual sensory environment of the scanner. In particular, for participants for whom this was their first ever MRI scan might have decreased motivation for other 'intense and unusual' sensory stimulation in the unusual, dark, and loud environment of the scanner, as this experience may be sufficiently intense and unusual in and of itself. This explanation is in line with previous observations of differences in sensory processing between lab and MR environments (e.g. Ellerbrock and May, 2014).

4.3.3 Functional imaging data

4.3.3.1 Categorical analysis

Points (economic) value of chosen stimuli

To identify brain regions sensitive to the economic (points) value of stimuli, we first examined the results of parametric contrast encoding points value of the chosen stimulus during the decision period. The positive contrast revealed no significant clusters at the whole brain level. However, examination of activity in the OFC/vmPFC ROI, revealed a significant cluster in the left medial OFC (mOFC) (**Table 5**). There was a trend-level significant cluster in the right mOFC (peak voxel [9, 44, -8], p_{SVC}=0.065). The vS ROI revealed no significant clusters.

The negative contrast (increasingly BOLD activity with *decreasing* points value of the chosen stimulus) revealed significant clusters at the whole brain level bilaterally in the medial frontal and inferior frontal gyri (MFG; IFG), bilaterally in the inferior parietal lobule (IPL), and left insula (with trend level significance in the right insula, peak voxel [33, 17, 4], p_{FWE}=0.090) (**Table 5**).

				MNI coordinates				
p	***k***	***t***	***Z***	***x***	***y***	***z***	**Corr**	**Region**
Points value (positive)								
0.046	4	3.62	3.20	-6	41	-8	SVC	Left mOFC
Points value (negative)								
0.002	213	5.35	4.30	-45	20	34	WB	Left MFG
		4.83	4.00	-45	5	31	WB	Left IFG
		3.96	3.44	-33	11	25	WB	Left IFG
0.001	219	5.07	4.14	36	56	7	WB	Right MFG
		4.21	3.61	45	32	28	WB	Right MFG
		4.18	3.58	45	41	13	WB	Right IFG
0.045	97	4.96	4.08	-33	-52	43	WB	Left IPL
0.024	117	4.82	3.99	36	-52	46	WB	Right IPL
		4.64	3.88	24	-61	34	WB	Right precuneus
		4.17	3.58	15	-61	43	WB	Right precuneus
0.027	113	4.74	3.94	-30	23	7	WB	Left insula
0.003	87	4.74	3.94	-30	23	7	SVC	Left insula
		4.66	3.90	-27	23	-2	SVC	Left insula
0.014	42	4.72	3.93	33	17	4	SVC	Right insula
		4.50	3.79	30	23	-2	SVC	Right insula

Table 5. Whole brain and ROI analyses for the points value contrast (Model 1). *k* = cluster size, Corr=significance correction: WB = whole brain FWE cluster-level corrected (with an initial cluster-forming threshold of $p<0.001$), SVC=small-volume corrected (FWE cluster-level corrected within ROI).

Choice of MES-associated vs non MES-associated stimuli

We next examined whether regional BOLD signal was sensitive to choice of CS+ (MES-associated) vs CS- (non MES-associated) stimuli across the whole group, during the decision period (an orthogonal contrast to the economic or points value of chosen CSs). There was significantly greater activity when choosing CS+ as opposed to CS- stimuli in the right superior frontal gyrus (SFG), in the IPL bilaterally, in the insula bilaterally, in the right thalamus, and in the right IFG (**Table 6**). Across all subjects, there was no significant increase in activity to CS+ *vs* CS- stimuli in the vS or vmPFC ROIs.

				MNI coordinates				
p	***k***	***t***	***Z***	***x***	***y***	***z***	**Corr**	**Region**
0.000	798	7.48	5.32	57	-28	31	WB	Right IPL
		7.18	5.20	63	-34	34	WB	Right IPL
		6.66	4.97	42	-19	16	WB	Right insula
0.001	227	7.13	5.17	-51	-31	28	WB	Left IPL
		6.58	4.93	-63	-25	25	WB	Left supramarginal gyrus
		4.09	3.53	-54	-46	34	WB	Left supramarginal gyrus
0.000	551	6.06	4.67	9	8	70	WB	Right SFG
		5.36	4.30	9	23	43	WB	Right MFG
		4.62	3.87	6	29	52	WB	Right SFG
0.000	299	6.00	4.64	-27	26	1	WB	Left insula
		5.97	4.63	-30	20	10	WB	Left insula
		5.18	4.20	-48	-1	7	WB	Left insula
0.000	436	5.98	4.64	30	26	4	WB	Right insula
		5.82	4.55	33	23	-5	WB	Right insula
		5.55	4.41	27	20	-14	WB	Right insula
0.045	91	5.86	4.57	42	5	40	WB	Right IFG
		4.00	3.47	51	5	52	WB	Right MFG
0.016	122	5.00	4.10	12	-13	4	WB	Right thalamus
		4.09	3.53	9	-22	-5	WB	Right thalamus
		3.71	3.27	12	2	10	WB	Right thalamus

Table 6. Whole brain analysis for choice of MES-associated (CS+) vs non MES-associated (CS-) stimuli. *k* = cluster size, Corr=significance correction: WB = whole brain FWE cluster-level corrected (with an initial cluster-forming threshold of $p<0.001$).

In order to investigate the effects of individual differences in preference for MES-associated stimuli (as indexed by θ) on brain activity when choosing between MES-associated and non-MES associated stimuli, we next examined the effects of the continuous θ value covariate on the CS+ *vs* CS- contrast. When examining the positive contrast at the whole brain level, we found that there was a significant positive relationship (i.e. greater activity when choosing CS+ stimuli in individuals with greater θ value) in the left parahippocampal gyrus (PHG), left precuneus, and the left cerebellum (**Table 7**).

Analysis of activity in our predefined vmPFC and vS ROIs revealed that θ value was a significant positive covariate of BOLD signal in both regions. Specifically, there was significantly greater activity when choosing CS+ as compared to CS- stimuli in individuals with greater θ value (higher behavioural sensation-seekers) in the central-left mOFC and the head of the caudate bilaterally (**Table 7, Figure 11**). Individuals who assigned a negative value to opportunity to receive the MES showed decreases in BOLD signal in these regions when choosing MES-associated *vs* non MES-associated stimuli; whereas individuals who assigned a positive value to opportunity to receive the MES showed the opposite. Thus, we found evidence for increasing activity in value-associated regions during choice of MES-associated stimuli, with increasing behaviourally-derived value of opportunity to receive the MES.

				MNI coordinates				
p	***k***	***t***	***Z***	***x***	***y***	***z***	**Corr**	**Region**
Theta covariate (positive)								
0.000	9300	11.7	6.68	-33	-40	-11	WB	Left PHG
		9.35	6.01	-27	-37	-20	WB	Left fusiform gyrus
		8.88	5.86	-54	-1	-20	WB	Left mid temporal gyrus
0.000	685	6.66	4.97	-33	-82	37	WB	Left precuneus
		6.44	4.86	-21	-79	43	WB	Left precuneus
		5.86	4.57	-42	-73	34	WB	Left precuneus
0.021	114	4.80	3.98	-33	-79	-32	WB	Left cerebellum
		3.82	3.34	-51	-61	-32	WB	Left cerebellum
		3.59	3.18	-48	-52	-41	WB	Left cerebellum
0.000	340	7.55	5.35	-12	47	-8	SVC	Left mOFC
		7.04	5.14	-12	38	-11	SVC	Left mOFC
		6.62	4.95	0	35	-11	SVC	Right mOFC
0.006	21	5.62	4.44	6	20	-2	SVC	Right caudate
0.005	26	5.45	4.36	-9	20	-5	SVC	Left caudate
		4.43	3.75	-3	11	-5	SVC	Left caudate
Theta covariate (negative)								
0.012	130	5.74	4.51	33	23	-5	WB	Right insula
		3.97	3.45	36	26	10	WB	Right IFG
0.050	88	4.84	4.00	-27	23	-2	WB	Left insula
		4.67	3.90	-30	20	10	WB	Left insula

Table 7. Whole brain and ROI analyses for effects of theta value on brain activity when choosing MES-associated (CS+) *vs* non MES-associated (CS-) stimuli. *k* = cluster size, Corr=significance correction: WB = whole brain FWE cluster-level corrected (with an initial cluster-forming threshold of$p<0.001$), SVC=small-volume corrected (FWE cluster-level corrected within ROI).

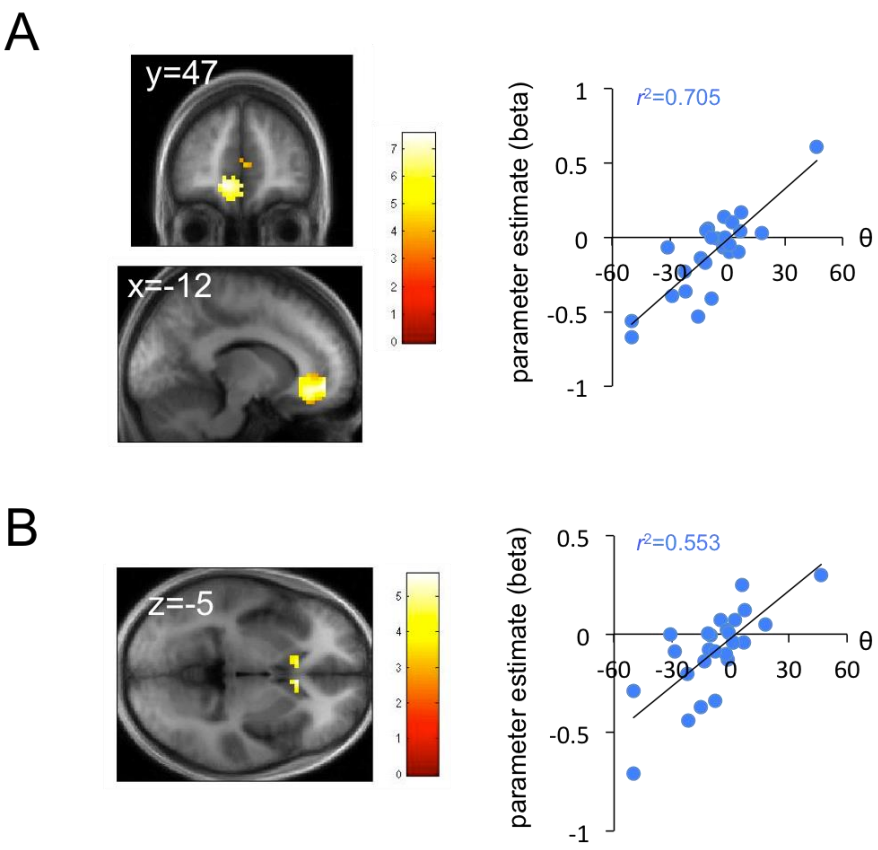

Figure 11. Significant positive effects of theta value (valued assigned to opportunity to receive the MES) on BOLD signal when choosing MES-associated (CS+) as opposed to non MES-associated (CS-) stimuli in (A) the central-left medial OFC and (B) the head of the caudate, bilaterally. Images are thresholded at $p<0.001$, uncorrected, and overlain on the average normalized anatomical image; colour bars represents *t* values. Scatter plots represent beta estimates extracted from the CS+/CS- contrast images at peak voxel coordinates, plotted against individual θ values. Data in (B) are illustrated for the left caudate.

Positive correlations between parameter estimates extracted at from the CS+ *vs* CS- contrast at peak voxel coordinates in the mOFC and vS and individual θ values remained strongly significant after exclusion of a potential outlier (θ=46.6, **Figure 11**; $r=0.769$, $r=0.698$, respectively, both $p<0.001$).

Theta value was also found to be a significant *negative* covariate of BOLD signal when choosing CS+ as opposed CS- stimuli in the insula bilaterally (**Table 7**, **Figure 12**). Individuals who assigned a negative value to opportunity to receive the MES showed increases in BOLD signal bilaterally in the insula when choosing MES-associated *vs* non MES-associated stimuli; whereas individuals who assigned a positive value to opportunity to receive the MES did not. There was also a non-significant trend towards negative modulation of BOLD signal by θ value on this contrast in the right MFG (peak voxel [6, 26, 43], p_{FWE}=0.080).

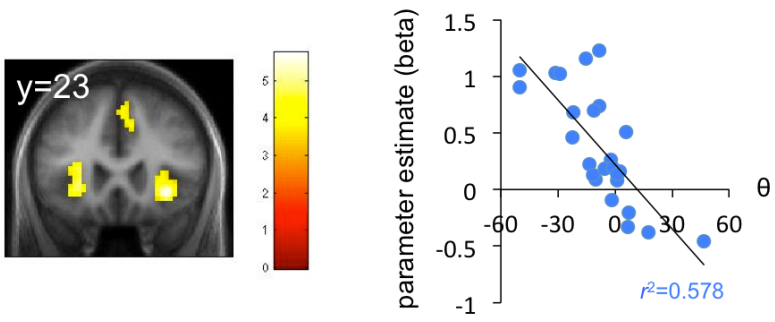

Figure 12. Significant negative effect of theta value (valued assigned to opportunity to receive the MES) on BOLD signal when choosing MES-associated (CS+) as opposed to non MES-associated (CS-) stimuli, bilaterally in the insula. Image thresholded at p<0.001, uncorrected, and overlain on the average normalized anatomical image; colour bars represents t values. Scatter plot represents beta estimates extracted from CS+/CS- contrast images at peak voxel coordinates, plotted against individual θ values. Data are illustrated for the right insula.

Conjunction analysis: common coding of economic and MES reward in high SSs?

Finally, we used a conjunction analysis to test the hypothesis that brain regions positively encoding the economic value of chosen stimuli would show positive activation when choosing MES-associated stimuli, selectively in individuals who assigned a positive to value to the opportunity to experience the MES (behavioural high sensation-seekers).

Specifically, we used an inclusive mask generated by the positive contrast of the points value parametric modulator (see above) to test for differences in activity on the *orthogonal* CS+ *vs* CS- contrast with individual differences in θ value. Activity in the points value-sensitive mOFC cluster was greater when choosing CS+ stimuli in individuals who assigned greater value to opportunity to receive the MES (i.e. θ was a significant positive covariate of activity in this region; peak voxel [-6, 44, -8], Z=4.88, p_{SVC}=0.002) (**Figure 13**).

Further, activity in this points value-sensitive region was *positively* signed when choosing CS+ stimuli in high behavioural SSs (θ>0), but *negatively* signed in low behavioural SSs (θ<0; significant difference between groups in parameter estimates from the CS+ *vs* CS- contrast extracted from the peak voxel, t_{22}=-2.916, p=0.008, independent samples t-test with p and df adjusted for violation of Levene's test for equality of variance) (**Figure 13**). This suggests that opportunity to experience the intense sensory stimulus was encoded in the same region as opportunity to gain points (monetary reward) during the decision period, only in high behavioural sensation-seekers.

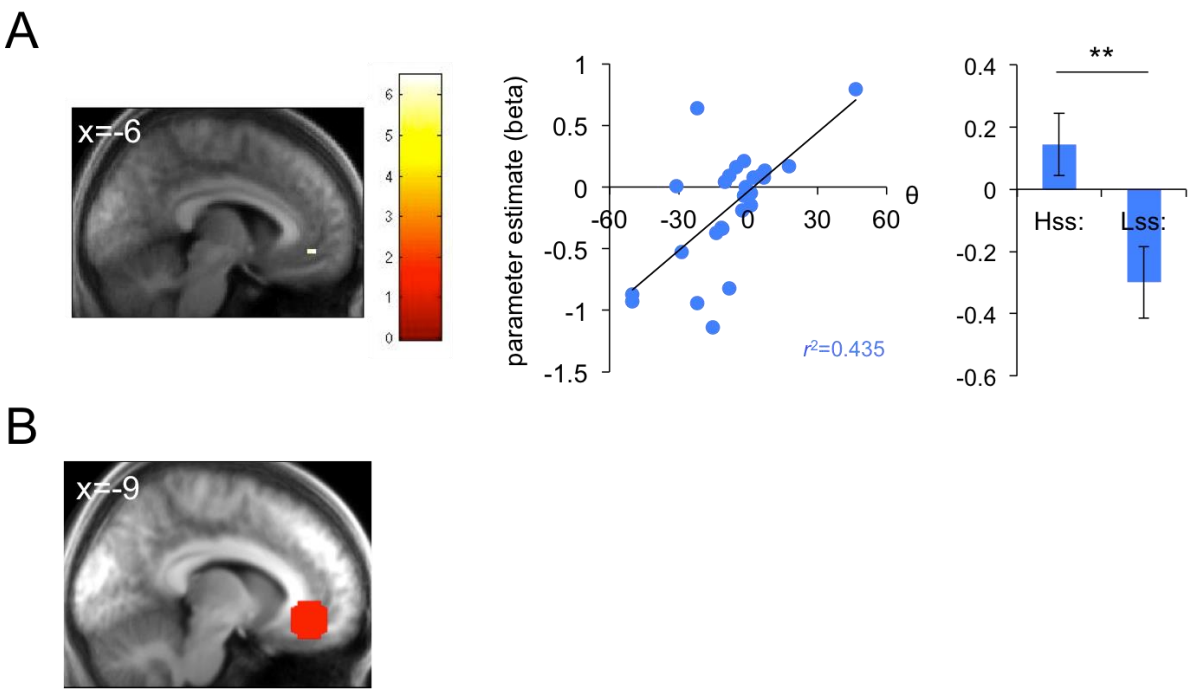

Figure 13. Conjunction analysis revealed that a region in the mOFC cluster identified as showing increasing activity with *increasing* points value of chosen CSs, also showed *positive* modulation by individual θ value when choosing MES-associated (as opposed to non MES-associated) stimuli (A). Image thresholded at $p<0.001$, uncorrected, and overlain on the average normalized anatomical image; colour bar represents *t* values. Scatter plot and bar chart show individual parameter estimates from the CS+ *vs* CS- contrast, extracted at the peak mOFC voxel identified from the positive points value contrast, plotted against θ values. Hss=behavioural high sensation-seekers (θ>0), Lss=behavioural low sensation-seekers (θ<0). Error bars represent SEM. **$p=0.008$. For comparison, the left vmPFC/OFC region identified from a meta-analysis of functional imaging studies probing common representation of different reward types (Levy and Glimcher, 2012) is plotted on the average normalized anatomical image for our study participants (B).

Conversely, when masking this contrast with areas that showed increased activity with *decreasing* points value of the chosen CS, θ value was a significant *negative* covariate of activity bilaterally in the insula (right peak voxel [-7, 23, -2], Z=4.00, p_{SVC}=0.006; left peak voxel [33, 23, -5], Z=4.51, p_{SVC}=0.010). Individuals with low θ values (low behavioural sensation-seekers) showed positive activity in a brain region negatively associated with economic value when choosing MES-associated stimuli, but individuals with high θ values (high behavioural sensation-seekers) did not (significant difference between groups in parameter estimates from CS+ *vs* CS- contrast when extracted from the peak insula voxel identified from the negative points value contrast; t_{24}=2.609, p=0.015, independent samples *t*-tests) (**Figure 14**).

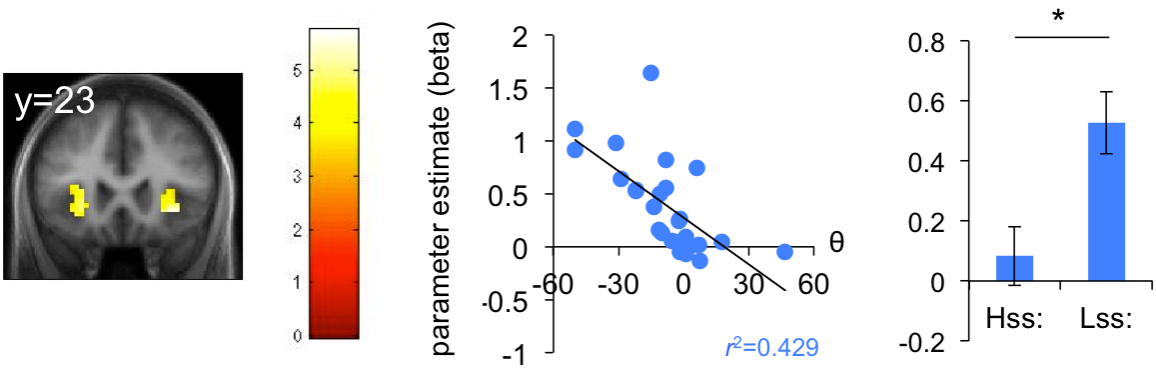

Figure 14. Conjunction analysis revealed that insula clusters identified as showing increasing activity with *decreasing* points value of chosen CS also showed *negative* modulation according to θ value when choosing MES associated (as opposed to non MES-associated) stimuli. Image thresholded at $p<0.001$, uncorrected, and overlain on the average normalized anatomical image; colour bar represents *t* values. Scatter plot and bar chart show individual parameter estimates from the CS+ *vs* CS- contrast, extracted at the peak insula voxel identified from the negative points value contrast, plotted against θ values. Hss=behavioural high sensation-seekers (θ>0), Lss=behavioural low sensation-seekers (θ<0). Error bars represent SEM. *$p=0.015$

4.3.3.2 "Model-based" trial-by-trial analysis

Points (economic) value of chosen stimuli

Analysis of brain regions where BOLD signal was sensitive to the points value of chosen stimuli during the decision period again revealed a significant left mOFC cluster for the positive contrast under SVC (**Table 8**). Similarly, the negative contrast again revealed significant clusters in the IPL, IFG, and MFG at the whole brain level, and bilaterally in the insula under SVC (**Table 8**).

				MNI coordinates				
p	***k***	***t***	***Z***	***x***	***y***	***z***	**Corr**	**Region**
Points value (positive)								
0.024	15	3.85	3.36	-6	41	-8	SVC	Left mOFC
Points value (negative)								
0.000	304	5.70	4.49	36	56	7	WB	Right MFG
		4.03	3.49	45	35	31	WB	Right MFG
		3.98	3.45	51	14	34	WB	Right MFG
0.008	162	5.43	4.34	-36	-49	43	WB	Left IPL
		4.18	3.59	-39	-37	40	WB	Left IPL
		4.08	3.52	-42	-40	49	WB	Left IPL
0.000	273	5.32	4.28	-45	5	28	WB	Left IFG
		5.03	4.12	-42	20	31	WB	Left MFG
		4.24	3.63	-33	2	34	WB	Left IFG
0.005	72	4.76	3.95	-33	20	7	SVC	Left insula
		4.70	3.92	-27	23	-2	SVC	Left MFG
0.042	20	4.44	3.76	30	23	-2	SVC	Right insula
		4.30	3.67	33	17	4	SVC	Right insula

Table 8. Whole brain and ROI analyses for the points value contrast (Model 2). *k* = cluster size, Corr=significance correction: WB = whole brain FWE cluster-level corrected (with an initial cluster-forming threshold of $p<0.001$), SVC=small-volume corrected (FWE cluster-level corrected within ROI).

Shock associative value of chosen stimuli

We next examined whether BOLD signal was significantly related to our modelled internal probability estimate of receiving the MES, when choosing a CS (i.e. trial-

by-trial variation in SA_{CS} values). Analysis of the positive contrast for SA_{CS} value of the chosen CS on each trial across the whole group revealed a significant cluster in the left insula (peak voxel [-27, 29, 1], k=26, Z=3.56, p_{SVC}=0.020), and a trend-level significant cluster in the right insula (peak voxel [36, 14, -11], k=11, Z=3.37, p_{SVC}=0.064). This suggests that, across all subjects, modelled internal probability of receiving the MES was being tracked in the insula during the choice period. The negative contrast revealed no significant voxels.

There was no evidence for a (linear) effect of θ value on the positive contrast at our significance threshold. In order to explore any group level differences undetected by this analysis (e.g. due to non-linear effects of θ value on BOLD signal), individual contrasts were entered into a 2-sample t-test at the second level, with participants divided into high behavioural sensation-seekers (θ>0) and low behavioural sensation-seekers (θ<0). This grouping was then used to explore differences between high and low behavioural sensation-seekers in coding of shock associative value (SACS), by contrasting activity between the two groups in brain regions previously found to be sensitive to SA_{CS} value on each trial.

This analysis revealed significantly greater parameter estimates for the SA_{CS} contrast in low, compared to high, behavioural sensation-seekers in the left insula (peak voxel [-33, 23, -5], k=23, Z=3.81, p_{SVC}=0.028) (**Figure 15**). Thus, there appeared to be significant positive coding of shock associative value in the left insula for low sensation-seekers, but not high sensation-seekers. There were

no significant clusters where activity was found to greater for high, compared to low, sensation-seekers.

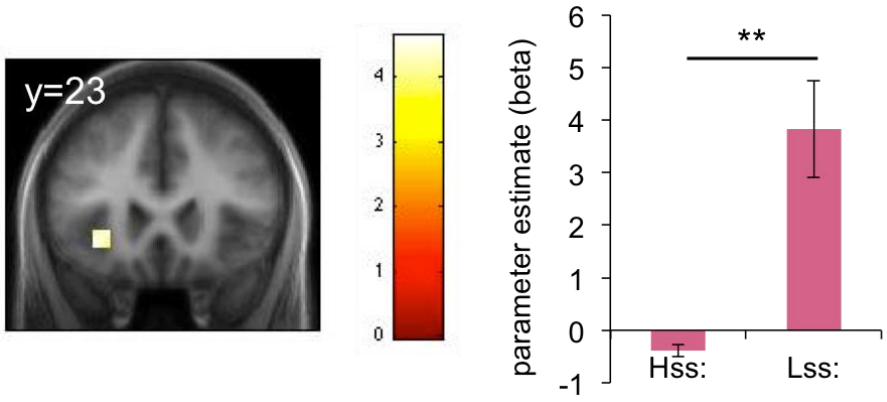

Figure 15. An insula region positively coding the shock associative value of chosen CSs showed significant activation in low, but not high behavioural sensation-seekers, during the decision period. Image thresholded at $p<0.001$, uncorrected, and overlain on the average normalized anatomical image; colour bar represents *t* values. Bar chart represents parameter estimates extracted from contrast images at peak voxel coordinates; Hss=behavioural high sensation-seekers ($\theta>0$), Lss=behavioural low sensation-seekers ($\theta<0$). Error bars represent SEM. $^{**}p<0.001$

Conjunction analysis

We next examined whether brain regions significantly associated with the economic (points) value of chosen stimuli also showed significant activation to

the modelled shock associative value of chosen stimuli (an *orthogonal* contrast), during the decision period.

When masked by regions significantly negatively encoding the points value of chosen CSs (i.e. exhibiting increasing activation with decreasing points value), there was again greater activity in low sensation-seekers than high sensation-seekers on the shock associative value contrast in the left insula (peak voxel [-30, 23, -5], k=21, Z=3.79, p_{SVC}=0.036). There was positive coding of modelled probability of receiving an MES in regions tracking negative economic value in low, but not high, sensation-seekers (significant difference between groups in parameter estimates from the SACS contrast when extracted from the peak voxel identified from the negative points value contrast, t_{20}=2.754, p=0.012, independent samples t-test, p and df adjusted for violation of Levene's test for equality of variances) (**Figure 16**).

Low sensation-seekers thus appear to be tracking the probability of receiving the intense sensory stimulation in the same way as receiving low economic value (fewer points), whereas higher sensation-seekers do not. This is despite the fact that we found no evidence for a difference in learning about MES-predicting *vs* non MES-predicting stimuli prior to entering the scanner in high *vs* low sensation-seekers (see **section 4.3.2.1**).

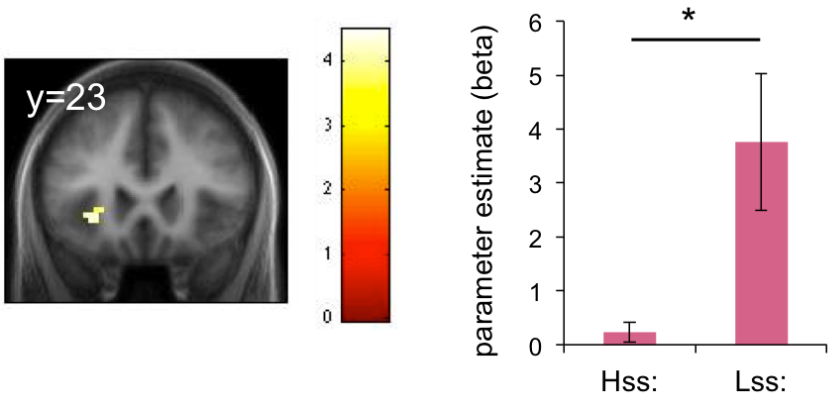

Figure 16. Conjunction analysis revealed that an insula region identified as showing increasing activation with decreasing economic value of chosen stimuli showed positive coding of the shock associative value of chosen CSs in low, but not high, behavioural sensation-seekers, during the decision period. Image thresholded at $p<0.001$, uncorrected, and overlain on the average normalized anatomical image; colour bar represents *t* values. Bar chart represents parameter estimates extracted from shock associated value contrast images, extracted at peak insula voxel coordinates from the negative points value contrast. Hss=behavioural high sensation-seekers ($\theta>0$), Lss=behavioural low sensation-seekers ($\theta<0$). Error bars represent SEM. *p=0.012

Analysis of activity on the SA_{CS} contrast in the peak voxel identified from the *positive* points value contrast (i.e. the peak voxel across all subjects exhibiting increasing activation with increasing points value, located in the left mOFC), revealed there was only a non-significant trend towards greater parameter estimates in high, as opposed to low, sensation-seekers (independent samples *t*-test, p=0.052) (**Figure 17**).

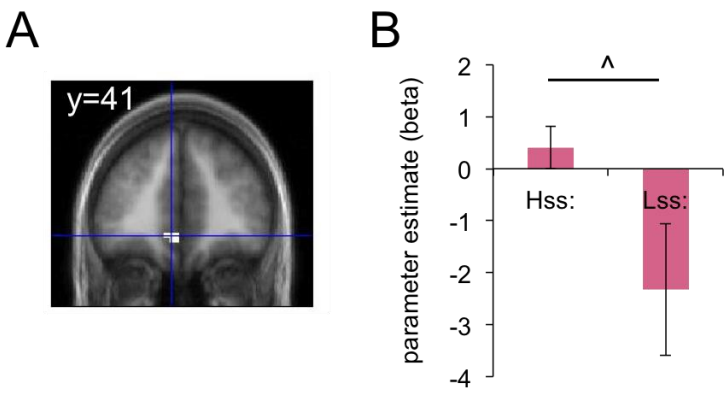

Figure 17. BOLD signal extracted from the peak voxel identified from the positive points value contrast (i.e. significantly positively encoding the economic value of chosen CSs, located in the mOFC, A) was marginally greater in high (Hss), compared with low sensation-seekers (Lss) on the shock associative value contrast (B). ^p=0.052

4.3.3.3 "Model-based" sensory prediction error analysis

Finally, we examined whether there were differences in the encoding of sensory prediction error (SPE) signals between high and low behavioural sensation-seekers, during the period where participants did/did not receive the MES.

First, we investigated whether BOLD signal in any brain region was significantly associated with the trial-by-trial prediction error signals generated using our model. Across the whole group, we found no significant clusters either at the whole brain level, or in our pre-specified ROIs, for the positive SPE contrast. However, there was a significant negative encoding of SPEs in clusters in the

IPL/superior temporal gyrus (STG) and superior frontal gyrus (SFG) (**Table 9**). This suggests that, overall, our participants negatively coded imperfectly predicted receipt of the MES (equivalent to coding S=-1 vs S=0, instead of S=1 vs S=0, in **Equation 4**). This is unsurprising, given that the majority of our participants assigned a negative value to opportunity to receive the MES inside the scanner.

				MNI coordinates				
p	***k***	***t***	***Z***	***x***	***y***	***z***	**Corr**	**Region**
0.002	202	6.34	4.81	48	-64	40	WB	Right IPL
		4.42	3.74	57	-61	25	WB	Right STG
0.013	135	4.67	3.90	24	32	52	WB	Right SFG
		4.37	3.71	15	35	55	WB	Right SFG
		4.34	3.69	33	17	58	WB	Right SFG

Table 9. Negative contrast for sensory prediction errors across the whole brain. *k* = cluster size, Corr=significance correction: WB = whole brain FWE cluster-level corrected (with an initial cluster-forming threshold of $p<0.001$).

We next tested our hypothesis that SPEs might be positively signed in behavioural high sensation-seekers (where receipt of the MES represents a better than predicted outcome), but negatively signed in behavioural low sensation-seekers (where receipt of the MES represents a worse than predicted outcome).

Using sensitivity to SPE signals across the whole group (**Table 9**) as a mask, we found there to be greater BOLD signal in response to SPEs in high, *vs* low, sensation-seekers in a cluster in the left posterior cingulate cortex (PCC), although this cluster did not survive correction for multiple comparison at the whole brain level. As the PCC did not constitute an *a priori* region of interest for this study (although previously shown to encode reward prediction errors; McCoy et al., 2003; Rutledge et al., 2010), we applied an exploratory *a posteriori* correction to this contrast, correcting for the search volume of the whole group mask (subthreshold PCC, plus IPL and SFG clusters as recorded in **Table 9**). Under this exploratory correction, SPEs appear to be coded *positively* for high sensation-seekers, but *negatively* coded for low sensation-seekers, in the PCC (peak voxel [-9, -55, 28], k=11, Z=4.14, p_{SVC}=0.045) (**Figure 18**).

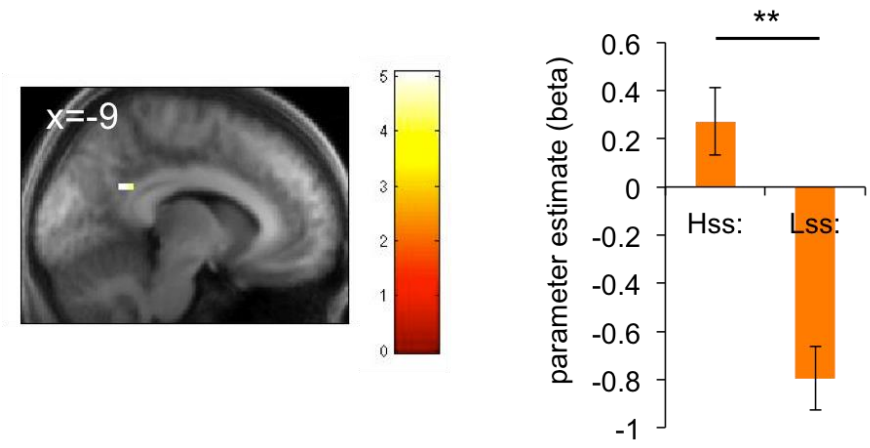

Figure 18. Results of an exploratory analysis suggest that sensory prediction error signals may be positively signed for high sensation-seekers, but negatively signed by low sensation-seekers, in the PCC. Image thresholded at $p<0.001$, uncorrected, and overlain on the average normalized anatomical image; colour bar represents *t* values. Bar chart represents parameter estimates extracted from sensory prediction error contrast images, extracted at peak voxel coordinates from the Hss>Lss contrast, when masked by voxels sensitive to sensory prediction error signals across the whole group. Hss=behavioural high sensation-seekers ($\theta>0$), Lss=behavioural low sensation-seekers ($\theta<0$). Error bars represent SEM. $^{**}p<0.001$

4.4 Discussion

In a large novel sample, performance on our sensation-seeking paradigm probing individual differences in preference for mild electric stimulation (MES) was found to be significantly (and selectively) related to self-reported sensation-seeking, relative reaction time for MES-associated stimuli, change in 'liking' rating of MES-associated stimuli, 'liking' rating of the MES itself, and self-reported sensitivity to sensory stimulation. This evidence provides a further replication of our previous key behavioural findings, and supports the construct validity of this paradigm as a probe of sensation-seeking-like behaviour in the lab.

In this study, we used three different models of BOLD signal data to derive three novel empirical findings about the neural activity underlying individual differences in performance on this measure.

Firstly, we found that there were significant positive associations between the value individuals assign to the opportunity to receive mild electric stimulation, and activity in brain regions associated with value processing (the medial OFC and ventral caudate), during choice of MES-associated as opposed to non MES-associated stimuli. Critically, we used conjunction analysis to show that there was selective activation of a brain region encoding positive economic value when choosing MES-associated stimuli in high behavioural sensation-seekers. Conversely, there was selective activation of brain regions encoding negative economic value when choosing MES-associated stimuli in low behavioural sensation-seekers. This suggests that individuals weighed the opportunity to

experience the MES in the same way as the economic value of chosen stimuli, and, crucially, that this opportunity was encoded in the same regions as economic reward in high behavioural sensation-seekers.

Secondly, we found that there was a significant difference between low and high sensation-seeking individuals in the way that participants' BOLD signal tracked the modelled internal probability of receiving an MES, given selection of a particular stimulus (shock associative value of that stimulus). During the decision period, low sensation-seeking individuals showed significantly greater activity associated with the shock-associative value of chosen stimuli in the left insula compared with high sensation-seekers. Importantly, we found no evidence for difference in explicit learning of the MES-CS associations between high and low sensation-seekers prior to entering the scanner, suggesting that this difference is not due to decreased knowledge of experimental contingencies.

Thirdly, we found tentative evidence from neural activity during the trial period where individuals may or may not actually receive the mild electric stimulation that sensory prediction errors (difference between modelled internal probability of receiving the MES on that trial, and actual trial outcome) were *positively* coded in high sensation-seekers, but *negatively* coded in low sensation-seekers, in the posterior cingulate cortex. This finding would be consistent with the idea that a positive prediction error (actual MES receipt) represented a better than expected outcome in high sensation-seekers, but a worse than expected outcome in low sensation-seekers.

A large number of functional imaging studies have related variation in BOLD signal in the OFC/vmPFC and ventral striatum (including head of the caudate nucleus) to the expected value of choice options (Knutson et al., 2001; Abler et al., 2006; Levy and Glimcher, 2012). Thus our finding of increased signal in these regions when choosing MES-associated options, as a linear function of the additional value participants assigned to opportunity to receive the MES (positive or negative), is consistent with the proposal that participants used a common valuation currency for the points and sensory value of different choice options.

Critically, we found evidence for common value coding of points and intense sensory stimulation (MES) value in behavioural high sensation-seekers in a ROI derived from a meta-analysis of previous functional imaging studies probing common representation across different types of rewards (Levy and Glimcher, 2012; **Figure 13**). Interestingly, previous studies have also reported greater BOLD signal in medial orbitofrontal and prefrontal regions during anticipation of or whilst viewing 'high-arousal' emotional stimuli in higher self-reported sensation-seekers (Joseph et al., 2009; Bermpohl et al., 2008).

Our finding that the shock associative value of chosen stimuli was tracked during the decision period in the left insula (particularly in low sensation-seeking individuals) is consistent with previous report suggesting that insula has a role in tracking 'salient' events (e.g. showing greater activation during anticipation of events of uncertain outcome, and particularly but by no means exclusively during

unpleasant or aversive events; Preuschoff et al., 2008; Menon and Uddin, 2010; Rutledge et al., 2010).

However, this observation, as well as our finding of increased activity in the insula bilaterally in lower sensation-seekers when choosing MES-associated as opposed to non MES-associated stimuli, may appear to contradict previous investigations which reported *increased* insula activation in *higher* sensation-seekers during viewing of high arousal emotional stimuli (Joseph et al., 2009; Straube et al., 2010). Significantly, the latter study found a positive correlation between insula activation and self-reported sensation-seeking during viewing of "scary' clips (i.e. greater activation in higher sensation-seekers), but a negative correlation during viewing of 'neutral' film clips (i.e. less activation in higher sensation-seekers). Thus our findings of decreased insula activity in anticipation of MES delivery in behavioural higher sensation-seekers may reflect an effect of habituation to (and thus decreased salience of) the MES. Note that high sensation-seekers, by definition, will experience a greater number of these stimuli over the course of the task.

Intriguingly, bilateral anterior insula activity has previously been found to predict whether or not a subsequent sensory stimulus (noxious heat) is perceived as painful: with greater prestimulus activity predicting greater likelihood that the stimulus will be rated as painful (Ploner et al., 2010). Further studies have reported that this effect depends on information about the contextual salience of the upcoming sensory stimulus (Wiech et al., 2010). Thus increased anticipatory insula activity in low sensation-seeking individuals when

choosing MES-associated stimuli might relate to decreased 'liking' ratings of the sensation of the MES by low sensation-seekers (see section x), despite all participants endorsing a description of the stimulus as "non-painful".

Finally, although only preliminary in nature, our findings from the sensory prediction error analysis are consistent with previous observations of reward prediction signals in the posterior cingulate cortex in both non-human primate electrophysiological and human fMRI data (McCoy et al., 2003; Bruijn et al., 2009; Rutledge et al., 2010). Recently, Rutledge and colleagues have proposed that one reason that fewer studies have historically reported reward prediction error signals in the PCC is that the haemodynamic response function (HRF) in this region is dissimilar to the canonical HRF used in standard regression analyses (Rutledge et al., 2010). This may provide an additional explanation as to why our finding of differently signed parameter estimates for SPEs in the PCC failed to reach significance under whole brain correction.

A major limitation of the current study is the unfortunate decrease in preference for the MES (behavioural sensation-seeking) between lab-based prescreening and in-scanner performance: resulting in a loss of data points from our functional imaging sample with (particularly intermediate) positive theta values (for a discussion see **section 4.3.2.2**). We have therefore tried, where possible, to use a continuous covariate approach in our analyses, although we accept that even using this approach trends in the positive portion of the theta spectrum are under-evidenced and may be driven by outliers. Thus, inferences about the direction of effects in high behavioural sensation-seekers must be treated with

caution, and would particularly benefit from future replication. It is also possible that a lack of power explains why we did not find a significant conjunction between regions encoding positive economic value and shock associative value in high sensation-seekers (although we did find the converse).

Further, by definition, there are systematic differences in total CS+ choice, and associated outcome frequencies, between high and low behavioural sensation-seeking individuals. This may lead to issues of increased noise where choice is relatively less frequent, or conversely the presence of habituation effects only in individuals exhibiting more frequent choice. However, we have attempted to ensure via our task design and number of trials that there will be sampling of all response types across all individuals.

Despite these limitations, we propose that the data summarised above contribute significantly to the extant literature on the neural correlates of sensation-seeking behaviour. Using a novel fMRI paradigm, we have demonstrated for the first time that intense sensory stimulation may activate brain areas encoding economic reward selectively in high sensation-seekers. Furthermore, high sensation-seekers show decreased activity in a brain region implicated in 'salience' detection (the insula) during anticipation of intense sensory stimulation, which may be related to their increased approach of these stimuli. In addition, high sensation-seekers may show positively signed responses to imperfectly predicted delivery of intense sensory stimulation (whereas low sensation-seekers show negatively signed responses), in the posterior cingulate cortex. Significantly, differences in anticipatory reward processing in both the insula and

the posterior cingulate cortex have been identified as being related to the phenomenon of craving in drug addiction, for which high self-reported sensation-seeking has been identified as a risk factor (Naqvi et al., 2007; Verdejo-Garcia et al., 2012; Garavan et al., 2000; Sinha et al., 2007).

Chapter 5 Dopamine, risky decision-making, and self-reported sensation-seeking

5.1 Introduction

Several strands of evidence implicate the dopamine D2-type receptor system in risky decision-making (choices involving a degree of uncertainty about outcome). In the animal literature, direct manipulations of D2 function by both agonist and antagonist agents have been shown to influence 'risky' decision-making across a variety of paradigms (e.g. uncertainty in outcome magnitude *vs* possibility of aversive outcome; St Onge and Floresco 2009; Zeeb et al. 2009; St. Onge et al. 2010; Simon et al. 2011; Mitchell et al. 2014) – including the ability to induce shifts in preference between uncertain and certain outcome options of the same expected value (risk-seeking *vs* risk-aversion; Cocker et al. 2012).

In humans, treatment with D2 agonist drugs across a variety of clinical conditions is related to increased incidence of *de novo* impulse control disorders, including pathological gambling (Claassen et al., 2011; Dang et al., 2011; Djamshidian et al., 2011). Variation in function of D2 receptor genes has also been related to risk for disordered gambling (Comings et al., 1996) and changes in striatal D2-type receptor 'availability' as estimated using ^{11}C-raclopride PET have been associated with performance on the Iowa Gambling Task (Linnet et al., 2011).

However, previous studies directly testing the effects of D2ergic drugs on risky decision-making paradigms in humans have predominantly revealed non-significant or only very minor effects on choice behaviour (Zack and Poulos 2007; Hamidovic et al. 2008; Riba et al. 2008; Tremblay et al. 2011; Porchet et al. 2013). Although choosing the correct dose of D2ergic agents in human studies presents

some difficulties (e.g. sufficient dose to be centrally active whilst avoiding potentially unblinding side effects, consideration of pre- vs post-synaptic site of action), this is perhaps in part also due to lack of detection of individual differences in drug effects that may be masked in a group level analysis.

Sensation-seeking (SS) personality has been previously been linked to variation in D2 system function (Hamidovic et al., 2009; Gjedde et al., 2010; Campbell et al., 2010; Nyman et al., 2009). Furthermore, high trait SS has been associated with increased risk-taking across a variety of measures. In the broadest sense, links have been established in the general population between high SS scores and increased engagement in 'health risk' behaviours (behaviours that may endanger the self and/or others; (Arnett, 1994; Zuckerman, 1994; Hoyle et al., 2000; Roberti, 2004; Zuckerman, 1994).

Laboratory studies in healthy volunteers have also found medium to high effect sizes for self-reported SS on gambling behaviour (Anderson and Brown, 1984; Roberti, 2004; Ashrafioun et al., 2012), and several studies have reported elevated SS in samples of pathological gamblers compared with controls (Blanco et al. 1996; Whiteside et al. 2005; Fortune and Goodie 2009; Hodgins et al. 2012). Although some have found no differences in scores (Michalczuk et al. 2011; Clark et al. 2012), this may be because the relationship depends on the particular form of problematic gambling engaged with (Coventry and Brown, 1993; Carver and McCarty, 2013).

In this chapter, we present the results of two complementary studies which investigated the effects of a D2 receptor antagonist and agonist, respectively, on the same probabilistic choice task as a function of baseline SS trait. We provide evidence that a D2 *agonist* may exert greater effects on risky decision-making in *lower* SS individuals, whereas, conversely, a D2 receptor *antagonist* may exert greater effects on choice in *higher* SS individuals. These findings are then discussed in terms of hypothesised differences in D2 system function between low and high sensation-seekers.

5.2 Study 1

In this study, we sought to extend previously inconclusive results on the pharmacological manipulation of risk-taking behaviour by D2 agonists (Hamidovic et al., 2008; Riba et al., 2008) using cabergoline – a drug which has both greater affinity and greater relative specificity for D2-like receptors than agents used in former studies (Kvernmo et al., 2006). Importantly, we also took into account the possibility of variation in drug effects with self-reported SS.

Based on functional imaging evidence from individuals undergoing chronic dopamine agonist treatment indicating that these medications may increase appetitive responses towards expected rewards (Abler et al., 2009), we predicted that cabergoline would increase the impact of information about the probability of upcoming *rewards* on choice, and possibly also diminish the effect of expected *negative consequences*, when choosing under conditions of risk or uncertainty. Although previous studies have reported greater responses to DAergic stimulant drugs in high SS volunteers, it has also been suggested that lower sensation-seekers might have a relatively higher gain striatal DA system (Gjedde et al., 2010; see also Discussion), which would predict a greater response to specific agonists in lower SS subjects. To anticipate, in the investigation reported here cabergoline significantly influenced choice sensitivity to information about probability and potential loss, and, critically, the magnitude of these effects was strongly dependent on baseline differences in self-reported SS.

5.2.1 Materials and methods

5.2.1.1 Participants

Participants were 20 healthy males, mean age 26.7 (SD 5.67). Exclusion criteria consisted of any current major illness, current or historic incident of psychiatric illness, and/or recreational drug use on more than one occasion during the past 6 months. All subjects gave informed written consent and the study was approved by the University College London ethics committee. Data from one subject were corrupted and therefore excluded from the analysis, yielding a final *N* of 19.

5.2.1.2 Design

The study was carried out according to a within-subjects double-blind placebo-controlled design. On the first session, participants were screened for drug contraindications, gave informed consent, and were familiarised with the risky decision-making paradigm. Subjects also completed BIS-11 and UPPS self-report measures of impulsivity and SS (Patton et al., 1995; Whiteside and Lynam, 2001), a measure of working memory capacity (forward digit span according to the Wechsler Adult Intelligence Scale-III; The Psychological Corporation, 1997), and a standardised non-verbal measure of mental ability (Raven's 12-item Advanced Progressive Matrices; Pearson Education, 2010). On the second and third (test) sessions, participants arrived in the morning and were administered a tablet

containing 20mg domperidone (an antiemetic), followed 20 minutes later by either 1.5mg cabergoline or a placebo (drug and placebo tablets were indistinguishable). This dose was chosen to be greater than that given in a previous study where inconsistent effects on behaviour were observed (1.25mg; Frank and O'Reilly, 2006), with the addition of domperidone masking in order to mitigate against potential physical side-effects.

Testing commenced two hours after ingestion of the second tablet, in order to allow drug plasma levels to reach maximum concentration (Andreotti et al., 1995). On each test session participants completed visual analogue scale (VAS) measures of mood, affect, physical side effects and knowledge of the drug/placebo manipulation. Drug/placebo order was counterbalanced across subjects, with a minimum two weeks washout period between the two test sessions.

5.2.1.3 Risky decision-making paradigm

Risky decision-making was probed using the probabilistic choice task described previously by Rogers and colleagues (Rogers et al., 2003; Murphy et al., 2008). Briefly, on each trial subjects are required to choose between two simultaneously presented gambles. Each gamble is represented visually by a histogram, the height of which indicates the *relative probability* of winning a given number of points. The *magnitude of possible gains* is indicated in green above each histogram, with the *magnitude of possible losses* indicated underneath in red.

On each trial, one gamble always consists of a 50:50 chance of winning or losing 10 points (the 'control' gamble, expected value zero). The alternative ('experimental') gamble varies in:

a) probability of winning (0.6 or 0.4)

b) magnitude of possible gains (30 or 70 points) and

c) magnitude of possible losses (30 or 70 points).

These gamble properties are completely crossed, yielding eight trial types. Visual feedback (win/lose) is given after each choice is made, and the revised running total of points is presented before the next trial.

Subjects completed four blocks of 20 trials, and were instructed that the highest total score they managed to achieve would be converted into pence and paid at the end of the task as a cash bonus. Deliberation (response) times were also recorded.

5.2.1.4 Choice data analysis

Data were analysed as proportion of choices of the 'experimental' gamble, as a function of probability of winning, size of possible gains, and size of possible losses. Specifically, proportionate choice data were entered into a repeated-measures ANOVA with within-subjects factors of drug, probability of winning,

size of expected gains, and size of expected losses. Treatment order (active preparation on the first *vs* second test session) was included as a between-subjects factor in the model. A similar analysis was carried out for the response time data. Choices were also assessed in terms of expected value and 'riskiness' of chosen gambles, with the latter defined as the standard deviation of the possible outcomes of each chosen gamble. All reported simple effects analyses are via pairwise comparisons using the Bonferroni adjustment for multiple comparisons. All reported statistical tests were two-tailed, with an alpha of 0.05.

5.2.2 Results

5.2.2.1 Proportionate choice data

No significant main effect of drug order, or interaction between factors of drug and drug order, was found (both $p>0.09$). Drug order was therefore discarded from the model for subsequent analyses, in order to maximize power. In general, participants chose the 'experimental' gamble significantly more often when its *probability of winning* was high compared to when it was low ($F(1,18)=40.305$, $\eta_p^2=0.691$, $p<0.001$). This pattern of decision-making was significantly exaggerated under cabergoline relative to placebo (drug*probability of winning; $F(1,18)=6.733$, $\eta_p^2=0.272$, $p=0.018$).

Subjects also chose the 'experimental' gamble significantly more often when *expected gains* were large than when expected gains were small ($F(1,18)=50.522$,

η_p^2=0.736, p<0.001). However, there was no strong evidence that this pattern of choice was different under cabergoline (drug*size of possible gains, F(1,18)=3.615, p=0.074).

Finally, volunteers chose the 'experimental' gamble significantly less often when its *expected losses* were large than when its expected losses were small (F(1,18)=56.486, η_p^2=0.758, p=0.001). This pattern of decision-making was significantly attenuated under cabergoline (drug*size of possible losses; F(1,18)=6.773, η_p^2=0.273, p=0.018). For a summary of these effects see **Figure 19**.

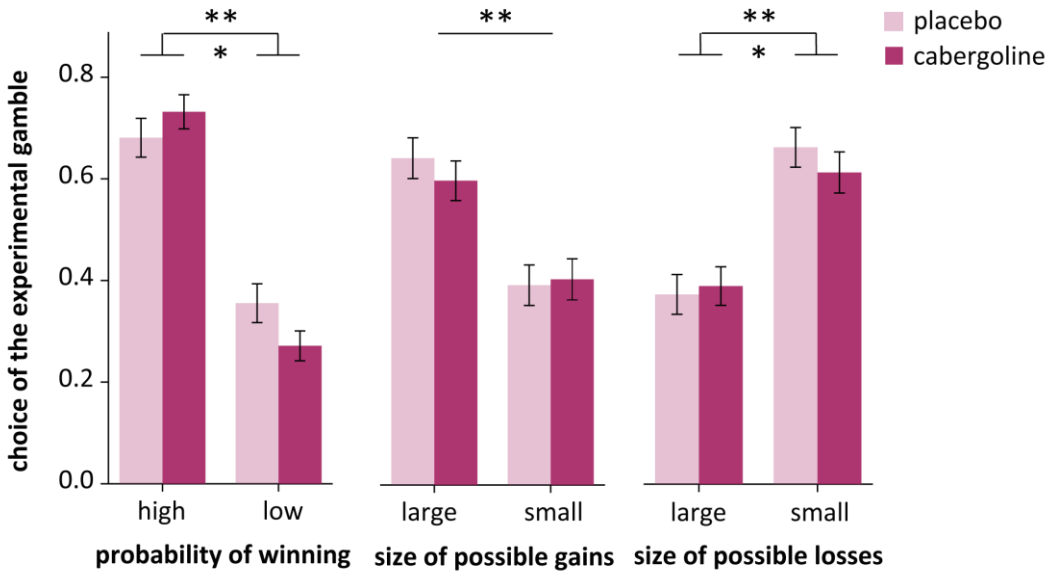

Figure 19. Proportionate choice of the 'experimental' gamble according to gamble properties, under placebo and cabergoline. There was no effect of cabergoline on overall proportion of choices of the 'experimental' gamble (p=0.480), and no significant higher-order interactions involving the factor of drug (all p>0.2). **p<0.001, *p<0.05.

5.2.2.2 Interaction with individual differences

UPPS 'sensation-seeking' (SS) subscore was found to interact significantly with both effects of drug on choice behaviour (drug*pwin*SS score: $F(1,17)=6.331$, $\eta_p^2=0.271$, $p=0.022$; drug*losses*SS score: $F(1,17)=11.501$, $\eta_p^2=0.404$, $p=0.003$; by comparison interactions with age, estimated IQ, working memory capacity and total self-reported impulsivity were all $p>0.3$).

Indeed, drug interactions with the factors probability of winning (pwin) and size of expected losses appear to be driven mainly by subjects with *lower* SS scores (**Figure 20A**). Simple effects analysis revealed that, when defining 'low' and 'high' SS groups by a median split of SS scores, low sensation-seekers (LSSs) chose more 'experimental' gambles when pwin was high ($F(1,17)=5.996$, $p=0.025$) and fewer when pwin was low ($F(1,17)=7.808$, $p=0.012$), on drug relative to placebo. By contrast, the HSS group did not differ in their choice of low or high pwin options between drug and placebo conditions ($p>0.2$).

LSSs also showed non-significant trends towards choosing fewer gambles when potential losses were small ($F(1,17)=4.262$, $p=0.0546$), and more gambles when potential losses were large ($F(1,17)=3.052$, $p=0.090$; **Figure 20A**), on cabergoline compared with placebo. Neither of these effects approached significance in the high sensation-seeking (HSS) group ($p>0.2$). HSS and LSS groups did not differ significantly in terms of any other self-reported impulsivity subscale scores, age, digit span, or estimated IQ (all $p>0.3$).

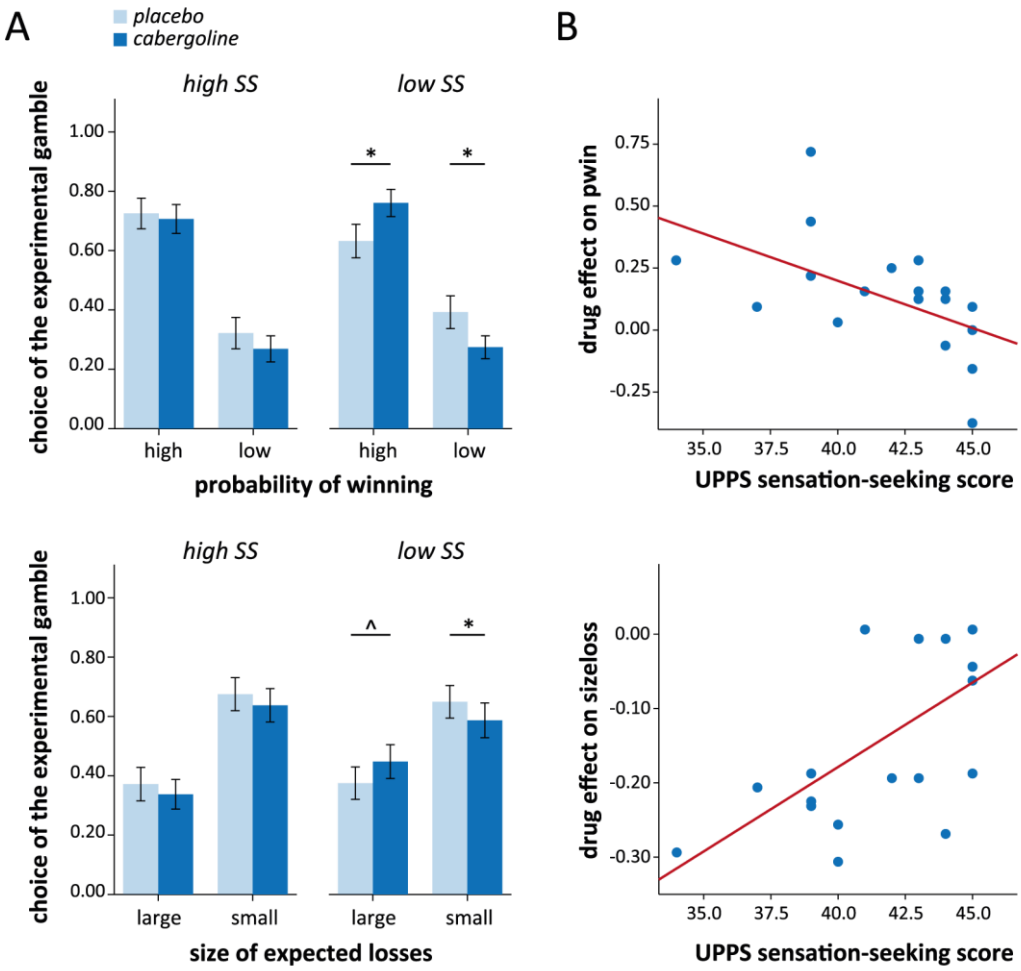

Figure 20. Effects of cabergoline on choice behaviour (II)

A Effects of cabergoline on subjects' choice behaviour, divided into 'high' and 'low' sensation-seeking (SS) groups via a median split of UPPS SS subscale scores. For low SS subjects only, modulation of choice behaviour was significantly exaggerated in accordance with information about the probability of winning, and tended to be attenuated in accordance with information about the size of expected losses, on cabergoline relative to placebo (*nb* SS score was a significant continuous covariate of both effects of drug on choice). *p<0.05, ^^p=0.0546, ^p<0.10.

B Relationships between magnitude of drug effect indices (difference in magnitude of effect of a change in probability of winning or magnitude of expected loss on proportionate choice of the experimental gamble between drug and placebo conditions) and UPPS SS score (r=-0.521, p=0.022; r=0.611, p=0.005). In both cases, individuals with lower SS scores showed larger effects of cabergoline on their choice behaviour.

In order to quantify these effects at the individual level, two indices of magnitude of drug effect on choice were calculated for each subject (difference in magnitude of the effect of a change in probability of winning, or magnitude of possible loss, on proportionate choice of the experimental gamble between drug and placebo conditions). SS score was found to be a significant predictor of both these indices (r^2_{adj} = 0.229, p=0.022; r^2_{adj} = 0.336, p=0.005; linear regression analysis), but not estimated IQ, digit span, or other self-reported impulsivity score (all p>0.1). In both cases, participants with lower SS scores were more influenced in their behaviour by cabergoline (**Figure 2B**). The two indices themselves were not significantly correlated (p>0.1).

5.2.2.3 Deliberation times

There were no significant effects of probability of winning, size of possible gains or size of possible losses on participants' deliberation times (all F<1), and no significant effect of cabergoline on response timing (p>0.1). There were no significant interaction effects of drug, gamble properties and SS score on deliberation times (all p>0.1).

5.2.2.4 Expected value and risk

Expected value of gambles was significantly linearly related to proportionate choice under both placebo and cabergoline (r^2_{adj} = 0.890, p<0.001; r^2_{adj} = 0.737, p=0.004; regression coefficients not significantly different, p=0.924). Gamble riskiness (SD) was not significantly related to proportionate choice under either drug condition (p>0.1). There was no significant effect of drug on mean expected value or mean riskiness of chosen gambles (both p>0.1). There were also no significant interactions of drug and SS score on these measures (p>0.1).

5.2.2.5 Individual differences at baseline

When considering data from the placebo session alone, there were no significant interactions between SS score and the effects of gamble properties (pwin, size of expected gains and losses) on choice (all p>0.1). There were also no significant relationships between any single choice parameters (i.e. mean chosen gamble riskiness, mean chosen gamble expected value and total points won) and SS score (all p>0.1). There was, however, a significant negative correlation between SS score and mean deliberation time on placebo (r =-.479, p=0.038; **Figure 21A**), that was not evident under cabergoline (p>0.1). A repeated measures ANOVA of mean deliberation time with the between-subjects factor of SS group revealed that low SS subjects showed a trend towards significantly slower responding, on the placebo session only (drug*SS group interaction, F(1,17)=4.404, p=0.0511; **Figure 21B**).

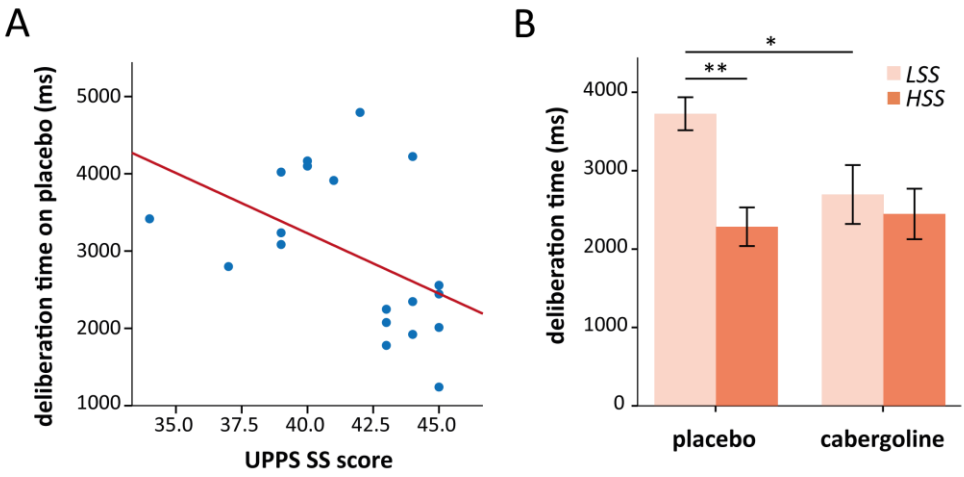

Figure 21. Baseline differences in deliberation time according to self-reported sensation-seeking.

A Mean choice reaction time on placebo is negatively correlated with UPPS sensation-seeking (SS) score (r=-.479, p=0.038).

B Low SS (LSS) subjects show slower choice RTs than high SS (HSS) subjects on placebo sessions only. **p<0.001, *p=0.023.

5.2.2.6 Subjective effects of drug treatment

At an uncorrected threshold, participants were significantly more calm (p=0.033) and drowsy (p=0.017), and also reported slightly more headache (p=0.02), on cabergoline relative to placebo. However, change on any of these measures was not significantly related to either of the drug effect indices, or self-reported SS score (all p>0.1) – suggesting this did not contribute to either main effects, or individual differences in effect of, cabergoline. No significant effects of drug were found on any other potential physical side effects (p>0.1), mood or affect scales

(p>0.1; 26 measures in total) and knowledge of the drug/placebo manipulation was not found to differ significantly between test sessions ($t_{1,18}$=1.681, p>0.1).

5.3 Study 2

In the previous study, we found greater effects of a D2 agonist in *lower* SS participants (**section 5.2**). Based on this finding and hypothesised D2 system function in low and high-SS individuals (as outlined in Gjedde et al. 2010, see **section 5.4**), we next sought to examine whether a D2 *antagonist* might selectively *attenuate* risky choice in (clinically relevant) higher SS individuals.

5.3.1 Methods

5.3.1.1 Participants

Participants were 30 healthy males, mean age 22.3 (SD 2.74), as described for **Chapter 3**. Although the original power calculation for this study was carried out based on predicted effect size for a different task (see **Chapter 3**), supplementary analysis based on the results of **Study 1** suggested this would also represent a sufficient sample size for this study. Specifically, we previously found moderately strong (r=0.521–0.611) relationships between self-reported SS and magnitude of effects of a D2ergic drug on risky decision-making (see **section 5.2)**. A power calculation determined that a sample of 29 participants would reliably allow us

to detect a true effect size of *r*=0.50 or higher in this study, with an alpha of 0.05 (two-tailed) and conventional power of 80%. One participant was unable to attend for a final test session and so their data were excluded from the analysis, yielding a final *N* of 29.

5.3.1.2 Design

The study was carried out according to a within-subjects double-blind placebo-controlled design, as described in **Chapter 3**.

5.3.1.3 Risky decision-making paradigm

The risky decision-making paradigm was exactly as described for study 1 (see **section 5.2.1.3**).

5.3.1.4 Analysis

Choice and response time data from the risky decision-making task were analysed in the same way as described for **Study 1** (see **section 5.2.1.4**). Non-normally distributed demographic information was compared between low and

high SS participants via the non-parametric independent-samples median test. All reported statistical tests were two-tailed, with an alpha of 0.05.

5.3.2 Results

5.3.2.1 Proportionate choice data

Overall, participants were significantly influenced in their choice of the 'experimental' gamble by all three gamble parameters. They chose the experimental gamble significantly more often when the probability of winning was high than when the probability of winning was low (mean proportion of trials (± SEM) 0.730 ± 0.030 *vs* 0.248 ± 0.043; $F(1,27)=109.275$, $\eta_p^2=0.802$, $p<0.001$), when the magnitude of the expected gains was large compared to when it was small (0.606 ± 0.034 *vs* 0.372 ± 0.029; $F(1,27)=81.552$, $\eta_p^2=0.751$, $p<0.001$), and when the magnitude of the expected losses was small compared to when it was large (0.627 ± 0.030 *vs* 0.351 ± 0.033; $F(1,27)=131.754$, $\eta_p^2=0.830$, $p<0.001$).

There was no significant main effect of drug treatment ($p>0.1$), or interaction between the factors of drug treatment and treatment order (drug*drug order; $p>0.1$), on proportionate choice of the experimental gamble. There were no significant interactions of drug treatment with gamble parameters of probability of winning, size of expected gains, or size off expected losses (all $p>0.1$) – nor

interactions of any of these factors with treatment order (all $p>0.1$). Drug order was non-significant overall as a between-subjects factor ($p>0.1$).

There were no significant effects of drug treatment on mean chosen gamble EV or mean chosen gamble riskiness (SD); all $p>0.1$ (or drug*drug order interactions, $p>0.1$).

5.3.2.2 Individual differences in drug effects on choice

The planned check for any drug effects dependent on individual differences in trait SS was next carried out. As previously no effects of treatment order were found on any choice measures, drug order was discarded from subsequent analyses of these data in order to maximize sensitivity.

When UPPS sensation-seeking score was included as a covariate in the model of proportionate choice data, there was a significant interaction between drug treatment and SS score on choice of the experimental gamble (drug*SS score: $F(1,27)=4.850$, $\eta_p^2=0.152$, $p=0.036$), and trend towards a three-way interaction with probability of winning on the experimental gamble (drug*pwin*SS score $p=0.096$; all other interactions $p>0.1$).

Simple effects analysis revealed that *higher* SS individuals chose a lower proportion of (riskier) experimental gambles overall on haloperidol compared

with placebo ($F(1,27)=4.783$, $\eta_p^2=0.151$, $p=0.038$; low SS subjects $p>0.1$; **Figure 22**).

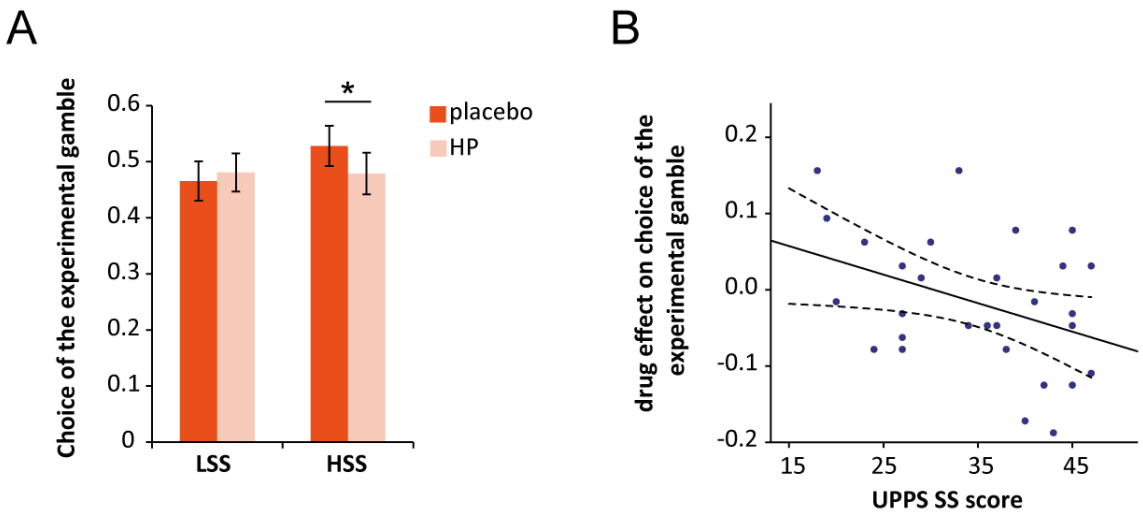

Figure 22. Effects of haloperidol and self-reported sensation-seeking on overall choice of the experimental gamble

A Only high sensation-seeking (HSS) individuals showed a reduction in choice of the (overall riskier) 'experimental' gambles on haloperidol (HP) compared with placebo (SD experimental gamble ≥29, SD control gamble=10; difference between drug and placebo for low sensation-seekers, LSSs, $p>0.1$). *$p<0.05$

B Relationship between self-reported sensation-seeking (SS) score and change in overall preference for experimental gambles on drug vs placebo ($r=-0.390$, $p=0.036$): higher SS individuals showed a shift in preference towards the less risky control gamble under haloperidol. Dotted lines represent 95% confidence intervals.

Exploratory investigation of simple effects for the three-way interaction indicated that this may have been driven by a decrease in choice of low probability of *winning gambles* selectively in *high SS* participants on drug *vs*

placebo ($F(1,27)=8.460$, $\eta_p^2=0.242$, $p=0.007$; all other conditions $p>0.1$; **Figure 23A**).

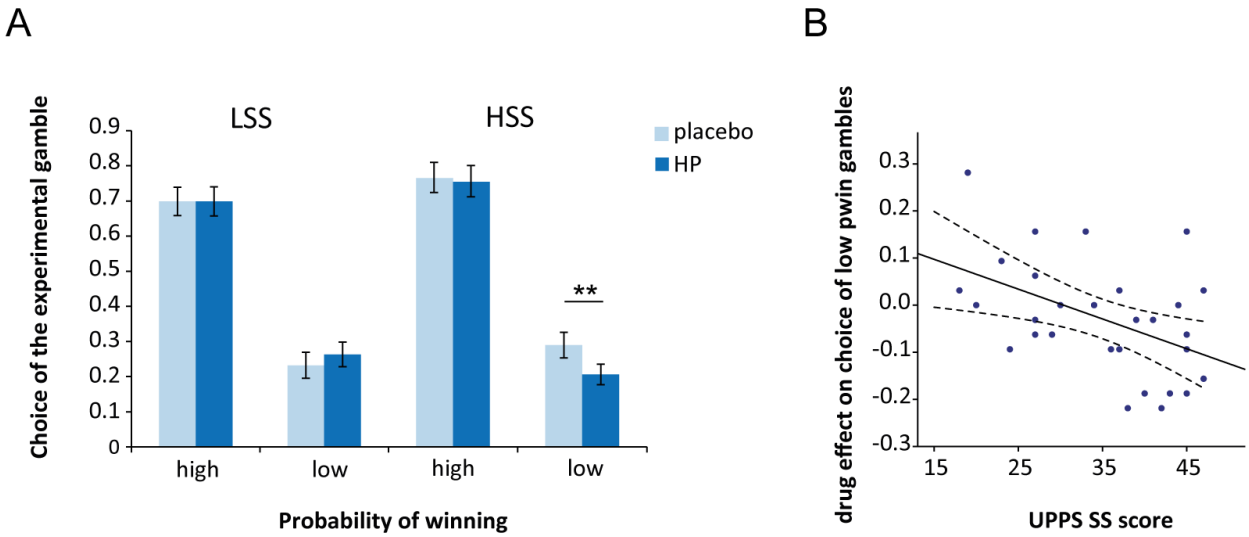

Figure 23. Effects of haloperidol and self-reported sensation-seeking on choice of low probability of winning experimental gambles.

A High sensation-seeking (HSS) individuals only chose significantly fewer low probability of winning gambles on haloperidol (HP) compared with placebo ($p=0.007$, all other conditions $p>0.1$; *nb* drug*SS group*probability of winning, $p=0.096$). Error bars represent within-subjects SEM. **$p<0.01$, drug *vs* placebo.

B Relationship between self-reported SS score and the degree of change of choice of low probability of winning (low pwin) gambles on drug vs placebo ($r= -0.471$, $p=0.010$): individuals higher in trait SS showed the biggest decreases in choice of low probability of winning gambles. Dotted lines represent 95% confidence intervals.

Indeed, there was a significant relationship between change in choice of low probability of winning gambles between drug and placebo sessions and UPPS sensation-seeking score (greater decrease in choice observed in higher-scoring SS individuals, r=-0.471, p=0.010; **Figure 23B**). No relationship was found between effect of drug on choice of low probability of winning gambles and drug effects on VAS mood/alertness ratings, drug effects on ARCI subscale scores most likely to show significant effects of haloperidol treatment (PCAG 'sedation' or LSD 'dysphoria' subscales), or drug effect on general psychomotor (letter digit substitution task) performance (p>0.1). In support of the possibility that a change in choice of low probability gambles was driving the overall decrease in choice of experimental gambles in the high SS group, the two effects were found to be strongly positively correlated (r=0.796, p<0.001).

The findings from the main analysis were somewhat reflected in overall task performance measures: when self-reported SS score was entered as a covariate to the model of the summary statistic data, there was found to be a non-significant trend towards a drug*SS group interaction on the mean expected value of chosen gambles (p=0.081). Exploratory simple effects analysis revealed that high SS individuals chose gambles with a significantly higher mean expected value on haloperidol compared with placebo (F(1,27)=4.664, η_p^2=0.147, p=0.040), but that low SS individuals showed no change in the expected value of chosen gambles under drug treatment (p>0.1). There was no interaction of drug with SS score on the mean riskiness (SD) of chosen gambles (p>0.1).

5.3.2.3 Deliberation times

Overall participants were faster to choose between gambles when the probability of winning was high compared to when it was low ($F(1,27)=6.584$, $\eta_p^2=0.196$, $p=0.016$; mean RT (±SEM) 1316 ± 76.9ms *vs* 1427 ± 91.9ms), and when potential gains were large compared to when they were small ($F(1,27)=19.351$, $\eta_p^2=0.417$, $p<0.001$; 1324 ± 84.9ms *vs* 1419 ± 89.2ms). There was no effect on deliberation time of magnitude of expected losses ($p>0.1$).

There were no overall significant effects of haloperidol on mean deliberation time ($p>0.1$), and no significant interactions between factors of drug and probability of winning, size of expected gains, or size of expected losses on response timing (all $p>0.1$). Drug order was also not significant overall as a between-subjects factor in the response time model ($p>0.1$).

However, there was a significant drug*drug order interaction on mean deliberation time ($F(1,27)=9.019$, $\eta_p^2=0.250$, $p=0.006$). Simple effects analysis showed that participants responded *faster* on haloperidol compared with placebo only when the drug was taken on the second test session ($F(1,27)=10.995$, $\eta_p^2=0.289$, $p=0.003$; 1325 ± 117ms *vs* 1570 ± 122ms; for those who took the drug first there was no difference in mean RT between sessions, $p=0.339$). This suggests that receiving the active treatment on the first session may have blocked a general effect to decrease deliberation times between the first and second test sessions (as observed in participants who took the drug on the second test session).

If SS score was added to the main response time model, there was no evidence for an interaction of SS status with any gamble properties on response timing (all $p>0.1$). Drug*SS score and drug*drug order*SS score interactions on response timing were also non-significant ($p>0.1$). It is therefore unlikely that SS score*drug effect interactions observed on choice measures were due to timing differences, e.g. high sensation-seekers being more rushed under haloperidol.

5.3.2.4 Individual differences at baseline

When considering data from the placebo session only, there was no interaction of SS score with experimental gamble properties of probability of winning, size of expected gains or size of expected losses (all $p>0.1$). There was no significant effect of SS status on the mean expected value or riskiness (SD) of chosen gambles on placebo ($p>0.1$). There was no effect of self-reported SS on mean deliberation time on either drug or placebo ($p>0.1$).

High sensation-seekers scored significantly higher than lower sensation-seekers on both self-reported number of alcoholic drinks consumed per week and the Alcohol Use Disorders Identification Test ($p=0.025$, $p=0.008$, independent-samples median tests on median split groups; cigarettes per week, age, weight and estimated IQ all $p>0.1$).

However, we found no evidence that differences in history of substance exposure underlies the differential effects of haloperidol treatment between SS groups

observed in our dataset. There were no significant relationships between weekly alcohol or cigarette consumption or AUDIT score and magnitude of drug effects (all $p>0.05$). High SS subjects who had/hadn't ($N=8$ vs $N=7$) ever engaged in recreational drug use (other than alcohol or tobacco) over the past year also did not differ in magnitude of any drug effects (all $p>0.1$).

5.3.2.5 Subjective and general psychomotor drug effects

There were no significant effects of haloperidol on VAS ratings of mood, affect, or potential physical side effects (16 scales, all $p>0.1$). There was also no effect of haloperidol on any subscale of the Addiction Research Centre Inventory (MBG 'euphoria', PCAG 'sedation', LSD 'dysphoric and psychotomimetic effects', BG and A 'stimulant-like effects' scales all $p>0.1$), or cardiovascular measures (blood pressure and heart rate, $p>0.1$). There was no effect of drug treatment upon participant ratings of whether they believed they were on the drug or placebo session ($p>0.1$). Finally, there was no effect of haloperidol on general psychomotor function as indexed by letter digit substitution task performance ($p>0.1$).

5.3.2.6 Comparison to study 1 sample

Characteristics of samples from study 1 and study 2 on all measures available from both groups are recorded in **Table 10.** Participants from our second sample

were significantly younger, and scored significantly more highly on Raven's 12-APM (a test of nonverbal reasoning) than study 1 participants. The study 2 group also had a significantly lower mean sensation-seeking score, due to a wider range of scores in this sample (see Discussion).

	Study 1 (cabergoline)	**Study 2 (haloperidol)**
N	19	29
Age	28.3 (5.7)	22.4 (2.7)**
Raven's 12-APM score	7.1 (2.8)	8.9 (2.6)*
UPPS total score	110 (11.5)	108 (17.7)
UPPS urgency	27.2 (6.1)	27.6 (5.1)
UPPS lack of premeditation	22.4 (4.5)	23.5 (5.9)
UPPS lack of perseveration	19.1 (3.7)	21.8 (4.7)*
UPPS sensation-seeking	41.2 (3.6)	35 (9.1)*
range	33 – 45	20 – 45

Table 10. Demographic information for participants from study 1 and study 2. Unless otherwise specified, figures represent mean (SD). *p<0.05, **p<0.001 study 1 *vs* study 2.

5.4 Discussion

In our first study, we found significant effects of a single dose of the D2/D3 agonist cabergoline on decision-making under conditions of uncertainty or risk, which crucially depended on baseline differences in self-reported SS trait. Overall, the effect of cabergoline was to exaggerate modulation of choice behaviour in accordance with explicit signals about the probability of winning, and simultaneously to attenuate modulation of choice in accordance with information about the size of possible losses. Importantly, the magnitude of the drug effect was significantly moderated by baseline UPPS sensation-seeking score. In both cases, individuals who reported *lower* levels of trait SS showed a much stronger influence of cabergoline on their choice behaviour.

In our second study, we examined the effects of the D2 antagonist haloperidol on the same task. Although there were no overall effects of drug treatment on decision-making, we again found evidence of a significant interaction between self-reported sensation-seeking (UPPS SS score) and the D2ergic drug on risky choice. Specifically, we now found that *higher* sensation-seekers exhibited decreased overall choice of the riskier experimental gambles (SD 10 *vs* SD≥29) on haloperidol *vs* placebo. This effect appeared to be mainly driven by a decrease in choice of *low probability of winning* experimental gambles on haloperidol compared with placebo, selectively in *high* SS participants. This finding can be contrasted directly with results from our first study, where a decrease in choice of *low probability* of experimental gambles under cabergoline was selectively observed in *low* sensation-seekers.

Previous findings regarding the effects of D2 agonists and antagonists on risk-taking behaviour in human volunteers are mixed: for example recording a lack of effect on main dependent variables (Zack and Poulos, 2007; Riba et al., 2008; Porchet et al., 2013), or disruption of complex trial-to-trial effects (Tremblay et al., 2011), which may differ between healthy participants and patient samples. It is possible that this complexity is at least in part due to individual differences in drug effects. It is fairly well established that D2ergic drugs often have baseline-dependent effects. For example, effects of D2 receptor agonists have been found to depend on self-reported impulsivity in humans (Cools et al., 2007) and behavioural impulsivity in rodents (Moreno et al., 2013). Like impulsivity, individual differences SS personality have been linked to variation in the efficacy of D2ergic neurotransmission (Ratsma et al., 2001; Hamidovic et al., 2009; Gjedde et al., 2010), therefore it is reasonable to expect that differences in self-reported SS might predict differences in effects of D2ergic drugs.

Our finding of a greater effect of cabergoline in *lower* sensation-seekers (LSSs) might seem somewhat surprising given previous reports that higher sensation-seekers (HSSs) exhibit increased physiological and subjective responses to dopaminergic stimulants such as amphetamine (Kelly et al., 2006; Stoops et al., 2007), and that SS score correlates positively with amphetamine-induced DA release in the striatum (Riccardi et al., 2006). However, Gjedde and colleagues have recently argued on the basis of PET evidence that LSSs have both lower D2/D3 receptor density *and* lower endogenous DA levels than their HSS counterparts, such that the 'gain' of the DA system (reactivity to dopamine) in the

striatum is inversely related to SS score (Gjedde et al., 2010). Thus the less sensation-seeking individuals would be expected to have greater DA gain.

In support of this hypothesis, there is some evidence that LSSs may have lower endogenous DA levels than HSSs. LSSs exhibit higher platelet levels of monoamine oxidase (a DA catabolist, Zuckerman, 1985; Carrasco et al., 1999), and LSS status has been associated with relatively lower activity dopa decarboxylase (DDC; a rate-limiting enzyme for DA synthesis) in the striatum; via both variation in the *DDC* gene itself (Derringer et al., 2010) and the Taq1a polymorphism (Ratsma et al., 2001; Laakso et al., 2005; Eisenberg et al., 2007).

Thus LSS participants may have high DA gain. Direct D2 agonists, as used in our cabergoline study, would therefore be expected to exert greater effects in these individuals. Similarly, higher levels of endogenous dopamine in *higher* SS participants, leading to greater occupancy of D2 receptors by dopamine under normal conditions, could result in a greater effect of blocking the downstream signalling cascade usually evoked by binding of endogenous ligand by a 'silent' type D2 an*t*agonist (Cosi et al., 2006) in *higher* sensation-seekers.

The studies presented here have some clear limitations. Firstly, both psychopharmacological agents we have used are not absolutely specific in their D2 receptor affinity. Cabergoline also has limited agonist activity at 5-HT_{2A},5-HT_{2B} and D1 receptors (Kvernmo et al., 2006). Although haloperidol is considered to be a relatively selective D2-type receptor antagonist (Arnt and Skarsfeldt, 1998), it also has been shown to have modest affinity for the α-1 adrenoreceptor

and the serotonin 2A receptor (Richelson and Souder, 2000). Therefore it is not possible to be completely certain about the mechanism underlying the behavioural effects outlined above.

A further complication in D2-type receptor pharmacology is the existence of both pre and post-synaptic D2 receptors, which can potentially have opposing effects on dopaminergic transmission (Usiello et al., 2000). Whereas presynaptic D2 autoreceptors negatively regulate phasic DA responses, postsynaptic D2Rs regulate tonic DA signalling implicated in the representation of risk (Grace, 1991; Schmitz et al., 2003; Fiorillo et al., 2003; Schultz, 2010). This leads to difficulties in interpreting drug effects, particularly at low doses where only higher-affinity inhibitory autoreceptors might be stimulated.

In our first study, we attempted to ensure stimulation of post-synaptic D2Rs by using the high-affinity D2/D3 agonist cabergoline (Kvernmo et al., 2006), at a higher dose than a previous study where inconsistent drug effects were observed (Frank and O'Reilly, 2006). Domperidone masking was used to minimise potentially unblinding side-effects such as nausea, and overall subjects were unaware of the drug/placebo manipulation. We also found no evidence of increased negative affect on the drug, which previously has been taken as an indicator of predominantly pre-synaptic drug action (Hamidovic et al., 2008). Haloperidol has previously been reported to induce high levels of brain D2 receptor occupancy at relatively low doses (53%–74% at 2mg and 60–70% at 3 mg, orally; Nordström et al., 1992; Kapur et al., 1997), therefore we are fairly confident that the dose used in our study (2.5mg) was sufficient to occupy post-

synaptic receptor binding sites. However, in the absence of other indicators, we are unable to draw any strong inferences about pre *vs* post-synaptic drug actions in either study.

It is also possible that differential history of substance exposure between high and low SS individuals resulted in the SS-dependent drug effects in our studies, as recreational drugs have been shown to affect striatal D2 receptor distribution in animal models (e.g. Caprioli et al., 2013). This factor is to a certain extent confounded in our trait of interest, due to this kind of behaviour being specifically probed in SS questionnaire items. However, increased engagement in such activities is a core part of the conceptualisation of SS personality, and evidence of an association between SS and e.g. recreational drug use gives us some confidence that our between-subjects grouping was related to real-life behaviours of interest.

In our second study, overall levels and frequencies of substance use were low, and we found no evidence that differences in history of substance exposure underlay the observed differential effects of haloperidol treatment between SS groups (unfortunately this data was not available for the first set of participants). There was no significant relationship between total relevant demographic behaviour or alcohol use disorder (AUDIT) scores and magnitude of drug effect indices, and high SS volunteers who had/hadn't ever engaged in recreational drug use didn't differ in magnitude of any drug effects (although it is likely that this last comparison is underpowered).

Finally, there are some differences in participant characteristics that may limit the validity of comparing results from the two different pharmacological agents between samples (see **Table 10**). At *N*=20, results from the cabergoline study may not be optimally powered, and would benefit from future replication. Conversely, it should be noted that effect sizes were generally weaker for the second study (haloperidol). There was also a significantly lower mean SS score in our second study sample. However, it appears that this is due to additional participants at the lower end of the SS score range in this group (possible scores on the UPPS SS subscale range from 12-48), and the score ranges overlap fully between groups at the higher SS end. As the largest effects of study 1 were found in lower sensation-seekers, and the largest effects in study were found in higher sensation-seekers, this may not be problematic.

Despite its clear clinical relevance, pharmacological manipulation of decision-making under risk is currently relatively underexplored in both humans and animals (Winstanley, 2011). In these studies, we provide for the first time to our knowledge evidence for pharmacological manipulation of risk-taking behaviour, depending on baseline differences in SS trait. These findings emphasise the importance of considering individual differences such as SS when investigating risky decision-making, and may have relevance for the development of pharmacotherapies for disorders involving excessive risk-taking, such as pathological gambling.

General Discussion

A major aim of the work presented in this thesis was to devise a behavioural test of human sensation-seeking, designed to be directly comparable to those used in animal studies (**Chapter 2**). In the paradigm we developed, human participants chose whether or not to self-administer an 'intense and unusual' sensory stimulus (mild electrical stimulation or MES) during performance of an economic decision-making task (**Figure 3**). Across several samples of volunteers, we found that some individuals choose an above-chance proportion of stimuli associated with receipt of this intense tactile stimulus – even when this involved the sacrifice of economic gain. Importantly, the extent of this preference correlated positively with self-reported sensation-seeking personality, but not with scores on measures of other impulsive tendencies, anxiety, or hedonic state (**Figure 5**, **Figure 6**, **Figure 10**; **Chapters 2, 3, and 4**).

In support of the hypothesis that the intense sensory stimulus we utilised was appetitive for some individuals, participants who chose higher proportions of MES-associated options increased their 'liking' ratings of these stimuli following establishment of this contingency (**Figure 5**, **Figure 9**; **Chapters 2 and 4**). In our largest sample (N=94), we also recorded how participants rated their feelings about the electric stimulus *itself*, and found that increased choice of MES-associated stimuli was associated with higher 'liking' ratings of the sensation of MES receipt (**Chapter 4**).

Performance on our sensation-seeking task was also related to real-life behaviours of interest. Specifically, individuals who assigned a higher economic value to opportunity to receive the MES reported increased frequency of tobacco

smoking, and showed non-significant trends towards greater weekly alcohol consumption (**Chapters 2, 3, and 4).** Interestingly, we did not find that sensation-seeking task performance was significantly related to scores on substance use disorder screening questionnaires (for alcohol or illicit drugs; **Chapter 4**). This finding is consistent with the hypothesis proposed by some researchers that sensation-seeking trait is mainly related to initial experimentation and non-problematic substance use, rather than tendency to progress to compulsive drug use (e.g. Ersche et al., 2013; **Chapter 1**). However, it should be noted that scores greater than zero on these measures were rare in our healthy volunteers (indeed response data were substantially positively skewed). Therefore it is unlikely that we captured sufficient variance in scores in these measures to undertake a fair test of this relationship.

Thus data from several independent samples appear to support the assertion that our novel paradigm probes behaviour relevant to the personality construct of sensation-seeking. Significantly, in none of the samples was preference for the MES related to absolute stimulation intensity (all participants rated the MES as being the same *subjective* intensity), or explicit knowledge of stimulus-MES associations. Additionally, individual estimates of MES value exhibit reasonable to good test-retest reliability (**Chapters 3** and **4**), with no evidence for overall changes in MES preference over the course of the task (**Chapter 2**; even when extended to 300 test trials; **Figure 10**, **Chapter 4**). This absence of any obvious habituation supports the idea that performance on this measure probes preference for stimulus *intensity*, as opposed to novelty (for a discussion of the

relationship between the constructs of sensation and novelty-seeking see **Chapter 1**).

There was evidence of a significant decrease in MES value between laboratory and magnetic resonance imaging (MRI) scanner environments (**Chapter 4**). This perhaps represented the impact of the unusual sensory experience of being in the MRI scanner (for many of our participants, this was their first experience of undergoing an MRI scan). If this was indeed a contributory factor, recruitment of more MR-experienced participants for future studies might help ameliorate this effect. Difficulties in recruitment of high behavioural sensation-seekers who met local MR safety requirements with respect to tattoos, piercings, and past injury, as well as a minimum 3-weeks abstention from illicit substance consumption precluded the application of this criterion in the current study.

An important finding replicated across all studies using our novel paradigm was the observation of a strongly significant relationship between MES preference and relative reaction-times for MES-associated compared with non MES-associated stimuli. In all groups, we found a *speeding* of choice reaction-times for MES-associated stimuli in individuals who assigned a *positive* value to opportunity to experience the MES ('behavioural high sensation-seekers'), but *slowed* reaction times in individuals who for whom the MES had a *negative* value ('behavioural low sensation-seekers'; **Figure 4**, **Figure 6**, **Figure 10**; **Chapters 2, 3, and 4**). In line with previous observations of speeded relative reaction times for preferred choice options (e.g. Crockett et al., 2009; Wright et al., 2012), we

have interpreted this finding as indicating the involvement of low-level approach-avoidance mechanisms in sensation-seeking behaviour.

Several previous investigators have suggested that a key constituent of individual differences in sensation-seeking trait is the differential activation of approach *vs* avoidance processes in the face of the opportunity for intense or unusual sensory experience (Zuckerman, 1990; Lang et al., 2005). The work presented here may represent the first direct experimental evidence of approach-avoidance mechanisms at play *during* sensation-seeking-like behaviour in humans.

As outlined in **Chapter 1**, findings from diverse rodent models, as well as genetic and PET evidence from humans, has implicated individual differences in efficacy in transmission via D2-type (D2/D3/D4) dopamine (DA) receptors in sensation seeking trait, particularly in the midbrain (e.g. Bardo et al., 1996; Blanchard et al., 2009; Shin et al., 2010; Hamidovic et al., 2009; Gjedde et al., 2010). As striatal D2ergic function has been shown to be involved in the vigour of behavioural approach reactions (Salamone and Correa, 2002; Robbins and Everitt, 2007; Hoffmann and Nicola, 2014), inter-individual differences in this brain circuitry represents a candidate mechanism for the differential expression of approach (versus withdrawal) responses when faced with the opportunity to experience intense sensory stimuli (**Chapter 1**).

Here, we were able to make use of our novel paradigm to directly test the effects of a D2ergic agent on the expression of approach/avoidance reactions towards intense sensory stimulation within the same individuals (**Chapter 4**). Using this

approach, we were able to show that a relatively selective D2-type receptor antagonist (haloperidol) abolished the relationship between relative choice reaction-time for MES *vs* non MES-associated stimuli and the value participants assigned to opportunity to experience the MES (**Figure 7**). Specifically, haloperidol significantly decreased the (positive) economic value assigned to opportunity to experience the MES in individuals who exhibited approach-like speeded reaction times towards MES-associated stimuli under normal conditions, whilst leaving unchanged the (negative) MES value in individuals who showed slowed (avoidance-like) reaction-times (**Figure 8**). This finding supports the hypothesis that approach reactions towards intense sensory experiences in high sensation-seekers may indeed be at least partially mediated via the D2 receptor system.

How do our findings fit in with previous neurochemical theories of sensation-seeking in humans? Previously it has been argued on the basis of PET and other evidence that (1) higher sensation-seekers have higher tonic striatal DA levels, and (2) that the 'gain' (reactivity to the presence of DA) of the striatal D2 system is inversely related to trait sensation-seeking (Gjedde et al., 2010). Specifically, this hypothesis predicts greater amplification of the postsynaptic signalling cascade following DA binding to D2-type receptors in *higher* gain *lower* sensation-seekers, and a *lower* sensitivity reaction to DA binding (perhaps as a result of generally higher synaptic DA levels) in lower gain *higher* sensation-seekers.

Data from the psychopharmacological studies presented in this thesis are consistent with this account. The D2/D3 receptor *agonist* cabergoline had greatest effects on risky decision-making in *lower* sensation-seekers (**Figure 20**, **Chapter 5**), implying a greater sensitivity to direct D2 receptor agonism in these individuals. Conversely, we found greater effects of a silent D2-type receptor *antagonist* haloperidol in *higher* sensation-seekers (**Figure 8**, **Figure 22**, **Figure 23**; **Chapter 3, Chapter 5**). As application of haloperidol blocks post-synaptic signalling by endogenous ligand (but does not otherwise affect post-synaptic receptor function; Cosi et al., 2006), this suggests that higher sensation-seeking individuals (defined on the basis of both behavioural and self-report measures) were more sensitive to disruption of signalling by endogenous DA.

Although D2ergic agents have been shown to predominantly affect function in the striatum (Kuroki et al., 1999; Honey et al., 2003), this psychopharmacological evidence alone does not allow us to draw any inferences about the particular brain regions involved in individual differences in performance on our sensation-seeking measure. Therefore, in order to investigate in more detail how intense sensory stimulation might be processed as 'rewarding' in high sensation-seekers, we investigated individual differences in regional blood oxygenation level-dependent (BOLD) signal (a correlate of local excitatory neuronal activity, e.g. Lee et al., 2010) during sensation-seeking task performance using functional MRI (**Chapter 4**).

There was a significant positive relationship between the value participants assigned to opportunity to experience the MES and BOLD signal associated with

choice of MES-associated stimuli in both the ventral head of the caudate nucleus and the medial orbitofrontal cortex (mOFC; **Figure 11**). Crucially, there was a significant overlap between the encoding of positive economic value and MES-association in the mOFC, in high – but not low – behavioural sensation-seekers (**Figure 13**). Significantly, the cluster identified from this analysis was located within a region previously identified from a meta-analysis of functional imaging studies of brain regions jointly encoding the values of different kinds of rewards (Levy and Glimcher, 2012) (**Figure 13**). This suggests that only high sensation-seekers may encode opportunity to experience the sensory 'reward' of the MES in the same way as other rewards such as economic gain.

These functional imaging findings can also be interpreted according to the approach-avoidance framework outline above. Although somewhat speculative, the positive relationship observed between ventral striatal BOLD associated with choice of MES-associated options and individual estimates of MES value might reflect increased (dopaminergic) striatal activity. This is hypothesised to drive increased approach reactions towards the intense sensory stimulus in individuals who assigned a higher value to opportunity to receive the MES (i.e., higher sensation-seekers).

Conversely, we observed significant activation of the insula when choosing MES-associated stimuli in low, but not high, behavioural sensation-seeking individuals (**Figure 12**). Similarly, we found evidence for trial-by-trial variation in insula BOLD signal according to modelled internal probability of receiving the MES on that trial in only in low behavioural sensation-seekers (**Figure 15**). Notably, there

was no indication that MES-seekers and MES-avoiders (high and low behavioural sensation-seekers, respectively) differed in their knowledge of the choice stimuli-MES associations prior to entering the scanner. In conjunction with previous findings that the insula has a role in both the anticipation of aversive outcomes and avoidance of response options associated with loss or punishment (Nitschke et al., 2006; Samanez-Larkin et al., 2008; Palminteri et al., 2012), this suggests that the anticipation of receipt of intense sensory stimulation may have activated brain circuitry involved in avoidance responses in low – but not high – behavioural sensation-seekers. This interpretation would be consistent with the theory of sensation-seeking outlined in **Chapter 1**. Namely, that as well as displaying increased vigour of approach reactions towards intense and unusual sensory stimulation, higher sensation-seekers exhibit dampened – or even absent – activation of defensive withdrawal or avoidance systems to such stimuli (e.g. Lissek and Powers, 2003; Lissek et al., 2005).

In summary, data from the studies presented here provide considerable empirical support for the neurobiological model of human sensation-seeking outlined in **Chapter 1**. The development of a behavioural measure which appears to possess a certain degree construct validity as an index of the stable individual differences in preference for intense and unusual sensory experiences captured by questionnaire measures has allowed us to generate novel findings that may be directly comparable to the existing animal literature.

Convergent evidence from both sources supports the working hypothesis that higher sensation-seeking is driven by increased activation of approach

mechanisms when faced with the opportunity to self-administer 'intense and unusual' sensory stimulation. This increased approach tendency appears to be mediated, at least in part, by striatal dopamine function, particularly at D2-type receptors. High sensation-seekers additionally appear to lack the strong activation of brain circuitry associated with processing of highly salient and/or aversive stimuli observed in low sensation-seeking peers during anticipation of a similar subjective intensity sensory stimulus. Thus, the opportunity to experience such sensory stimulation may be encoded in the same way as other potential rewards in high sensation-seeking individuals. Conversely, intense sensory experiences that are explicitly endorsed as being "non-painful" appear to be processed in the same way as other aversive stimuli, and evoke avoidance responses in low sensation-seekers.

It is clear that the results presented here would benefit substantially from further exploration of the neural mechanisms involved. Additionally, it should be noted that findings drawn from analysis of relatively small sub-groups of behaviourally-defined high sensation-seeking individuals in some studies would particularly benefit from future replication.

One obvious extension study would be to carry out a complementary psychopharmacological study to our investigation of the effects of a D2-type receptor antagonist on the sensation-seeking task used here. Specifically, a crucial test would be whether MES-seeking could be *augmented* in some

individuals by application of a pro-dopaminergic agent, such as L-DOPA (a dopamine precursor), a direct dopamine receptor agonist, or a low dose of a psychomotor stimulant such as amphetamine. Although previous work has investigated the relationship between self-reported sensation-seeking and D2-type receptor 'availability', as measured using PET, it would be interesting to investigate the relationship between this measure and our behavioural index of sensation-seeking. In particular, it would be informative to determine possible relationships between MES preference and striatal dopamine release in response to amphetamine challenge (as measured by radio-ligand displacement) in striatal regions (*cf* Leyton et al., 2002; Riccardi et al., 2006).

It would also be interesting to further examine to what extent performance on our novel sensation-seeking paradigm relates to real-life propensity to engage in 'sensation-seeking' behaviours, in order to assess its ecological validity. For example, do individuals whom one might consider to be prototypical 'high sensation-seekers', such as regular recreational drug users or participants in high impact sports, exhibit increased preference for MES on our task? Indeed, it is possible that performance on our measure might relate to only certain sub-types of real-world sensation-seekers, limiting the generalizability of the findings presented here.

An important extension to our results from healthy volunteers would be to investigate behavioural sensation-seeking in relevant clinical populations. In particular, it would be very interesting to investigate whether individuals with diagnoses of substance use or pathological gambling disorders exhibit

heightened sensation-seeking on the task introduced here. Using an approach pioneered by Ersche and colleagues (Ersche et al., 2010, 2013), it could then be established whether differential task performance was specific to pathological populations (via comparison to non-addicted gamblers or drug users) or exhibits an endophenotype-like distribution (via comparison to non-affected siblings of patient samples). If behavioural task performance did reflect previous significant findings from these groups using self-report measures, the neural mechanisms underlying such group differences could then further be investigated, for example using functional imaging.

Further, as evidence from both humans and animals suggests that heightened sensation-seeking trait may be related to increased susceptibility to relapse in substance use disorders (**Chapter 1**), it might be investigated whether behavioural sensation-seeking is a more sensitive prospective marker of risk of relapse than self-report scores (which might be more subject to conformity biases, particularly when illicit substance use is specifically probed in questionnaire items).

Conversely, longitudinal studies are required to provide further support for the hypothesis that individuals higher in trait sensation-seeking may exhibit increased resilience to exposure to high-intensity stressors. It would be particularly informative to examine how neural processing of intense sensory stimulation may change pre *vs* post extended exposure to high stress-environments in individuals for whom, unfortunately, such exposure is highly likely (e.g. military and emergency service workers). Specifically, it would be

important to examine whether any changes in processing of such stimuli might depend on baseline (pre-exposure) response.

A final way to extend the results presented here would be to explore the possibility of back-translating our findings to animal models of sensation-seeking behaviour, in order to more finely explore the mechanisms involved. For example, mechanisms underlying our psychopharmacological results could be further investigated using the rodent model most closely analogous to our human task, the operant sensation-seeking (OSS) paradigm of Olsen and Winder (Olsen and Winder, 2009).

It has previously been shown on this paradigm that subcutaneous injection of the D2 antagonist flupenthixol increased responding for the sensory stimulus-associated response option ('active' lever; *ibid*) in rodents in a dose-dependent manner, an effect the authors interpreted as being due to reduced 'efficiency' of the sensory reward at low drug doses. As discussed above, we found that systemic administration of a moderate dose of the D2 antagonist haloperidol selectively decreased the value of additional intense sensory stimulation in higher sensation-seeking humans. As previous studies have shown different, even opposing, effects of D2ergic drugs on impulsive behaviour depending on both dose and the brain region to which the psychopharmacological agent is applied (e.g. Besson et al., 2010; Moreno et al., 2013), it would be useful to further explore changes in response on the OSS paradigm to both pro- and anti- D2ergic agents, depending on dose and location of application. Additionally, as we have presented evidence here that experimentally-induced changes in sensation-

seeking-like behaviour (e.g. via manipulation of brain dopamine function) may critically depend on baseline individual differences, it may potentially prove useful for future studies of relevant phenomena using animals models to take this into account in their analyses.

Further, to our knowledge, previous work using the OSS paradigm has not explored differential response latencies towards interaction with the active (audiovisual stimulus-producing) *vs* inactive levers. As this measure could be considered to be analogous to relative choice reaction time for MES-associated *vs* non MES-associated choice options on our human task, it would be interesting to explore if stable differences in this measure occur in rodents, and similarly to our human work, if these differences may be under D2ergic control. Such studies could be crucial in further determining the low-level approach-avoidance mechanisms we have proposed are a crucial determinant of individual differences in sensation-seeking tendencies.

The psychopathologies mentioned in this discussion are heterogeneous and almost certainly multi-causal. Better phenotyping of individuals with a diagnosis of these disorders, aided by a better understanding of neurobiological mechanisms underlying this heterogeneity, may support the development of more effective therapies tailored to specific individuals. For example, in the case of misuse of prescription drugs, it has been shown that the perceived

harmfulness of such drugs lowers the likelihood of misuse in low – but not high – sensation-seeking individuals (Arria et al., 2008).

Such considerations are also highly relevant for targeted prevention therapies. Recently, clinical trials in adolescents at high risk for development of alcohol use disorders have reported that targeting different psycho-educational and cognitive behavioural strategies towards different 'high risk' personality types can be successful (Conrod et al., 2008, 2013). Interestingly, these interventions were found to be most effective in reducing risk in high sensation-seeking individuals (Conrod et al., 2008). Conversely, if there might be clinical utility in pre-emptively targeting interventions aimed at increasing stress resilience in *lower* sensation-seeking individuals, this knowledge could be very valuable for populations at increased risk of trauma-related psychopathology (Solomon et al., 1995; Neria et al., 2000; Clinton et al., 2014).

It is clear that we are still at a very early stage of translating knowledge about underlying neurobiology into the clinical arena. Nevertheless, the body of work presented here, shows the potential power of using emerging neuroscience techniques to probe the mechanisms underlying sensation seeking. Further understanding of sensation-seeking trait may shed light on the aetiology of the various psychopathologies discussed above, but perhaps, most crucially, might also aid in developing individualised therapies and prevention strategies for these disorders.

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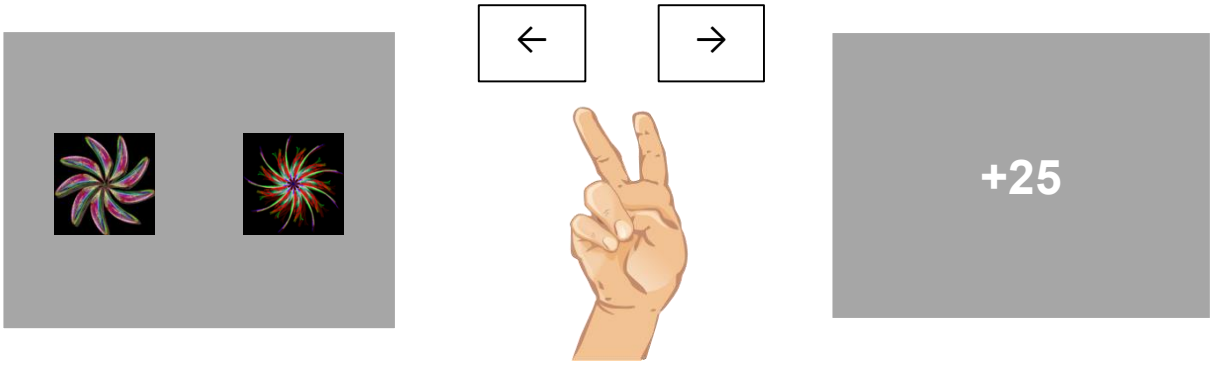
Appendix 1: Sensation-seeking task instructions

Instructions

In the first part of the experiment, you will see a pair of abstract pictures. Each picture is associated with winning a certain number of points.



On each trial, you must choose between the images by pressing the **left** or **right arrow keys** (to select the *left* or *right* image). The points you have won will then be displayed on the screen.

Your task is to try to learn for every pair which is the best image to choose, in order to win as many points as possible.

At the end of the experiment, you will get a cash bonus that depends on how many points you managed to collect.

In the second part of the experiment, you carry on doing exactly the same task – but some of the images are now associated with the chance of receiving an electric vibration on your hand. You will be told when you are about to enter this stage of the experiment.

Each picture has the same points value all the way through the experiment