Contextual Processing in Psychosis and Cannabis use

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Contents of Volume I

Main Thesis

Contextual Processing in Psychosis and Cannabis use.

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Abstract

Introduction

Cognitive models of psychosis highlight the role of underlying differences in cognitive function and information processing in the development and maintenance of psychotic symptoms. As a result there is now an interest in developing a greater understanding of these cognitive changes, in order to guide the development of evidence-based therapeutic interventions. An influential cognitive model of psychosis suggests that the core underlying cognitive difference in psychosis may be one of altered contextual processing. Recent work has suggested that this may be reflected in differential perception of visual illusions. However, it is not clear if such differences are present early in the development of psychosis. Such differences have also been reported to be associated with cannabis use. Further, it has been suggested that, in addition to being risk factors for the development of psychosis, psychoactive substances such as cannabis may provide a useful model for understanding psychosis. The current thesis thus investigated, in two separate studies: (1) the consequences of cannabis use on contextual visual processing and (2), whether reported contextual processing differences in psychosis are present at illness onset.

Study One

Two main hypotheses were tested. A. That THC, a key cannabis compound would reduce contextual visual suppression as measured using the Chubb illusion, and that this effect would be reduced via pre-treatment with another cannabis compound, cannabidiol (CBD). B. That THC would transiently induce symptoms of psychosis and that this increase would be reduced via CBD pre-treatment. No evidence was found to support the primary hypothesis. However, the secondary hypothesis was supported by the data.

Study Two

The primary hypothesis was that contextual visual suppression, again measured with the Chubb illusion, would be reduced in patients with first episode psychosis relative to a control group. Although not significant, the data supported this hypothesis.

Discussion

The results of Study One indicate that THC does not reduce visual contextual suppression as measured by the Chubb illusion. This is in contrast to evidence from other illusions,

and may reflect different neural mechanisms underlying contextual visual processing. However, the study provided clear evidence that THC can induce psychotic symptoms and that this effect can be reduced by CBD pre-treatment. Study Two replicates previous findings of reduced contextual processing in psychosis and provides evidence that this may be present from the onset of illness. These findings are discussed and interpreted with regards to study limitations, clinical implications and future work.

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1 Introduction

This thesis describes two separate but related studies investigating what may be referred to as context based processing. Stated very briefly, visual context based processing has been reported to be altered in schizophrenia such that people with psychosis have greater difficulty in establishing attentional biases and have a tendency to continue to allocate processing resource to background 'noise' or invariant contextual stimuli in contrast to the normative tendency towards tuning out these stimuli as 'irrelevant'. A similar pattern of processing has been found in non-clinical groups who score highly on measures of psychotic-like symptomatology, or schizotypy. Without these biases, people are more vulnerable to intrusions of unintended material into awareness, and thus such alterations of processing may plausibly underlie the development and maintenance of psychotic symptoms. Overlapping alterations in visual context processing have been induced in non-clinical participant following administration of THC, a key active constituent of cannabis.

The first study, based on the observation that psychotropic drugs can have psychotomimetic effects, and thus may inform us about the processes involved in psychosis, investigates the effect of the two primary psychoactive components of cannabis (delta-9-tetrahydrocannabinol and cannabidiol) on visual context processing. The second study attempts to replicate previous findings of reduced context based suppression in chronic schizophrenia, but in patients who have recently experienced a first episode of psychosis; thus providing further insight into the relationship between these reported effects and the development of chronic psychotic conditions.

Below I shall explore the background literature, before moving on to describe the extended rationale for the studies and state the primary hypotheses for these two studies. I shall begin with a description of the most relevant literature on information processing in schizophrenia and then discuss how this may fit with models of psychosis, with a particular focus on cannabis.

2 Literature Review

Before discussing schizophrenia and psychosis, it is worth briefly discussing what these terms mean and how they will be used in this thesis.

2.1 The Validity and Utility of The Term 'Schizophrenia'.

It has been suggested that the diagnosis of schizophrenia lacks validity and may be unhelpful from both clinical and research perspectives (Bentall, 2003; Read et al., 2004). It is certainly true that two patients with a diagnosis of schizophrenia may not only have quite dissimilar presentations, but actually may share no symptoms whatsoever; as pointed out by John Read, 'there are 15 ways in which two people can meet DSM-IVs criteria for schizophrenia without having anything in common' (Read et al., 2004, p. 46). Furthermore, disorders previously thought to be distinct from each other (perhaps because of the diagnostic aperture through which they have been viewed), are now increasingly considered to be overlapping. In particular, bipolar disorder and schizophrenia are now considered to overlap not only in terms of their symptomatology, but also their genetic and environmental basis (Lichtenstein et al., 2009). A detailed exploration of these issues and their implications is beyond the scope of the current discussion, however I shall briefly consider their relevance for psychological models of psychosis.

The heterogeneity of presentations encompassed by schizophrenia is a problem for researchers. The bio-psycho-social / stress-vulnerability model of schizophrenia suggests that underlying biological vulnerabilities, when exposed to a pro-psychotic environment, will result in the symptoms associated with schizophrenia (Zubin & Spring, 1977). Within this model, different symptoms may have different aetiologies (indeed similar symptoms may have different aetiologies in different people). Thus looking for the aetiology of schizophrenia, as a unitary construct, is likely to reduce a study's power relative to a more circumscribed, specific approach. A number of alternative research strategies have been proposed including: (1) The derivation of a valid and reliable factor structure for psychosis (2) The use of continuous, dimensional approaches.

Alternative Constructs. The reliable identification of subtypes of schizophrenia has been a goal since the term schizophrenia was first used. The DSM-IV has a number of subtypes (Paranoid, Disorganised, Catatonic, Undifferentiated and Residual), while researchers often divide the symptoms of schizophrenia into two/three types: positive (those things added to normative experience, such as hallucinations and delusions),

negative (those things removed from normative experience) and sometimes mixed (neither positive or negative being prominent) (Andreasen & Olsen, 1982). Other authors have used statistical techniques such as factor analysis to identify groups of symptoms that cluster together (factors). These attempts have led to a variety of solutions, with between three and seven factors (Cohen, 2005; Farmer et al., 1983; Nakaya et al., 1999). According to Bentall (Bentall, 2004, p. 196) the most common solution is the three factors solution, which maps onto positive symptoms, negative symptoms and cognitive disorganisation, although other authors argue that more factors are needed (Cohen, 2005; Liddle, 1987; Smith et al., 1998). This concept can be extended to a focus on individual symptoms, rather than clusters.

Dimensional Approaches. A symptom based approach to psychosis fits with the emerging view that psychosis may be considered as phenomena at one end of a continuum of normal experience. Strong evidence, from multiple perspectives supports this view, and has been recently reviewed by Van Os et al. (2010). Some of the most influential evidence comes from epidemiological studies; this is predicated on the idea that if psychosis is one extreme of a continuum, then there should be evidence of sub-clinical symptoms in the general population and that these symptoms will exist at a higher rate than diagnosable disorders. There is evidence for this in the domains of both persecutory ideation and hallucination. For instance, in the US national comorbidity study, 28% of individuals endorsed psychosis-screening items, while in the New Zealand Dunedin birth cohort, 25% of the sample reported hallucinatory or delusional experiences (Poulton et al., 2000). Similarly, in the Dutch NEMESIS study of over 7000 adults, 17.5% of the sample endorsed at least one psychosis item(van Os et al., 2000). With regard to hallucinations specifically, a 4% annual incidence was reported in white UK adults (Johns et al., 2002), while studies investigating lifetime prevalence have reported rates in the region of 10-15% (Tien, 1991).

Although the evidence appears to support the adoption of dimensional approaches to psychosis (certainly in research, but also clinically), the literature has mostly been built on categorical approaches. Thus for the purposes of discussion, the term “schizophrenia” will be used in those cases where classical diagnosis has been used as the basis of selection and analysis. Otherwise, the term psychosis will be used.

2.2 Differences of Information Processing in Schizophrenia.

It is now generally accepted that the schizophrenic syndrome results from the interplay of genetic and environmental factors that lead to the development of psychotic symptoms in an individual. However, the process by which this happens is not well understood. It is also clear that abnormalities of neurotransmitter function are important in psychotic states. Nonetheless, as noted by Fletcher and Frith, explanations such as 'hallucinations are caused by overactive dopamine receptors', while commonly repeated, leave an explanatory gap: 'how can dopamine cause a voice or belief?' (Fletcher & Frith, 2008). Cognitive models of psychosis may be able to help fill this gap.

Cognitive models of psychosis highlight the role of underlying abnormalities or differences in cognitive function and information processing (Bentall et al., 2007; Garety et al., 2001, 2007). However, although associations between schizophrenia and differences in cognitive functioning and information processing have long been recognised, the exact nature of the relationship remains unclear.

Theories of abnormal perception in schizophrenia posit that delusions are often interpretations of unusual perceptual experiences, and may be the most accessible way of explaining these perceptions (Maher, 1988). For instance if a person perceives usual events as being somehow changed and unusual, they may form different beliefs about such events than those who perceive them as normal. This idea is not new, Daniel Schreber's doctor is quoted in a 1955 book as describing how Schreber developed delusional ideas: beginning with his experiencing hyperintense sensations and hallucinations "which falsified his conception of things… and how from these pathological events, at last the system of [delusional] ideas was formed from which the appellant has recounted." (McAlpine (1955) via Bowers and Freedman (1966)).

According to authors such as Hemsley, Frith and Kapur, the primary problem underlying positive psychotic symptoms is a difficulty in distinguishing between ecologically relevant and irrelevant stimuli (Frith, 1979; Hemsley, 1993, 2005a; Kapur, 2003). Norma MacDonald described this vividly with regard to her own psychotic break (MacDonald, 1960):

> "Each of us is capable of coping with a large number of stimuli, invading our being through any one of the senses. We could hear every sound within earshot and see every object, line, and colour within the field of vision, and so on. It's obvious that we would be incapable of carrying on any of our daily activities if

> even one-hundredth of all these available stimuli invaded us at once. So the mind must have a filter which functions without conscious thought, sorting stimuli and allowing only those which are relevant to the situation in hand to disturb consciousness. And this filter must be working at maximum efficiency at all times, particularly when we require a high degree of concentration. What had happened to me in Toronto was a breakdown in the filter, and a hodge-podge of unrelated stimuli were distracting me from things which should have had my undivided attention"

Fitting with MacDonald's interpretation, evolutionary psychologists have argued that, in any given natural situation, the human brain must filter out relevant stimuli from irrelevant stimuli so that attention can be paid to those stimuli that are important to survival (Foster & Kokko, 2009).

A number of different, but complementary approaches have been adopted to explain how the brain might achieve this task and how psychopathology may arise when it does not do so optimally. Three interrelated concepts are particularly relevant to the current thesis: context, salience and the Bayesian brain.

2.2.1 Context, Salience and Dopamine

The term 'context' is used very widely and with rather varied meanings. The word context (as noted by Hemsley (2005b)) is derived from the Latin "contexere'', to weave together, and can mean variously, the 'connection or coherence between parts of a discourse' and concretely 'The whole structure of a connected passage regarded in its bearing upon any of the parts which constitute it'. Perhaps of most relevance here is its figurative use as illustrated in the Oxford English Dictionary with the quotes:

> "It is literally impossible, without consulting the **context** of the building, to say whether the cusps have been added for the sake of beauty or of strength" (Ruskin, 1851)

> "The position of facts in the **context** of experience" (Caird, 1877, p. 281).

> "We carry on with us from day to day the whole moral **context** of the day gone by. We are to-day all we were yesterday, and something more. We have no breaks in our personal identity—no new beginnings of our moral life" (Manning, 1843).

Here, context is temporal in nature, a fact, person or inanimate object cannot be considered independently of past experience. We cannot know the function of an object without reference to how it has been experienced in the past. We experience the world with reference to how we have experienced it before. Contextual information, though developed through experience, is applied in the here-and-now. The spatial and very recent temporal context in which we view a stimulus affects how we respond to it.

Recently, increased attention has been given to the possible role of altered contextual processing in psychosis. A highly influential model of the 'basic cognitive difference' in psychosis is that of Hemsley (2005b). Hemsley suggests that contextual processing may be altered in psychosis and that this abnormality may underlie positive psychotic symptoms and a number of experimental paradigms have demonstrated reduced influences of context in acute psychosis (Hemsley, 2005b). As he notes, the suggestion that context processing is abnormal in people with psychosis is not new, however, a number of recent studies have focused attention on the subject (these will be described later).

How does the brain determine whether a given stimulus or stimuli set is worthy of attention and action? An answer to this question is of course not readily forthcoming, but one thing seems clear: context is key. On the savannah it may be useful to consider any rustling in the grass to be a potential predator, but this does not necessarily follow for a suburban garden. The appropriate (adaptive) stimulus-response function clearly depends on context. Thus, one's vigilance and response to a stimulus must be able to change depending on the situation. Risking a small number of false positives may be beneficial to an individual (as in the case of the lion in the savannah), but if the individual begins to consistently see irrelevant stimuli as important, their ability to function will be impaired.

Distinguishing between relevant and irrelevant stimuli is thus dependent on their context, and in keeping with the continuum model, variations in the ability to adaptively do this may result from individual differences in contextual processing mechanisms. 'Context' here does not simply mean the current situation, but refers to a function of all previous experiences and their influence on the present. Thus, contextual processing allows the brain to use past experience (and perhaps evolutionarily hardwired information) in reacting to a current stimulus.

Phillips and Singer (Phillips & Singer, 1997) via (Hemsley, 2005b) suggest that:

> "the contextual input is used to selectively enhance the transmission of that information in the processor's receptive field that is coherently related to the context".

This however, as we will see later (see discussion of Bayesian processing), may actually be the opposite of what is happening in the brain. The brain may be working to selectively identify that information which is inconsistent with its context, and is thus surprising and potentially important. Nevertheless, the principle remains; the brain's job is to distinguish relevant stimuli (appetitive or aversive) from irrelevant stimuli and doing this depends on the context of the stimuli.

An influential current explanation of psychosis is that dopamine mediates the 'salience' of the elements of an individual's perception (Gray et al., 1991; Kapur, 2003). Here, 'salience' refers to the degree to which a stimulus attracts attention and influences goal orientated behaviour, due to association with reward or punishment. The salience mechanism allows the organism to focus attention where it is most important and convert motivation into action. Kapur suggests that while under normal circumstances, dopamine mediates the process of salience development, it does not create this process; following from this, he suggests that in the psychotic state, neurochemical alteration "usurps the process of contextually driven salience attribution and leads to *aberrant assignment of salience to external objects and internal representations"* (Kapur, 2003, p. 15). It should perhaps be noted here that while dopamine is implicated in salience, it does not necessarily follow that dopamine dysfunction is the basic cause of aberrant salience. Changes in salience can be induced by sensory deprivation or manipulation of other neurotransmitters. Dopamine changes may thus be cause or consequence, depending on the situation. Dopamine dysregulation is thus proposed as the final common pathway thorough which these factors influence psychosis (Howes & Kapur, 2009).

Salience and context can be considered as two sides of the same coin, context is the milieu within which stimuli are processed. If a stimulus does not fit with its context, it becomes more salient. One cannot have salience without context.

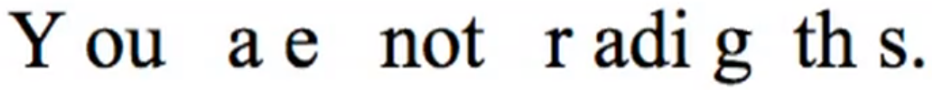
A variety of evidence suggests that context processing is abnormal in schizophrenia (Hemsley, 2005b). Before reviewing this however, it may be useful to first consider how contextual processing may be implemented in the brain and how this might link with psychosis.

2.3 Cognitive Function and Psychosis: A Bayesian Framework

2.3.1 The Bayesian Brain: A Very Brief Primer

Various authors (Clark, n.d.; Corlett et al., 2009; Friston, 2005; Hemsley, 2005a) have suggested that the brain can be seen as a Bayesian information processing system (sometimes called the 'Bayesian Brain'), and that the psychopathology of psychosis may be explained in terms of dysfunction of this system. A full review of this rationale is beyond the scope of this thesis, but is provided in a recent clear and fascinating review (Clark (in press)). In such a system, all incoming information is processed within the context of our prior experiences. That is to say our cumulative prior experiences may be seen to lead to our current beliefs (priors) about the world and these in turn influence how we perceive and react to our environment[1]. This is a powerful explanation in that it can be applied to the results of most, if not all, psychological problems (of course this may also be a significant weakness!). To take just one example from a talk from Beau Lotto (*Beau Lotto,* 2009), the reason we have no problem reading Figure 2.1, is that our prior experience tells us that, statistically, given the overall context of the letters and their distribution, it is most likely that there should be an 'r' (rather than an 'l') in 'a e', and an 'i' (rather than a 'u') in 'th s'.

Figure 2.1. Example from Beau Lotto.



In this Bayesian framework, learning occurs as the result of processing of mismatches between expected and actual inputs (prediction error). Given a certain sensory input, the brain will produce a prediction of a future sensory input; if there is a mismatch, the system should update so as to reduce future prediction error. The more accurate the brain is at predicting its immediate environment, the lower the prediction error will be.

The Bayesian brain framework is radical in its implications, the full scope of which extends beyond the consideration of this current thesis. However, one particular implication is worth emphasising here; in the Bayesian brain, *the only information that is passed upwards in the system is the error signal*. If we see, hear, feel, smell, taste or otherwise sense only what we expect to, no upwards signalling is necessary. The signal

[1] Priors may also be preset by evolution and thus our genetic coding. Such priors have been described as 'hyperpriors' (Clark, in press).

passed downwards tells the lower levels what to expect, and if there is no mismatch (if our brain manages to predict our sensory input perfectly), no signal except noise is passed upwards in the system. This signal represents the effect of context, both present and past. If however, our predictions are not perfect, the resulting error signal will be passed upwards so that higher levels may adjust so as to better predict our environment in future. The real work of the brain is in detecting when our environment differs from what we expect and adjusting our model of the world to incorporate this new information.

In such a system, the influence of prior experience may be referred to as 'top-down processing', while the direct influence of sensory input may be referred to as 'bottom-up processing'. However, it is important to note that what is proposed is a cascading multi-level system, whereby there are top-down and bottom up processes at each level of the brain. Thus, for instance in the visual cortex (which consists of a number of areas, V1 to V5), V1 sends error signals to V2, while V2 sends prediction signals to V1; at the same time V2 sends error signals upstream while higher areas send prediction signals to V2. The exact architecture underlying this proposed system is currently unclear, however, it has been shown that the model can explain various aspects of visual processing (eg Rao & Ballard, 1999). The nature of these processes are necessarily constrained by the underlying neuroanatomy of the brain. For instance, early in the visual system, neurons only have access to information from one eye, higher up information from both eyes can be integrated, while higher structures such as the frontal lobes may integrate information from multiple senses.

2.3.2 The Bayesian Brain: How It Might (Not) Work.

Corlett, Frith and Fletcher (Corlett et al., 2009) provide a detailed description of how this system may be represented in the brain. The main points of relevance for this thesis are summarised below.

In Corlett's model, top-down processing may be represented by feedback from the NMDA system, while bottom-up processing (prediction error) may be represented by the feed-forward AMPA and GABA systems. The impact of prediction error may be modulated by neurotransmitters such as dopamine, acetylcholine and serotonin, which interact with membrane potassium channels (thus altering the likelihood of neurons firing). Friston has suggested that these modulatory transmitters may work as a form of 'confidence estimate' for transmitted information, thus the feed-forward signal is given both amplitude and uncertainty (Friston, 2005). At a single neuron level, feed-forward

inputs may be specified by glutamatergic signalling, while priors may be specified by the number and function of potassium channels in the cell membrane (potassium channels shape action potentials and specify a neuron's input response threshold). In support of this, Corlett notes that individuals with autoimmune disorders affecting potassium channels may experience delusional beliefs.

This hierarchical system, although efficient, is sensitive to disruption, such that a relatively minor alteration in prior beliefs may become progressively distorted. Corlett, (following Lyons and Kashima 2003) liken this to the children's game 'telephone' (or Chinese whispers) where children sit in a circle and a message is passed around one child at a time as they whisper in their neighbour's ear. At each transaction, the message is processed according to the priors at that level, until it bears little resemblance to the original. When the Bayesian system malfunctions in psychosis, it is possible that new prior beliefs start to develop and establish themselves, thereby aberrantly shaping our interpretations of the world in such a way that they become self-maintaining.

As noted by other authors (Hemsley & Garety, 1986), delusions may represent a deviation from optimal Bayesian interpretation of the world. Linking back to the earlier discussion (Context, Salience and Dopamine), psychotic symptoms arise when stimuli that would not normally be considered relevant become abnormally salient. This salience needs to be interpreted by the brain and this leads to delusions and hallucinations.

Corlett, Frith and Fletcher summarise the model as below:

> "Our beliefs and percepts emerge from the interaction of bottom-up and top-down processes. Strong top-down effects (akin to prior beliefs) change sensory experience, leading perhaps to sensory percept in the absence of a genuine stimulus (a hallucination). Conversely, aberrant bottom-up signals strongly indicate that the currect priors are wrong and that beliefs (priors) must be changed to explain the world. Such aberrant changes in beliefs may provide the germ of a delusion and will, moreover if they can account for the aberrant sensory signals, be maintained."

The authors suggest that delusional beliefs may result from giving too much weight to bottom-up signalling, especially in the context of weakened top-down processing. Conversely, hallucinations may result if too much weight is given to top-down processing, especially when combined with noisy or unpredictable bottom-up inputs (see (2009) for a detailed explanation with regard to auditory hallucinations). Strong top-down processing

may also result in the maintenance of established delusional beliefs. It should be noted, that the authors' admit that this is a simplistic model, and that the interaction between top-down and bottom-up processes is likely more complex.

We shall return to this model later in the introduction, when discussing the psychotomimetic effects of psychoactive substances. First though, we shall move to a discussion of evidence that some of these processes may be disrupted in schizophrenia.

2.3.3 Hallucinations Vs. Perceptual Distortions. A Note

Psychiatric researchers commonly treat hallucinations and perceptual distortions as separate phenomena. The reality may be more complex. The Oxford English Dictionary defines Hallucination as follows: "The apparent perception (usually by sight or hearing) of an external object when no such object is actually present.".

The definition is clear, but it may miss something about the experience of the psychotic patient. In clinical practice, 'auditory hallucinations', whether they are words or sounds, are often described as occurring 'on top of' other sounds, indicating that they may be misperceptions of those sounds. This is backed up by evidence that people prone to psychosis are more likely to hear words in white noise (Galdos et al., 2010). In this case, increased noise may be considered to produce an increase in bottom-up signalling. By itself, this might not result in hallucinations, but if paired with impaired top-down processes, may lead to false positive identification of sounds, i.e. Hallucinations. In the above case, the external object (a sound) does exist, but is misperceived.

Voice hearing has been attributed to misattribution of internal speech to an external source (Allen et al., 2007). Thus, a normal experience (internal speech) is turned into a 'hallucination', due to altered perception of that experience, considered to be a failure of self-monitoring. This is supported by the report that patients with auditory hallucinations/passivity phenomena are more likely to be able to tickle themselves(Blakemore et al., 2000), again interpretable as a result of impaired self-monitoring. In the case of internal speech being perceived as external, the OED definition would be met. However the case of tickling (or, to take a more clinical example, say unusual tactile sensations) may be considered as a misperception (the brain fails to identify the self generated nature of the sensation) rather than a classic hallucination.

With regard to visual hallucinations, the fact that hallucinations in the elderly (Charles Bonnet syndrome) are consistently reported to be associated with eye pathology again indicates that misperception may play a significant role in the hallucinatory experience (Berrios & Brook, 1984; ffytche, 2009). Here, hallucinations may occur as a misperception by a normal brain of visual input or they may result from damage to the brain itself or a combination of both factors. The key message is that a subjective report of hallucination, on a self-report measure may be either a 'true' hallucination or a perceptual distortion, and only with further investigation may the nature of the individual experience be better understood.

2.3.4 Visual Context Processing in Psychosis.

Having considered how contextual processing may occur in the brain, we may return to the evidence indicating that context processing may be altered in psychosis. Although there is a considerable body of evidence from other domains, especially language processing (e.g. Cohen & Servan-Schreiber, 1992), for the purposes of this thesis I shall focus on evidence from the visual processing literature. The majority of the evidence for visual context processing differences in schizophrenia comes from studies employing illusions. People with a diagnosis of schizophrenia have been shown to exhibit reduced susceptibility to a variety of illusions, which will be discussed below. Explanations of many visual illusions emphasise the importance of lateral inhibitory neurons, both in early cortical and sub-cortical visual areas, which (for instance) act to suppress the stimulus response of neurons based on spatial context. More recent developments have suggested that these explanations may not be sufficient and the involvement of other higher cortical layers may be necessary to fully explain some illusions. Regardless of the exact cortical mechanisms, recent literature has indicated that visual illusions should not be considered as perceptual failures, but as Bayes-optimal perception in the absence of clear information; that is to say, they represent the 'most likely explanation for ambiguous sensory input' (Brown & Friston, 2012). I shall start by focussing on two important relevant illusions, the Binocular Depth Inversion Illusion and the Chubb illusion and then broaden the discussion to other relevant evidence.

The Binocular Depth Inversion Illusion (BDII), is an illusion in which incoming visual information is manipulated so that the information normally reaching the left eye is replaced by that normally reaching the right eye, and vice versa. This should result in an inverted percept of the viewed object (e.g. a face should be seen as concave rather than convex). However, this generally does not happen, and the object is seen in the

objectively incorrect, but more plausible, normal manner. This may be interpreted as resulting from the interference of top-down processing, as the brain attempts to make sense of incoming information *in the context of past experiences* (see (Gregory & Langton, 1966)). Several studies have shown that people with a diagnosis of schizophrenia have a markedly decreased illusion susceptibility to the BDII (Emrich et al., 1997; Koethe et al., 2006, 2009; Schneider et al., 2002). This may be most pronounced in acutely psychotic states and may remit when symptoms recede (Schneider et al., 2002). This reduced susceptibly to illusions is often reported as being a deficit; however, the finding is of particular interest because it actually represents a more accurate (albeit less adaptive) perception of the world. Paradigms predicated upon more accurate performance by people with psychosis compared to the general population are valuable for psychological research, as deficient performance may be influenced by the generic negative impact of a history of illness, poor self-care, life adversity, poor schooling, and medication, rather than psychosis-specific processes (Hemsley, 2005).

In the Chubb Illusion (Chubb et al., 1989), the participant is shown a patch of random texture superimposed on a background of similar texture. Chubb et al. showed that the 'perceived contrast of the texture patch depends substantially on the contrast of the background'. If surrounded by a higher contrast texture, the bright points of the texture patch appear dimmer, while its dark points appear less dark. Participants may thus be said to demonstrate a bias when the surround is present. This effect is illustrated in Figure 2.2.

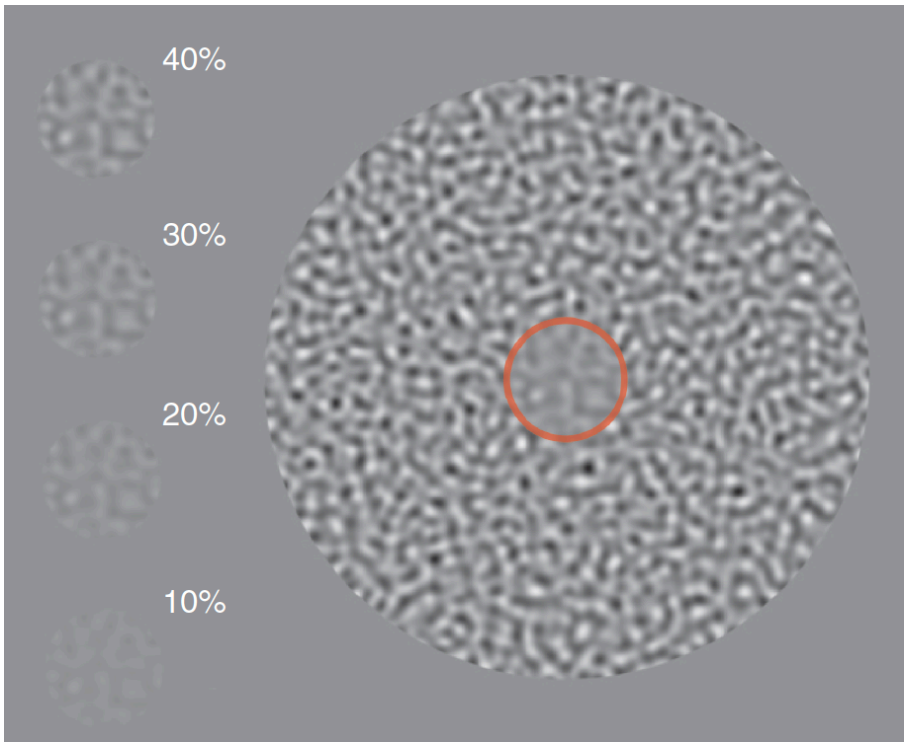


Figure 2.2 Chubb Effect.

The physical contrast of the ringed target is 40%. However contextual suppression makes it appear lower.

Chubb's initial and plausible explanation for this effect was that neurons tuned to detect similar spatial contrast frequencies were acting to inhibit each other. However, Lotto and Purves (Lotto & Purves, 2001), inspired by top-down explanations of other brightness illusions, have shown in an elegant series of experiments that this explanation may not be correct. Essentially they show that the Chubb illusion is dependent on the patch of foreground texture representing a imperfectly transmitting medium (for instance a cloudy piece of glass). For instance, in Figure 2.3 (top row only), the foreground patch is identical in A, B and C and the background is identical in B and C, yet, the foreground patch looks lighter in B than in C. The only difference is that the background is rotated so that C is not consistent with the patch representing a cloudy transmitting medium.

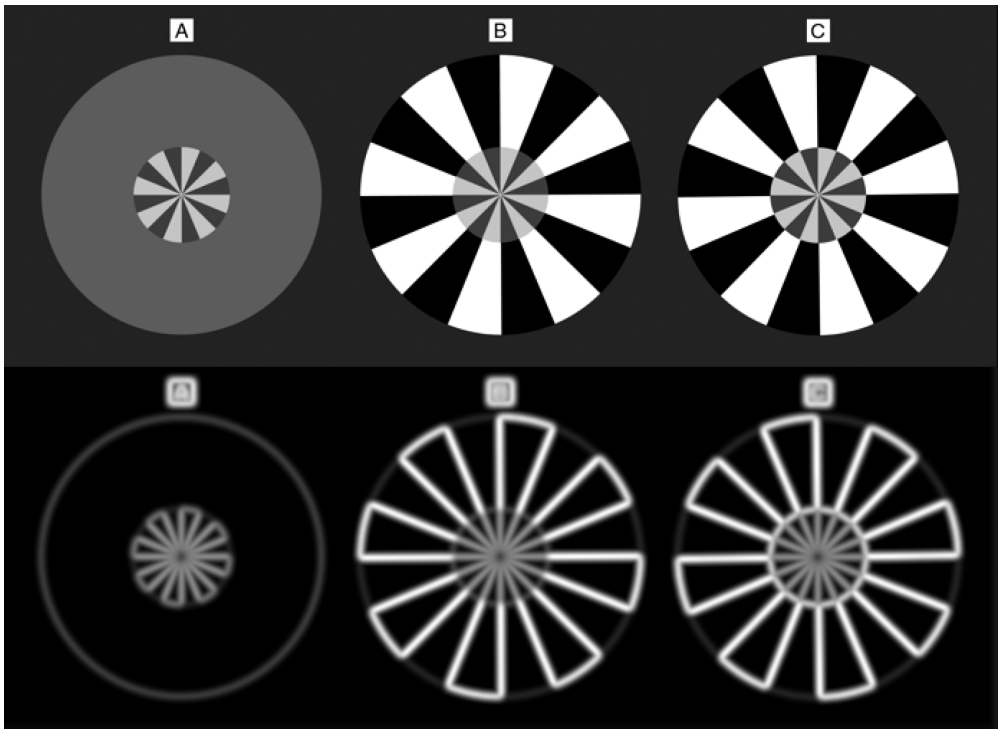


Figure 2.3 Example adapted from Lotto and Purves (2001)

Thus they propose that the Chubb illusion can be explained 'in wholly empirical terms', and that their experiments "add further support to the general conclusion that visual percepts are entirely determined by the experience of the human visual system [presumably both evolutionary and recent] with the frequency of occurrence of the possible sources of inherently ambiguous stimuli". However, it is not clear that the invocation of higher level processing is necessary to explain Lotto and Purves' observations . For instance, in the above example, by rotating the stimuli, extra luminance contrast has been introduced (at the centre-surround border). This can be seen in the bottom row of Figure 2.3 (which we have generated by calculating the RMS luminance contrast values from Lotto & Purves' example). Thus, it is possible that the perceived difference is due to local luminance mechanisms, rather than the influence of higher level processing.

Dakin, Carlin and Hemsley reported that when viewing the Chubb illusion, patients with paranoid schizophrenia (15 males from a forensic inpatient ward) showed a significantly reduced bias compared with both psychiatric controls (13 male and female psychiatric inpatients from the same hospital) and non-psychiatric controls (20 male and female participants recruited either from a job centre or university offices) (Dakin et al., 2005). This was interpreted as representing a weakened suppression of visual context. As with

the BDII, this finding is striking in that it represents a more accurate view of the world and is perhaps less likely to be part of a general deficit.

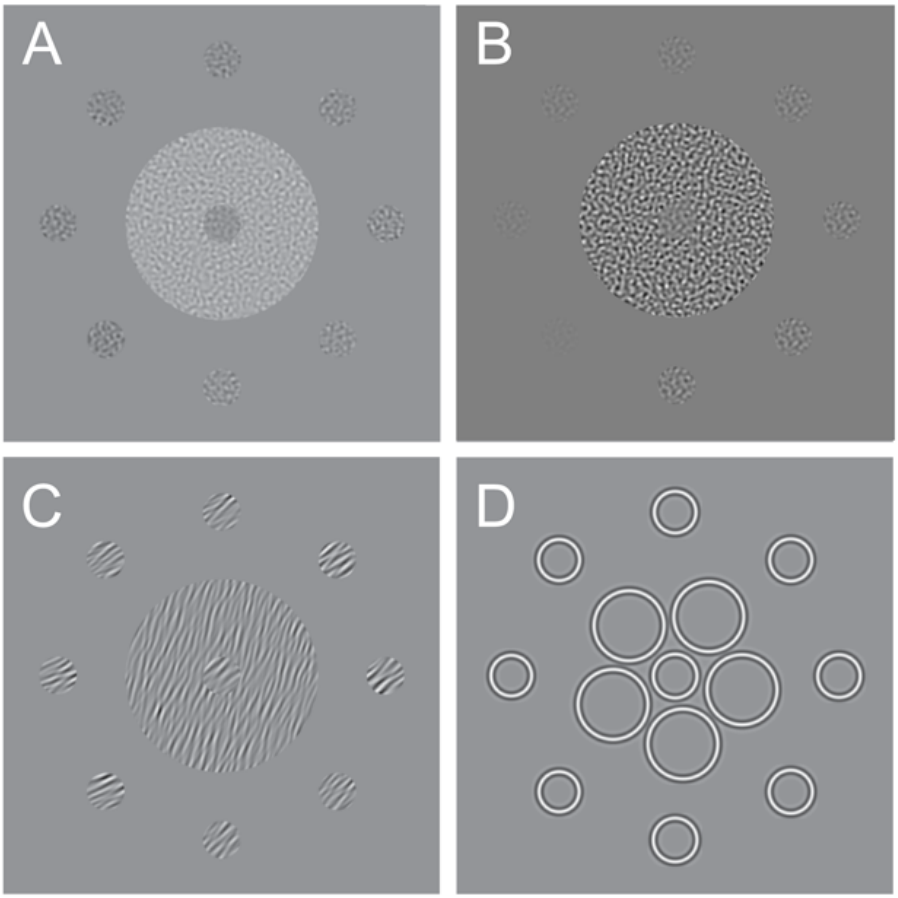
Deanna Barch and colleagues recently published a replication of this study with a much larger sample of 130 healthy control participants and 132 participants with a diagnosis of schizophrenia (Barch et al., 2012). A modified version of the Chubb task was used with an adaptive algorithm to reduce the amount of time needed to collect data. The authors found that the patient group showed a reduction of normal bias in the Chubb illusion, but that this reduction was of smaller magnitude that that found by Dakin et al. The authors suggest three possible explanations for this finding: 1. The study, for pragmatic reasons used less sophisticated methods; 2. The patient group were stable outpatients, as opposed to chronically ill forensic inpatients in Dakin et al.; 3. The sample size was much larger, and effect sizes tend to be smaller in large N studies. Of more concern, however, is the fact that when the authors attempted to control for inattention (as measured by performance on 'catch' trials where the correct response should have been obvious), the difference between groups was no longer significant. However, controlling for variables on which groups differ significantly (the SZ group showed greater inattention) is, as the authors note, problematic, as group membership and performance cannot be easily disentangled (eg Miller & Chapman, 2001). This finding is also in contrast to Dakin et al, who found no evidence of reduced attention in their patient group.

Most recently Tibber et al (submitted), have expanded on Dakin et al's study. Patients with schizophrenia (n=24) and controls (n=24) were tested with the Chubb task and three analogues that used size, luminance and orientation stimuli in place of contrast stimuli. In this study, participants had to say which of two stimuli were larger, brighter or tilted closer to the horizontal. As for the Chubb task, one of the stimuli was surrounded by a background of similar consistency, which is predicted to bias processing of the central stimuli (see Figure 2.4). The schizophrenia group demonstrated reduced bias in contrast, orientation and size tasks, but not the luminance task. Thresholds were greater in all conditions, indicating a generalised increase in response variability associated with patient status. This study provides evidence that reduced contextual suppression is a more general effect in schizophrenia and that it is not limited to contrast effects. Furthermore, this pattern of results provides insight into a neuroanatomical specificity of processing differences. Luminance signals are believed to be processed early in the visual pathway, in the retina and lateral geniculate nucleus, while size and orientation are believed to be reliant on cortical mechanisms. Contrast, as noted above, is perhaps

intermediate, being processed by early cortical mechanisms. Thus contrast suppression effects in schizophrenia may be predominantly cortical in nature. The authors also argue out that the effects noted are unlikely to be an artefact of inattention, as they were not common to all conditions, with patients showing no reduction in bias for the luminance task, which was well matched to the other tasks, which were also presented in random order.

Figure 2.4. Representation of Stimuli Used by Tibber et al (submitted).

A. Luminance. B. Contrast. C. Orientation. D. Size. Reference patch shown centrally, surrounded by contextual surround. Eight example target patches are shown (in the actual experiment these are shown centrally).



Complementary evidence of reduced context suppression comes from a study of center-surround interactions in visual motion processing (Tadin et al., 2006). In human vision, it has been shown that ability to perceive the motion of the stimulus decreases as the size of the stimulus increases, a finding that has been explained in terms of center surround suppression mechanisms in the MT area of the human brain (part of the dorsal stream and sometimes known as V5). Tadin et al found that this suppression was abnormally weak

in patients with schizophrenia especially those with severe negative symptoms. Further they found that in those patients with the weakest surround suppression, ability to detect the direction of motion was better than that of control subjects.

Other evidence supporting these findings comes from studies that utilise tasks that require the integration of spatial information, a process commonly thought to rely on cortical inhibition. For instance, patients with schizophrenia have been shown to have difficulty with contour integration tasks, in which participants are asked to detect shapes embedded in an array of locally oriented elements (Silverstein et al., 2000; Uhlhaas et al., 2004, 2006). In such tasks, identification of shapes is normally impaired by nearby elements with similar properties – an effect which is reduced in schizophrenia (Robol et al, under review). However, these findings are not consistent, a study by Silverstein (Silverstein et al., 2006) attempted to show that performance on contour tasks could not simply be explained by lateral inhibition, but involves top-down processes evidenced by practice effects (learning by experience is conceptualised as top-down). Learning effects were observed, and these were reduced in schizophrenia. However, there was no evidence of a general deficit associated with schizophrenia; this failure to replicate may be explained by reduced chronicity/severity of the sample compared to other studies, as indicated by a trend relationship between severity and performance.

2.3.5 Schizophrenia Subtypes and Context Processing

Some evidence suggests that visual context processing may be particularly affected in those patients with disorganised schizophrenia. In a sample of 32 schizoptypal and 37 non-schizotypal participants selected from a large nonclinical population, Uhlhaas found that thought disordered schizotypal participants had more accurate performance on a size perception task (Ebbinghaus) than non-disordered schizotypal and non-schizotypal participants (Uhlhaas et al., 2004). The opposite pattern of performance was found for a contour detection task. This finding fits with that of Silverstein, who also found that disorganisation correlated with impaired performance on a contour detection task. Finally, Longevialle-Hénin (article in French so based on abstract) reported that for two tasks (the Faverge task and The Group Embedded Figure Task) involving temporary maintenance of visuospatial information and executive functioning of visual working memory system, patients with disorganised schizophrenia had impaired functioning, while patients with non-disorganised schizophrenia did not (Longevialle-Hénin et al., 2005).

2.4 Cannabis as a model for understanding psychosis

It has been suggested that psychopharmacological models of psychosis have the potential to play an important role in understanding how cognitive changes may result in psychotic symptoms (eg (Fletcher & Honey, 2006)). Cognitive pharmacology provides ways of exploring links between drug and psychotic states in terms of both cognitive abnormalities and symptoms. Importantly, experimental pharmacological manipulations may provide an invaluable tool for testing and developing models linking cognitive alterations to psychosis like symptoms in non-clinical groups. Understanding these processes in the general population can cast light on processes involved in the development of psychosis (Garety et al., 2007), without the confounding factors associated with the status of a psychiatric patient. Although non-clinical samples are not without problems (for instance, non-clinical samples do not typically match clinical samples in terms of social economic class and gender distribution (see Maric et al (2003)), they have significant potential for aiding in psychosis research. Better understanding of cognitive processes will inform both psychological models of psychosis and, in turn, therapeutic approaches. Further, such studies may provide insights into the neural substrates of both specific cognitive processes and symptoms of psychosis, allowing further development of pharmacological treatments, and even the potential for better informed synergistic pharmacological and psychological interventions (Menon et al., 2008).

A wide variety of psychoactive compounds have been used to produce symptoms of psychosis in healthy volunteers. These compounds include NMDA antagonists such as ketamine and PCP, dopamine agonists such as amphetamine, serotonergic substances such as LSD and cannabinoids such as delta-9-tetrahydrocannabinol (Δ9-THC). Each of these substances has its own psychoactive profile, however there is considerable overlap in the symptoms produced by each substance. Of these substances, cannabis has recently gained significant prominence due to the hypothesis that it may trigger psychosis (see below: Cannabis and Psychosis: Evidence of a Causal Link.) and this, along with the identification and cloning of endogenous cannabis receptors has triggered renewed interest in how it may affect the brain.

For the purposes of the current thesis, discussion will focus on cannabis. Before moving on, it may be useful to consider the face validity of this link, which I will do via a discussion of the phenomenological similarities between the effects of drug intoxication and psychotic disorders. I shall then move on to discuss the specific effects of cannabis

and then to explanations of possible mechanisms of the psychotomimetic effects of cannabis.

2.4.1 Phenomenological Similarities between drug intoxication and psychotic disorders.

It is commonly acknowledged that the symptoms of drug intoxication and psychosis overlap, yet little has been published on the phenomenology of the association between substance use and psychosis. Of particular interest is a paper by Nelson and Sass (Nelson & Sass, 2008), which compares the experience of the 'psychotic break' to hallucinogen intoxication, in particular Huxley's writings on the experience of mescaline ingestion (Huxley, 2010). Although this hallucinogen (mescaline is perhaps most similar to LSD, with effects on the serotonin and dopamine systems) is not the focus of the current thesis, there are enough commonalities with the experience of cannabis use to make an interesting comparison.

The authors conclude that a shared factor in psychosis and drug use, described as 'psychotic-like experience' involves the 'breakdown of the sign-referent relationship (see below) and the relationship with the common-sense, practical world'; they go on to suggest that a key difference is that in psychosis, this breakdown is experienced as a sense of alienation from self and world, while in the hallucinogenic state, a sense of mystical union and revelation may predominate [although this is often a temporary state in psychosis]. Another significant difference between the two experiences, is that in psychotic disorder, onset is normally insidious, over days, weeks, months or even years, while in drug induced psychosis, onset is typically within minutes or hours (Kapur, 2003; Nelson & Sass, 2008) . An important psychological difference not raised by these authors, that may alter the perception of experience is that when one takes a drug, one generally knows what is causing the experiences, whereas, in psychosis, the explanation for the experience is missing, and thus the experience is potentially more frightening and alienating. Perhaps, the negative experiences of drug taking (such as extreme transient paranoia and panic) may also be explained by a loss of perceived causal link between trigger and symptom, and thus a loss of sense of control.

Sass and Parnas (Sass & Parnas, 2003) describe a kind of aura at the onset of psychosis, in which all aspects of experience are suffused by a strange and enigmatic atmosphere, where the person becomes suspicious and restless, often filled with dread and altered awareness. There is a sense of unveiling of reality in which the world feels qualitatively

different. This shift may fascinate and disturb the individual leading to their staring intently at the world trying to find meaning. Sass calls this the 'truth-taking stare' and refers to the state of mind that accompanies this stare as the *Stimmung*; this may include contradictory feelings of significance and insignificance, and a perception of world in which familiar coherent meanings have given way in favour of new idiosyncratic meanings. This state of mind is hypothesised to lay the foundation for more obvious and elaborated later symptoms. Sass argues that the *Stimmung* may be broken down into three related elements, Unreality, Mere-Being and Fragmentation, and their putative consequence, Apophany. Unreality describes experiences such as the feeling that the world has changed subtly or that objects and people seem unreal or fake. Mere-Being describes the sense of disconnection between objects and their functions and meanings. Fragmentation describes the loss of relationships between different objects in a scene, such that each object gains its own individual importance, this may also be considered as a 'loosening of overall Gestalt'. Apophany, sometimes described as the 'delusional mood' is a resulting sense of meaningfulness, in which everything seems significant, but it is not yet clear why. This state may be followed by the 'delusional percept' in which this sense of significance resolves into a specific delusional interpretation of experience.

The above, rather philosophical concepts have a parallel in the ideas of contextual processing, salience and the Bayesian brain. When Nelson and Sass talk of a breakdown in sign-referent relationships, they are referring to a change in how people perceive the world. For instance, a chair is no longer seen as a chair, but is seen in a new light, stripped of its normal meaning (mere-being). This can be seen as a loss of context, that is to say our past experiences of a chair (or person, place, experience) no longer hold dominance, and new, less usual meanings may take the place of past experience. Likewise, fragmentation and 'more-being' may be considered as a loss of figure-ground relationship or loosening of Gestalt, but may also be considered as a loss of contextual awareness or reduction in top-down processing. The loss of usual top-down influence may result in a greater intrusion of bottom-up signalling, resulting in normally insignificant stimuli becoming aberrantly salient. The brain, deprived of normal contextual meaning, fills the vacuum with whatever it can based on the inputs and context it has available. At some stage, perhaps, the balance shifts back towards top-down processing, except now the priors are dysfunctional and a delusion is established.

2.4.2 Cannabis and the Cannabinoid System

Cannabis is prepared from plants of the genus Cannabis (generally Cannabis sativa or Cannabis indica), and is unique in producing compounds known as cannabinoids. Cannabis has been used, both in contemporary culture and traditionally, for both its psychoactive and putative medicinal properties. Cannabis can be smoked like a cigarette, in water pipes or using a vaporiser; it can also be ingested with food or drunk as an extract. Cannabis contains over 400 compounds, including over 60 cannabinoids (Ashton, 2001). The most potent of these cannabinoids is delta-9-tetrahydrocannabinol (Δ9-THC, hereafter referred to as THC), which along with another important compound, cannabidiol (CBD), has been isolated and synthesised.

2.4.2.1 Delta-9-tetrahydrocannabinol (Δ9-THC)

Δ9-THC binds to cannabinoid receptors CB1 and CB2, which are the primary known receptor sites for endogenous cannabinoids. As noted by Ashton (2001), the identification of CB1 and CB2 receptors (in 1988 and 1993 respectively) stimulated a search for endogenous ligands. A number of these have now been identified and are referred to as 'endocannabinoids'. Endocannabinoids and their receptors may reside primarily within neuronal lipid membranes and act as neuromodulators that control calcium and potassium ion flow (they are G-protein coupled receptors). Through this mechanism, they may have regulatory effects on neurotransmitter release, and have been shown to inhibit acetylcholine, noradrenaline, GABA and glutamate release, and may indirectly influence the dopamine system (Fujiwara & Egashira, 2004; Sviženská et al., 2008). For a more detailed review of the pharmacokinetics and pharmacodynamics, please see Sviženská et al (2008).

Although the exact mechanisms are unclear, it has been suggested that a reciprocal interaction between endocannabinoid and dopamine systems may explain the psychotomimetic effects of cannabis (D'Souza et al., 2004; Henquet et al., 2010). As noted, in normal function, CB1 activation has been shown to inhibit presynaptic neurotransmitter release, thereby modulating the action of other neurotransmitters such as GABA and glutamate and indirectly influencing dopamine. Δ9-THC may disrupt the normal modulatory functioning of the cannabinoid system. For instance Δ9-THC increases dopamine concentrations in the striatum (Bossong et al., 2008). Linking to the salience hypothesis of psychosis, striatal dopamine is implicated in the attribution of salience to stimuli – and thus excess dopamine may result in false attribution of salience. Further, Δ9-THC has been shown to inhibit GABA neurons in the hippocampus,

disrupting neuronal synchronisation and inducing psychotic symptoms (D'Souza et al., 2004). As neuronal synchronisation in the hippocampus has been linked to sensory integration, it is possible that this interference in synchronisation may account for cannabis effects such as altered sensory association and perhaps altered contextual processing.

2.4.2.2 Cannabidiol (CBD)

Unlike THC, CBD does not cause psychotomimetic effects. Indeed importantly it has been reported that CBD has both anxiolytic and antipsychotic effects (Leweke et al., 2000, 2007). CBD appears to be an antagonist of CB1 and CB2 receptors, although it has low affinity for these receptors, and its antagonism is hypothesised to work via other, as yet unclear, mechanisms (Mechoulam et al., 2007). Confirmation of CBDs antagonistic effects has come from studies that have shown that the anxiolytic and psychotomimetic effects Δ9-THC can be reduced via co-administration (Zuardi et al., 1982) or pre-treatment with CBD (Bhattacharyya et al., 2010).

2.4.2.3 A Potent Change

The amount of Δ9-THC found in modern cannabis preparations can be very significantly higher than it was in the heyday of 1960s and 1970s counterculture, although there is some controversy over the degree of difference. It is reported that the Δ9-THC content of the average joint has increased from 10mg to 60-150mg since the 1970s (Ashton, 1999). In South East London, where much research has been conducted regarding cannabis and psychosis, skunk sinsemilla (cannabis both selected and especially grown for its potency) is estimated to contain between 12-18% Δ9-THC and <1.5% CBD, compared to 2% THC for low grade cannabis. In the Netherlands, THC levels have doubled from 10% to 20% between 2000 and 2005 (*UN World Drug Report*, 2006). This is likely the effect of years of selective breeding, advanced cultivation techniques and market forces. As pointed out by Ashton (1999), as the effects of THC are dose dependent, this makes much of the research into cannabis (which was carried out in the 1960s and 1970s) out of date. Cannabis use currently has a high prevalence rate in the UK. For instance, in a survey of over 3000 university students, 60% reported having used cannabis, with 20% reporting at least weekly usage (Webb et al., 1996).

2.4.2.4 Subjective Effects of Cannabis

In popular culture, the psychotomimetic effects of cannabis are well documented (e.g. the 1938 film 'Reefer Madness' (Gasnier, 1936)). By contrast there are surprisingly few

attempts to formally describe these effects in the literature. Much of the research into the subjective psychological effects of cannabis was carried out in the 1970s (Dornbush & Kokkevi, 1976; Keeler et al., 1971; Tart, 1970). A classic Nature paper by Charles Tart (Tart, 1970), using a questionnaire based on initial qualitative interviews, attempted to identify common and less common experiences associated with cannabis. The list is long and includes effects in all sensory domains, as well as in perception of time, body and movement, sexual effects, effects on thought processes, memory, emotions, identify, perceived self-control and sleep. Tart quotes:

> "Sensations are enhanced and clarified; sight, hearing, taste, touch. Time perceptions changes. Attention becomes more unified, and moves more into awareness. The many broad processes of association, such as social meanings, memory images, expectancies and plans, reduced in number and relevance. Inhibitions and submissions relax, allowing emotions, thoughts, fantasies and memories to flow more freely. The development and strength of these effects will depend on the individual, the times he has used marijuana, how he has used marijuana, and the environment".

In the same paper, Tart comments that due to the probable enthusiasm of his participants, more negative aspects of cannabis use were probably underreported. At the least, it seems likely that those people who experience significant adverse effects will be more likely to discontinue from using cannabis than those who don't, leading to a bias in more chronic users. The most common negative effect was paranoia, which 80% of participants had experienced. 20% of participants reported that they 'had lost control and been 'taken over' by an outside force or will which is hostile or evil in intent for a while'. Asked how often they had seen others 'freak out', 36% of respondents said fewer than 1 in 20 times, 2% said more often and the rest said never.

More recently D'Souza (D'Souza et al., 2004) have explored the subjective effects of Δ9-THC in a randomised, counterbalanced, double blind, laboratory study, in which participants received either 2.5mg, 5mg or no IV Δ9-THC. Transient effects were reported including increases in positive symptoms, negative symptoms, perceptual alterations, euphoria, anxiety, and deficits in working memory, recall, and the executive control of attention without altering general orientation. Positive symptoms included suspiciousness, delusions (paranoid and grandiose), disorganisation, derealisation, altered sensory and body perception, unreality and slowing of time. Negative symptoms included blunted affect, reduced rapport and spontaneity, psychomotor retardation and

emotional withdrawal. The authors conclude that given the overlap between the symptoms induced by cannabis and those of psychotic disorder, the study provides evidence for a cannabinoid model of psychosis. A limitation of this study is that it was conducted (unsurprisingly) in a laboratory under carefully controlled conditions in which fixed doses of IV Δ9-THC were administered. This does not mimic real life conditions in which the environment in which cannabis is used may vary dramatically and in which the user has some control over their intake and generally smokes or ingests a mixture of cannabinoids. It is likely that an individual's response to cannabinoids will be mediated by a number of factors such as how comfortable they feel with the people with whom they are sharing the experience. To date, only one study has addressed these issues, and found no significant effect of setting, however it is arguable how well the study manipulated the affective components of the setting(Hollister et al., 1975).

Morrison et al (2009), in a double blind, placebo controlled study, also report that 2.5mg of Δ9-THC induced positive symptoms in 22 healthy controls, increases anxiety and results in deficits in cognitive function (working memory/executive function). There was no relationship between degree of psychotic reaction and either anxiety or cognitive impairment.

Individual predispositions may play a significant role in an individual's reaction to cannabis. In an experience sampling study, Henquet et al (2010) investigated the effects of cannabis is the daily life of 42 patients with psychotic disorder and 38 controls. They found that cannabis use predicted increases in positive affect in both groups, with decreases in negative affect seen in patients. Cannabis also predicted increased levels of hallucinatory (primarily auditory, but also visual) experience in patients, but not controls. In terms of temporality, mood effects were reported as acute effects, while psychosis effects were reported as sub-acute. Thus, in this study, cannabis appears to enhance hallucinatory experiences in those who are predisposed, but not induce them in those who aren't. This data also fits with Spencer's model of cannabis use in psychosis, where patients are better aware of the acute, rewarding effects of cannabis, and less aware of the chronic and negative affect inducing effects.

2.4.3 A Bayesian Interpretation of the Psychotomimetic Effects of Cannabis

Corlett, Frith and Fletcher(Corlett et al., 2009), have used a Bayesian model to explain the effects of psychotomimetic compounds (ketamine, cannabinoids, amphetamine, LSD)

and sensory deprivation. The authors suggest that the different psychoactive compounds exert their psychotomimetic effects by causing perturbations in the normal function of the Bayesian system. They summarise these effects in a table, which is presented in adapted form below:

Table 2.1 Effects of Pharmacological Manipulation on Top-down and Bottom-up processing (adapted from Corlett et al.)

Manipulation	Bottom-up	Top-down	Delusional Ideation	Hallucinations
Cannabinoids	↔	↓	++	--
Ketamine	↑	↓	++	--
Amphetamine (repeated dose)	↑	↑	++	++
Amphetamine (single dose)	↔	↑	+	--
LSD	↓	↔	--	++
Sensory Deprivation	↓	↔	?	++

Corlett at al suggest that cannabis reduces top-down influence in the brain, while leaving bottom up processing relatively unchanged. It may do this via its effects on dopamine and glutamate, which are, according to the earlier discussion, implicated in the specification of priors. According to the discussion of the Bayesian brain, delusional beliefs may arise from *relative* increases in the influence of bottom-up processing. Such increases may either represent an increase in bottom-up signalling or a reduction in top-down processing. Reduction in top-down processing proposed as a consequence of cannabis use may reduce the impact of past regularities on interpretation of the present, thus allowing the formation of novel, and dysfunctional beliefs about the world. Corlett's theory could be extended to explain the long-term maintenance of delusions. As the effect of cannabis wears off, one would expect the delusional ideas to reduce, and indeed this is consistent with what is commonly seen. However, if priors are updated during cannabis use such as to encode the new beliefs, and such priors can plausibly explain the world, they may persist. Furthermore, one might speculate that if experiences under the influence of cannabis are particularly salient (as they might be in traumatic paranoia), they may be more likely to inform the development of new priors. Equally, if the cannabis user has had a traumatic past, it is possible that a shift to priors encoding a 'dangerous world' might be more likely, thus biasing future perception of the world. It is interesting to consider how this process might fit within the Sass and Parnas' (2003) ideas (discussed earlier) of a progression in psychosis from 'Unreality' though 'Mere Being' and 'Fragmentation' to 'Apophany' and the 'Delusional Percept'. Further, these ideas,

although speculation fit with the evidence on cannabis use as a risk factor for psychosis (discussed below).

2.4.3.1 Hallucinations.

It is noteworthy that hallucinations are not considered by Corlett et al. to be an effect of cannabis. Although delusional beliefs, especially paranoid ideation, are prominent effects of cannabis, hallucinations are also reported in non-scientific literature and on cannabis Internet forums. In the scientific literature, however, hallucinations are not widely reported. Tart refers to experiences that may be described as perceptual changes rather than hallucinations (seeing patterns forms and figures in visual material), while Bressloff reports that cannabis has been associated with people seeing geometric patterns (Bressloff et al., 2002). Peters et al, in a retrospective questionnaire study of cannabis experiences, report that 2% (1/50) of controls reported auditory hallucinations and 8% (4/50) report unusual visual experiences. Percentages in ultra high risk for psychosis were 18 and 25% respectively; and for patients with schizophrenia 27% and 29% (Peters et al., 2009). In the scientific literature, auditory hallucinations associated with cannabis mostly appear only in reference to those who have experienced psychotic episodes. Even if cannabis is not associated with hallucinations in the general population, it is definitely associated with perceptual distortions (as reported above). Interestingly, one suggested explanation for the relative prevalence of auditory hallucinations over that of visual hallucinations in psychosis considers the degree of environmental structure in each domain. Margo (Margo et al., 1981) played people with auditory hallucinations auditory stimuli with varied degrees of interest and structure, from interesting speech to white noise. They found a strong correlation negative between degree of structure and duration and loudness of hallucinations. Following Feinberg (Feinberg, 1962), they suggest that the predominance of auditory hallucinations in psychosis may reflect the relatively lack of structure in natural auditory input (relative to visual input). Arguably, typical experimental environments are especially high in visual structure and low in ambiguity, and thus may lead to reduced reports of visual distortions and hallucinations.

2.4.3.2 Experimental Evidence of Cannabis Induced Reductions of Top-Down Processing

Experimental evidence for the hypothesis that cannabis reduces top-down processing comes from one of the visual illusions that were discussed earlier as evidence for

reduction in top-down processing (of which contextual suppression is an example) in psychosis: the Binocular Depth Inversion Illusion (BDII). In schizophrenia, susceptibility to this illusion is decreased. Similarly, regular cannabis users have been found to exhibit decreased illusion susceptibility on the BDII (Semple et al., 2003) and to be indistinguishable in terms of illusion susceptibility to either prodromal or antipsychotic naïve patients with schizophrenia (Koethe et al., 2006). The BDII illusion is commonly explained in terms of the top-down brain processes overriding bottom-up processing based on existing priors. Thus reduced susceptibility to the illusion may be interpreted as representing weakened top-down processing. A cannabis-induced reduction in top-down processing may underlie both this reduction in susceptibility to the illusion and contribute to delusional ideation in cannabis users.

2.4.4 Cannabis and Psychosis: Evidence of a Causal Link.

It is now generally agreed that there is a connection between cannabis use and psychosis, however the question of causality remains controversial. This question has attracted growing attention over the last decade, perhaps partly due to concerns about the possible public health consequences of increasing cannabis use (Webb et al., 1996) and concerns regarding the increasing potency of available cannabis (Ashton, 1999; Murray et al., 2007).

Proponents of the idea that cannabis use may trigger psychotic disorders point to a variety of evidence. For instance, cannabis use is greater in those with a diagnosis of a psychotic disorder than those without and there is a strong relationship between age of onset of psychosis and cannabis use (Large et al., 2011). Epidemiological evidence suggests that cannabis is associated with a twofold increase in the risk of psychosis onset (Tien & Anthony, 1990); this is supported by a survey of 50,000 Swedish army conscripts that reported a similar overall risk, and found that the risk was usage related, with those who had smoked more often having greater risk, with a risk ratio of up to 6.7 for those who had smoked more than 50 times (Manrique-Garcia et al., 2011; Zammit et al., 2002). Results from longitudinal studies are also supportive (Arseneault, 2002; Van Os et al., 2002; Stefanis et al., 2004; Weiser et al., 2002); for instance in the Dunedin multidisciplinary health and development study, people who were cannabis users before the age of 15 had a fourfold increased risk of developing schizophrenia (Arseneault, 2002). There is also evidence that an individual's experience of cannabis use may be moderated by their vulnerability to psychosis, such that individuals at high risk are less likely to experience the euphoric effects of cannabis and more likely to experience

unusual perceptions and thought influence (Verdoux et al., 2003). However, Verdoux et al fail to consider how an individual's environment may affect their perception of experiences. People at high risk of psychosis may have poorer support networks and be more isolated, which may interact with their experience of cannabis. Such possible psychological interactions are often overlooked and untested in the biological literature.

Despite the evidence of a connection between cannabis use and psychosis, causality is hard to prove. Smit et al (Smit et al., 2004) examined five possible hypotheses that might explain the link between cannabis and psychosis: 1, that people use cannabis to self medicate; 2, that the other drugs used by cannabis smokers explain the link; 3, that confounding factors explain the link; 4, that there is a stronger effect in predisposed people; and 5, that cannabis can directly trigger psychosis. They argue that converging evidence makes hypotheses 1 and 2 unlikely, and while confounding factors may play a part, they are unlikely to explain all the relationship. They conclude that there is strong evidence for both hypotheses 4 and 5. Thus they conclude that cannabis likely makes its own unique contribution to the risk of psychotic disorder and that this risk is moderated by an individual's other vulnerabilities to psychosis.

More recently, authors such as Shapiro and Buckley-Hunter (Shapiro & Buckley-Hunter, 2010) have argued that the evidence for causality is convincing and the research fulfils most of Bradford Hill's criteria[2] for causation; in reviewing the evidence, they conclude that cannabis poses a significant risk to adolescent health and that, in at least some vulnerable individuals, it may trigger chronic psychosis. The authors and others go further and say that these results should inform public health policy (Large et al., 2011; Shapiro & Buckley-Hunter, 2010). It should be noted that the authors do show rather selective interpretation of some of the papers they quote, for instance, Harley's (Harley et al., 2010) report of an additive effect of childhood abuse and cannabis use on later psychosis is reported as an a multiplicative effect of 'brain trauma' and cannabis use.

One explanation for how drug use could have a causal relationship to chronic psychotic experience is that the individual is given a 'taste of psychotic like experience under the influence of a hallucinogen, which then triggers, or somehow inspires further psychotic experience independent of substance use' (Nelson & Sass, 2008). It is possible that if a

[2] Sir Austin Bradford Hill and Richard Doll are credited as the first researchers to demonstrate the connection between lung cancer and smoking. The Bradford Hill criteria are minimal conditions necessary to provide evidence of a causal relationship.

person has a particularly traumatic drug experience, then this, in a manner similar to PTSD, may be re-experienced as a flashback. If the person who had previously experienced symptoms under the influence of a drug now experiences them without this known trigger, they may well find the experience more aversive and perhaps begin to search for alternative explanations of their experience ('I'm going mad', 'something has changed' etc.). To quote from admission interview of a person who experienced a psychotic episode two years after using LSD: "It's the same now as it was with the drug, only then I knew I was coming back. Now there is nothing to hold onto" (Bowers & Freedman, 1966). Perhaps also, if these flashbacks are experienced as aversive, they may become self-sustaining though a feedback loop where they are experienced as continuing traumas, leading to further flashbacks. This would fit with evidence showing that distress at hallucinatory experiences is a consequence of catastrophic/negative appraisals of the experience (Chadwick & Birchwood, 1994) and that distress/anxiety may trigger symptoms of psychosis. In such a formulation, we may consider the negative drug experience to be equivalent to a traumatic life experience.

One's idiosyncratic reaction to drug use (or its sequelae) may depend on a variety of factors at different levels of explanation including genes, biology, past experience (especially childhood trauma), personality and setting of drug use and affective state at the time of use.

What is beyond dispute is that cannabis use can result in experiences that closely parallel those of people with diagnosed psychotic conditions. Although these experiences are generally confined to the acute stage of cannabis use, they may continue afterwards and may be experiences as 'flashbacks' weeks or months later.

3 Aims And Hypotheses

It is clear from the preceding literature review that altered contextual processing may underlie the symptoms of psychosis, and that cannabis has clear psychoto-mimetic effects and is linked to psychosis onset. Cannabis may also impact on contextual processing, and it has been hypothesised that this may be the common mechanism through which cannabis and psychosis are linked. However, this area of research is in its infancy, and cannabis is a complex substance with multiple ingredients varying in their neural impact. Further investigation of the effect of the component compounds of cannabis on both context processing and psychotic symptoms, and of context processing in psychosis, are required.

This thesis consists of two related but separate studies. Both studies focus on the relationship between psychosis and contextual processing. The rationales for the individual studies are presented separately below:

3.1 Study 1: The effects of THC and CBD on a task engaging top-down processing.

This study aims to investigate whether cannabinoids, in particular THC (delta-9-tetrahydrocannabinol), result in alterations of processing matching those observed in clinical psychosis. To my knowledge, the BDII study detailed above is the only experimental study to date to support the theory that the psychotomimetic effects of cannabis are due to reduction in top-down processing.

The main aim of the study is to build on the current literature attempting to elucidate the mechanisms underlying the ability of THC to elicit paranoid thinking. If THC does indeed weaken top-down processing, we would expect it to also weaken susceptibility to the Chubb illusion.

The secondary aim of the study is to investigate the relationship between THC and CBD. Due to the potentially schizophrenogenic nature of cannabis strains with low CBD/THC ratios, understanding of the relationship between THC and cannabidiol is important from a public health perspective.

3.1.1 Hypotheses:

1. The primary hypothesis is that, following administration of THC, participants will show a psychotic-like reduced influence of context on processing manifested as reduced susceptibility to the Chubb illusion. This will be reflected by a reduction in bias.
    a. The THC induced bias reduction predicted in hypothesis 1 will be blocked by pre treatment with CBD.
2. Administration of THC will increase symptoms of psychosis as measured by PANSS (positive and negative) scores as well as State Social Paranoia Scale.
    a. The THC induced increase in symptom scores will be blocked by pre-treatment with CBD.
3. Susceptibility to the Chubb illusion (bias) before THC administration will be negatively correlated with
    a. Scores on the Cardiff Anomalous Perceptions Scale.
    b. Scores on the paranoid-dysphoric factor of the cannabis experience questionnaire.
    c. Scores on the Green Paranoid Thoughts Scale.
    d. Scores on the Schizotypal Personality Questionnaire.

3.2 Study 2: An investigation of contextual processing in first episode psychosis.

There is compelling evidence that contextual processing is altered in schizophrenia. In particular, various studies have shown that patients with psychosis show reduced susceptibility to visual illusions, indicting a reduction in suppression mechanisms or top-down processing. Limited evidence indicates that this may be linked to the chronicity of psychosis. Study 2 aims to investigate whether the reported differences in contextual processing are present in patients who have recently experienced a first psychotic episode.

3.2.1 Hypotheses:

1. 1st Episode Patients will show a reduced influence of context, indicated by reduced bias on the Chubb illusion
2. Susceptibility to the Chubb illusion (bias) before THC administration will be negatively correlated with:
    a. Scores on the Cardiff Anomalous Perceptions Scale.
    b. Negative symptoms as measured by the SANS
    c. Positive symptoms as measured by the SAPS

4 STUDY One. The effects of cannabinoids on contextual processing and psychosis symptoms

4.1 Methods

Data collection for this thesis was conducted as part of the larger ESCAPE study, of which this thesis formed a part. The complete study protocol is described briefly in order to provide relevant context. However, only the data from measures directly relevant to the current thesis was analysed.

4.1.1 Ethical approval and Consent.

The study was approved by the Joint Institute of Psychiatry and Maudsley Hospital Ethics committee. All subjects provided written informed consent. Safety protocols have previously been described (Morrison et al., 2009).

4.1.2 Study Design

The study employed a 2 X 3 mixed design in order to detect change due to THC and pre-treatment with placebo. Administration of cannabidiol was randomised and double blinded. All participants received THC. Each participant was assessed in three separate sessions: 1. Baseline, 2. Post-capsule (CBD/placebo), 3: Post THC. All participants were administered THC.

Groups from the two arms of the study are hereafter referred to as 'Placebo' and 'CBD'.

4.1.3 Experimental Task and Measures

The measures can be divided into state (baseline predictive) measures, which were delivered just once, and trait measures which were delivered at all three timepoints.

4.1.3.1 Trait Measures:

The trait assessment battery involved the following measures:

- **Cannabis Experience Questionnaire (CEQ)**
  A measure of the subjective experiences of cannabis use. Has three subscales: pleasurable experiences, psychotic like experience and after effects.(Barkus et al., 2006)

- **Green Paranoid Thought Scale (GPTS).**
  A multi-dimensional measure of persecutory ideas developed for use across the general population(Green et al., 2007).
- **Schizotypal Personality Scale (SPQ)**
  Measures presence of schizotypal symptoms. Has a three factor structure: cognitive-perceptual, interpersonal and disorganised symptoms(Raine, 1991).
- **Wechsler Test of Adult Reasoning (WTAR)**
  The WTAR is a quick reading and pronunciation tool designed to estimate IQ. It has been co-normed to the WAIS-III and WMS-III.

4.1.3.2 State Measures

The State assessment battery involved the following measures:

Measure of Top-Down Processing / Contextual Processing

- **Chubb task.**
  This is the primary task in the present study and is described in detail below.

Measures of Affect

- **University of Wales Mood Adjective Checklist (uMACL).**
  Measures mood in three dimensions: energetic arousal, tense arousal and hedonic tone (Matthews et al., 1990). On each dimension, participants rate their levels of agreement with eight adjectives, four positive and four negative.
- **Beck Anxiety Index (BAI).**
  21 item anxiety scale measuring anxiety (Beck et al., 1988).

Measures of positive psychotic symptoms

- **Positive and Negative Symptom Scale (PANSS).**
  Standard scale for the assessment of psychotic symptoms. A 30-item scale with positive and negative subscales(Kay et al., 1987).
- **State Social Paranoia Scale (SSPS).**
  Measures recent paranoid thinking in social situations. The SPSS has ten persecutory items, each rated on a 5-point scale. The measure has ten items and has good internal, convergent and divergent validity and good reliability (Freeman et al., 2007).

Cognitive Measures

- **Hopkins Verbal Learning Task (HVLT).**
  Verbal learning and memory test providing a measure of immediate and delayed recall (Benedict et al., 1998). Similar to the California Verbal Learning Task, but is shorter and importantly has different forms to enable repeated measures. Participants are asked to remember a list of 12 items. For immediate recall, this is read three times with a recall stage after each reading. Delayed recall is after 25 minutes.
- **Digit Symbol Recoding (DSR)**
  Taken from the WAIS-III (Wechsler, 1939). A speed of processing task, requiring participant to match numbers to symbols using a provided key.
- **Digit span (DS)**
  Taken from the WAIS-III (Wechsler, 1939). A measure of attention and working memory.
- **N-Back**
  The N-back is a measure of continuous attention and working memory(Kirchner, 1958). This measure was selected specifically for the EEG component of the study. Unlike digit span, it is not co-normed with other tasks. Alternate forms were generated for repeated measures.
- **NAB-Mazes**
  Participants are scored on a composite measure of accuracy and speed on a series of seven progressively more difficult maze-tracing tasks(Hartman, 2006). Only two equivalent versions are available, thus the task was only delivered post-capsule and post-THC.

4.1.3.3 Chubb Illusion Procedure

The Chubb Illusion Task used was a modified version of that used by Dakin, Carlin and Hemsley (Dakin et al., 2005). In this task, the participant was sequentially presented with two stimuli disks of equal size. Both disks were centrally presented on a computer screen. One disc was presented in isolation (the 'test patch'), the other disk (the 'reference patch') was presented with a larger reference surround. The observer had to verbally report which of two stimuli (the reference or the target) was 'stronger', by reporting 'first' or 'second'. This response was entered by the researcher. If the observer reported losing concentration for a particular trial, the experimenter was able to repeat the presentation.

Each disk and the surround consisted of identically filtered noise (11.25cpd; 0.4 octave bandwidth, luminance fixed at 50cd/m2). The contrast of the test patch was varied from trial to trial, within a 4-80% range. The constrast of the reference patch and reference were fixed (at 40% and 95% respectively). Example test patch contrasts are shown in Figure 4.1. The reference patch and surround are shown in Figure 4.2

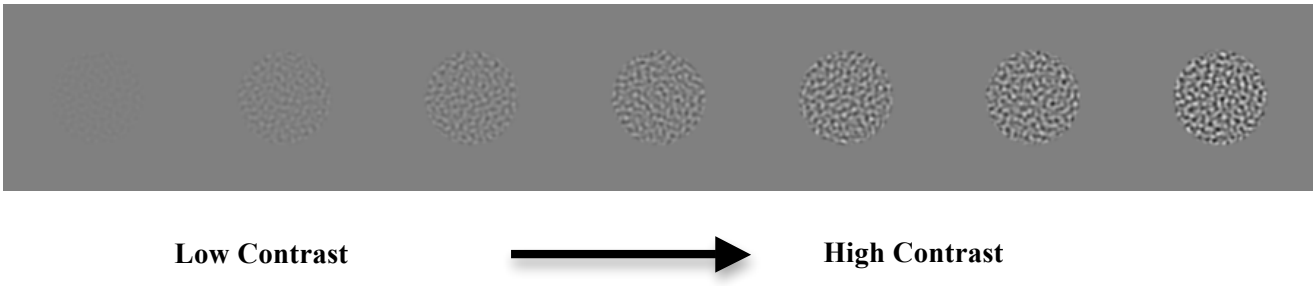


Figure 4.1. Example Test Patch Contrasts

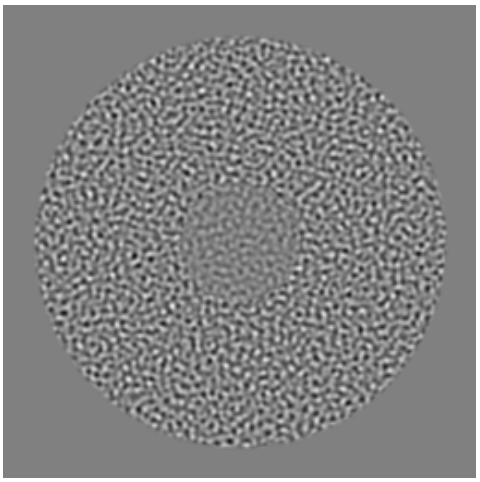


Figure 4.2. Example of Reference Patch and Surround

Reference and target stimuli were presented centrally in a randomized order for 500ms each, separated by an inter-stimulus interval of 1250ms. Stimuli were disks with a radius of 0.34 degrees of visual angle (DVA) when presented at a viewing distance of 120cm. The reference stimulus was embedded in a circular surround with a radius of 1.91 DVA. Fixation was assisted by the presence of a central black cross, which turned white when stimuli were presented onscreen.

Stimuli were presented on a CRT monitor (spatial and temporal resolution of 1024 x 768 pixels and 75 Hz respectively) fitted with a Bits ++ box (Cambridge Research Systems) operating in Mono ++ mode to give true 14-bit contrast accuracy. Experiments were controlled under the Matlab programming environment (MathWorks, Cambridge, MA) in conjunction with Psychtoolbox (Brainard, 1997; Pelli, 1997) running on an Apple MacBook computer.

Runs consisted of 64 trials, during which the signal level (contrast) was manipulated under the control of the adaptive probit estimation toolbox (APE; Watt and Andrews, 1982). Each participant undertook two runs of the test at each session, thus each participant completed 128 trials at each session. Data from the two runs was merged in Matlab, before functions were fitted.

Use of APE algorithm, Output and Outlier Removal.

There are a number of approaches to gathering the psychophysical data for analysis. The most rigorous approach is to systematically vary the contrast difference at set points across a range. This method however requires very many trials and is time

consuming for participants. Where sufficient time is not available to use this method, an adaptive method can be used. Such methods attempt to characterise the psychophysical function based on a smaller number of iterations. In this case the APE algorithm was used. Here, signal level (degree of contrast of the test patch) was manipulated under the control of the adaptive probit estimation toolbox (APE; Watt and Andrews, 1982).

Output: Threshold and Bias Variables:
Full psychometric functions were derived, so that the threshold (standard deviation of a cumulative Gaussian fit to the data) and bias (the point of subjective equality) could be obtained. Threshold corresponded to the signal level of the test needed to support 83% correct performance. Negative biases indicated suppressive effects. Previous research indicates that control subjects should demonstrate such negative biases.

Outliers: Ninety-five percent confidence intervals (C.I.s) of fit parameter estimates (threshold and bias) were obtained through bootstrapping (re-sampling) and re-fitting of the raw data. The level of confidence associated with each parameter estimate was subsequently used to exclude data points for which relative confidence was low. Thus, C.I.s for both parameters were converted into Z-scores (i.e. expressed as signed units of standard deviation), and any data points for which C.I.s exceeded 2.5 for either threshold or bias (i.e. fell beyond 2.5 standard deviations of the mean) were excluded.

4.1.4 Procedure

Recruitment and data collection for the study took place in four stages.

1. Recruitment and screening via email.
2. Initial data collection via online questionnaire.
3. Final screening and baseline data collection
4. Drug administration and testing

Details of the procedure are discussed below and parts two to three of the procedure are shown in diagrammatic form in Figure 4.3.

4.1.5 Recruitment, Screening and Initial Data Collection

Participants were recruited via a King's College London, University-wide email (see Appendix). The inclusion criteria were:

- Males or Females aged 21-50

- A history of cannabis use, but not meeting threshold for cannabis abuse disorder.
- No drug use in the last month
- Any gender or ethnic background
- No history of major psychiatric illness
- No current or past treatment with psychotropics
- No current physical illness
- No family history (first-degree) of psychiatric illness
- Not currently pregnant

The inclusion of a history of cannabis use was necessary to avoid exposing cannabis naïve participants to a potentially addictive substance.

The initial email received over 300 responses. A response was sent to all potential volunteers asking them to fill out three online questionnaires: The Cannabis Experience Questionnaire (CEQ) (Barkus et al., 2006), The Schizotypal Personality Questionnaire (Raine, 1991) and Green Paranoid Thought Scale (GPTS, (Green et al., 2007)). The CEQ was used to score potential participants based on their past experience of cannabis use.

Following completion of the online questionnaires, participants were invited to attend a session to complete screening and baseline measures. Screening took approximately one hour and the following assessments were administered.

- Mini-Screen-For SCD from Structured Clinical Interview for DSM-IV (SCID), to screen for psychiatric symptoms (Gibbon & Williams, 2002).
- Michigan Alcohol Screening Test (MAST) to assess for alcohol abuse.
- DAST-20 to assess drug use over the previous 12 months (Skinner & Ontario, 1982).

Following screening, the remaining trait measures were administered. Baseline data was collected for all trait measures with the exception of EEG measures, which were collected on the drug administration day. Basic socio-demographic data (gender, ethnicity, date of birth and level of education) were recorded at screening.

4.1.6 Assessment

Assessment for the study can be divided into trait assessments and state assessments. The trait assessment battery was carried out during the recruitment, screening and baseline stages. The state assessment battery was carried out at three time points: baseline, post oral tablet administration and post THC administration. The same battery of measures was administered at each point. However, in order to reduce the testing load on the main test day, most of the baseline testing was done in a separate session before the drug administration day. The order of administration and specific scales are detailed later.

4.1.7 Experimental Session

Participants were asked to abstain from recreational drugs for one week before the session and alcohol for one day. This was confirmed by use of a Urinary Drug Screen (UDS). Caffeine was allowed prior to the study if it was part of the participant's normal routine. A light lunch was provided and cigarette breaks were allowed. The experimental sessions ran from approximately 9am to 4.30pm.

The procedure for the day was as follows:

- Baseline EEG recording.
- 0h: Oral capsule administration of 600mg CBD or placebo
- 2.5h: Administration of test battery
- 3.5: IV administration of Δ-9-THC.
- 4.5: Administration of test battery

Following the experimental session, participants were asked to abstain from drinking alcohol, driving or operating heavy machinery for at least 24 hours. A follow up telephone call was made the next day. Participants were given £60 reimbursement for taking part in the study.

4.1.8 Pharmaceuticals and Drug Administration

CBD was administered orally, with a dose of 600mg (2 X 300mg capsules) based on past human studies, which have typically involved doses of 300-600mg per day (e.g. Bhattacharyya et al., 2010; D'Souza et al., 2004; Morrison et al., 2009). CBD was obtained from STI Pharmaceuticals UK. Double-blinding was achieved via over-encapsulation (doses are provided in indistinguishable capsule form). Capsules were administered 3.5 hours prior to IV THC challenge based on the available knowledge regarding the pharmacokinetics of CBT (Bhattacharyya et al., 2010).

Synthetic Δ-9-THC was supplied by THC Parm GmbH, Frankfurt, Germany and prepared as 1mg/ml vials for IV injection, by Bichsel Laboratories, Interlaken, Switzerland. After dilution in normal saline, preparations for injection contained 1.5% ethanol absolute. Sterile cannulae were inserted into veins into the antecubital fossa of both arms: one for administration of THC and one for plasma sampling. 1.5mg THC was administered in 1ml/min pulses over 10 minutes. The IV administration of Δ-9-THC allowed for a relatively rapid delivery, with a pharmacokinetic time course similar to that of smoked cannabis (Grotenhermen, 2003).

Blood samples were taken at 1:00, 2:00 , 3:45, 4:10 and 5:00 hours post capsule. Blood pressure and heart rate were also taken at this time. Samples were analysed for CBD and THC concentrations as previously described (Morrison et al., 2009). Rescue medicine, in the form of lorazepam (1-3mg), was available.

4.1.9 Data Analysis:

All analyses were performed in SPSS 19.0 (SPSS inc., Chicago). Data were assessed for normality using Kolmogorov-Smirnov test statistics. Baseline group differences were assessed using Pearson's Chi-square and independent t-tests, for categorical and ratio data respectively.

Normally distributed data were analysed using a repeated measures general linear model (GLM). The data was initially analysed using a 3 (SESSION) X 2 (GROUP) model.

As expected given the sample, data on PANSS and SSPS scales were highly positively skewed. This was the case for both state and change scores, thus necessitating the use of non-parametic approaches. Friedman's test was thus used to analyse symptom scores. In addition, following D'Souza, for the PANSS, within subject change was categorised according to whether it met a-priori criteria for clinically significant change (an increase of greater than 2 points). This categorical data was analysed using Fisher's Exact Test.

Relationships between psychosis scores and bias/cognitive data were analysed with Spearman's rank correlation coefficient. This was chosen to account for the possible distorting effect of outlier data. Significance was accepted at $p<0.05$, all comparisons were two tailed.

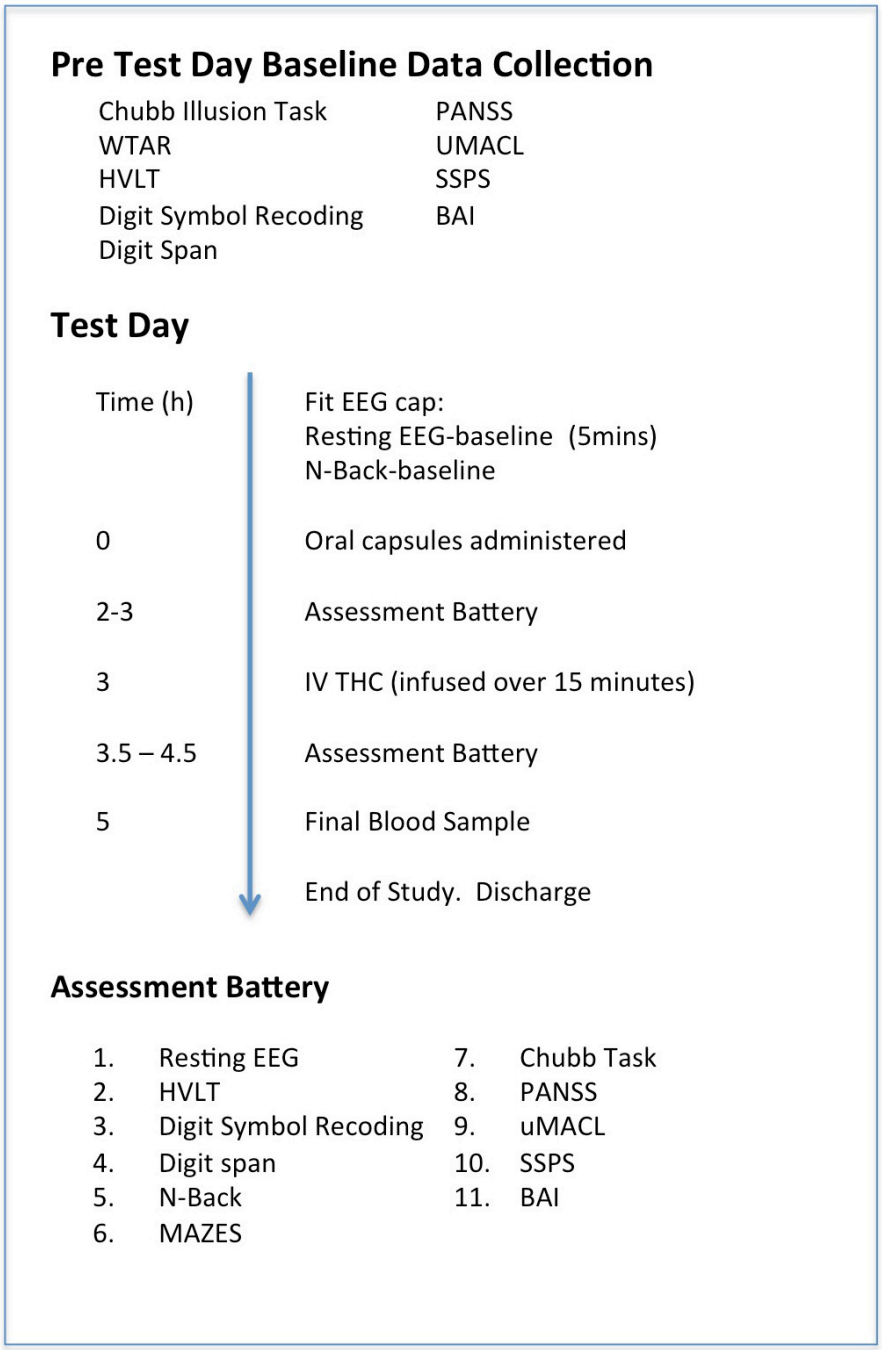


Figure 4.3. Data Collection Timetable

Please refer to the section 'Experimental Task and Measures' for details of individual tasks/measures.

4.2 Results

4.2.1 Participants

Fifty-one participants were tested. Of these, three had to be excluded due to failure of THC cannulation. Three more subjects did not complete the Chubb task at all three sessions. Thus 45 subjects were available for analysis.

Identification of Outliers.

The first step in the analysis was to identify possible outliers (as detailed in the methods) on the basis of performance on the Chubb task, either with respect to bias or threshold and on any session. Six participants were identified with outlier data on at least one session. Four of these participants were from the placebo group, and two from the CBD group. These participants were excluded from all further analysis, leaving 39 participants, 19 in the CBD arm and 20 in the placebo arm.

4.2.2 Demographics and Baseline Scores

Demographics and Baseline scores are shown in Table 2.1.

Table 4.1. At baseline, groups were matched on all demographic variables (age, sex, gender, ethnicity and education. Groups were also matched on their scores on the CEQ, CAPS (total score), GPTS, SPQ (total, suspiciousness and unusual perceptual experiences) and the number of times they had used cannabis.

Table 4.1. Demographics and Baseline Characteristics

	CBD			Placebo			p
Demographics							
N	19			20			
Sex (m:f)	12,7			12,18			ns
Ethnicity (White European/other)	15,4			17,3			ns
Education (A-level, vocational, university)	2,2,15			1,1,18			ns
Age (mean, med, sd)	23.9	25.0	2.5	25.7	25.0	3.9	ns
Baseline Scale Scores	mean	med	sd	mean	med	sd	
SPQ (total)	11.1	9	10.1	11.4	11.0	5.6	ns
SPQ (unusual perceptual experiences)	0.89	0.0	1.8	0.61	0.0	0.9	ns
SPQ (suspiciousness)	0.78	0.0	1.2	0.61	0.0	0.9	ns
Green Paranoia. Paranoid subscale	24.0	20.0	10.5	19.7	17.0	5.2	ns
CEQ (paranoia/dysphoria)	43.1	43	10.1	43.5	46	9.7	ns
CAPS (total)	2.3	1.0	3.2	2.1	1.0	2.2	ns
Previous cannabis use (episodes)	135	20	258	99	30	222	ns

4.2.3 Hypothesis 1. Effect of THC and CBD pre-treatment on Bias.

1. Following administration of THC, participants will show a psychotic-like reduced influence of context on processing manifested as reduced susceptibility to the Chubb illusion. This will be reflected by a reduction in bias.

a) The THC induced bias reduction predicted in hypothesis 1 will be blocked following pre treatment with CBD.

Bias data is shown in Figure 4.4, Figure 4.5, Figure 4.6 and Table 4.2.

Bias data was analysed using 3 (SESSION) X 2 (GROUP) mixed GLM. The factor 'SESSION' was treated as a repeated measure. Within subject difference data (between session) was normally distributed according to Kolmogorov-Smirnov. Results are shown graphically in Figure 4.4.

There was a significant linear effect of SESSION ($p=0.011$) and GROUP on bias ($p=0.035$), and no SESSION*GROUP interaction effect ($p=0.244$). Post-hoc contrasts revealed that bias was significantly greater in session 3 compared to session 1 ($p=0.007$), other differences were not significant.

As there was a significant group difference on bias, a supplementary analysis (2 X 2 (SESSION X GROUP) GLM) was conducted with baseline bias used as a covariate. Following adjustment for baseline bias, the effects of SESSION and GROUP remained significant ($p=0.049$ and $p=0.009$), with session 3 bias being significantly greater than session 2 bias. There was no significant SESSION*GROUP interaction.

4.2.3.1 Conclusions

The evidence did not support hypothesis one (that bias would be reduced following administration of THC). Furthermore, as there was no interaction between GROUP (placebo/CBD) and SESSION, the evidence does not support any effect of CBD pre-treatment on bias. There was however, an unpredicted effect of SESSION, with bias increasing over time, either indicating practice effects or a CBD independent effect of THC

The most striking finding was the effect of GROUP upon bias, with groups being significantly different at baseline and each timepoint thereafter. However, as groups

were selected through double-blinded randomisation, this difference must represent a random result.

Table 4.2. Measures by SESSION and GROUP

	CBD			Placebo			Overall		
Chubb	mean	med	sd	mean	med	sd	mean	med	sd
Bias									
Baseline	-17.0	-17.0	7.1	-11.9	-11.8	7.4	-14.4	-14.0	7.6
Post Capsule	-17.6	-17.5	7.0	-13.7	-11.9	7.1	-15.6	-17.0	7.2
Post THC	-19.3	-20.6	6.7	-15.2	-14.1	6.2	-17.2	-16.9	6.8
Threshold									
Baseline	11.6	11.3	1.7	10.8	10.6	0.9	11.2	11.1	1.4
Post Capsule	10.9	10.4	1.6	10.7	10.5	1.4	10.8	10.4	1.4
Post THC	11.7	11.6	2.6	10.4	10.2	1.2	10.8	10.8	1.5
PANSS									
Positive									
Baseline	7.0	7.0	0.0	7.0	7.0	0.0	7.0	7.0	0.0
Post Capsule	7.0	7.0	0.0	7.0	7.0	0.0	7.0	7.0	0.0
Post THC	8.0	7.0	1.4	9.3	7.5	3.0	8.6	7.0	2.4
Negative									
Baseline	7.2	7.0	0.5	7.3	7.0	0.7	7.2	7.0	0.6
Post Capsule	7.2	7.0	0.6	7.2	7.0	0.7	7.2	7.0	0.7
Post THC	8.1	7.0	2.6	8.0	7.0	1.7	8.1	7.0	2.2
SSPS (persecution)									
Baseline	10.1	10.0	0.2	10.0	10.0	0.0	10.0	10.0	0.2
Post Capsule	10.1	10.0	0.2	10.0	10.0	0.0	10.0	10.0	0.2
Post THC	10.2	10.0	0.5	11.0	10.0	2.3	10.6	10.0	1.7

Figure 4.4. Chubb Mean Bias by Group and Session.

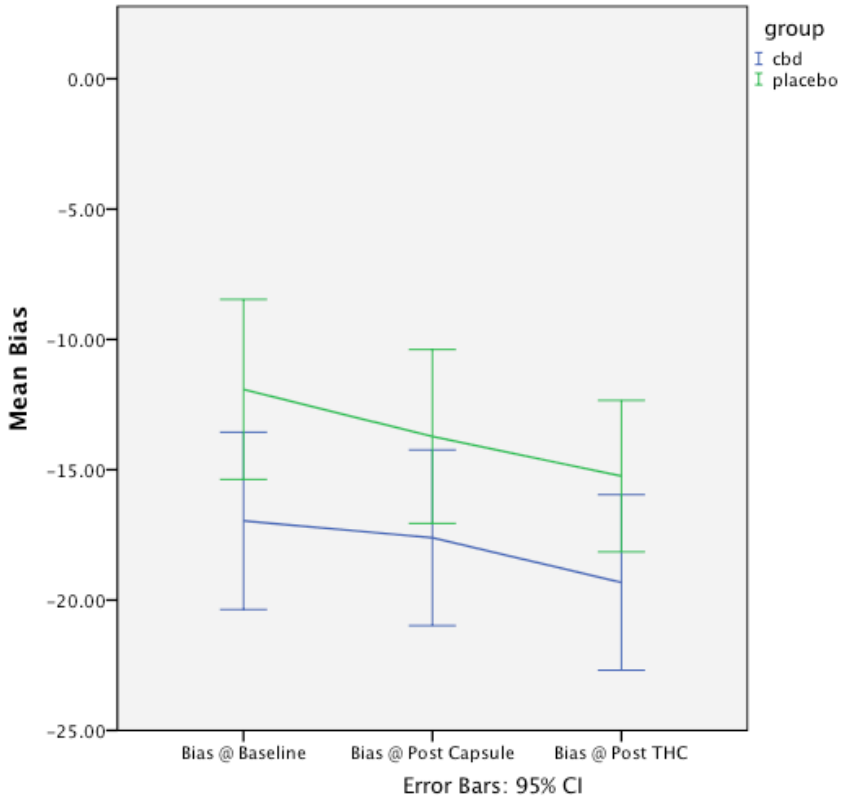


Figure 4.5. Chubb Median Bias by Group and Session

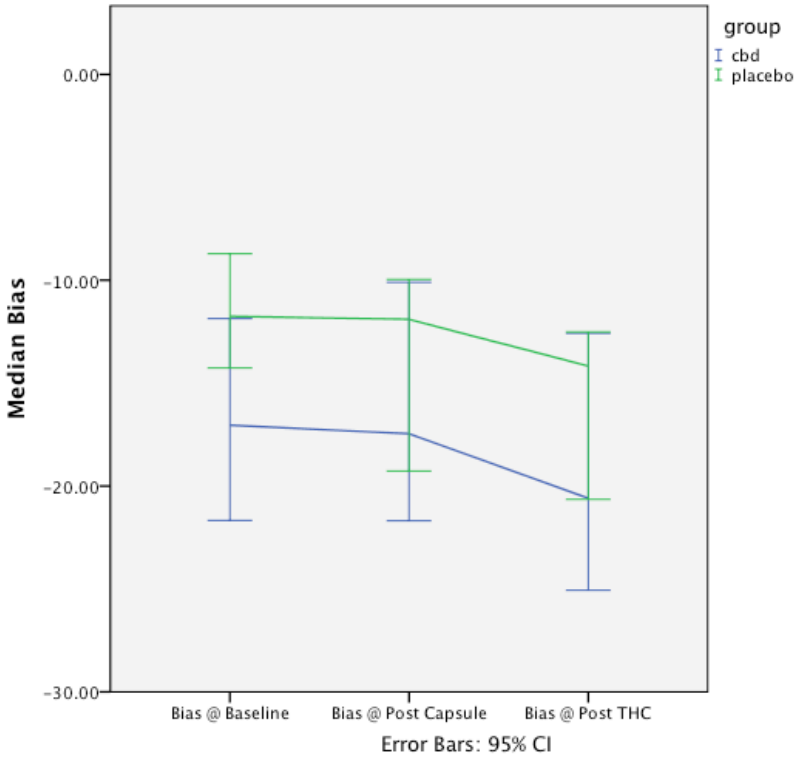
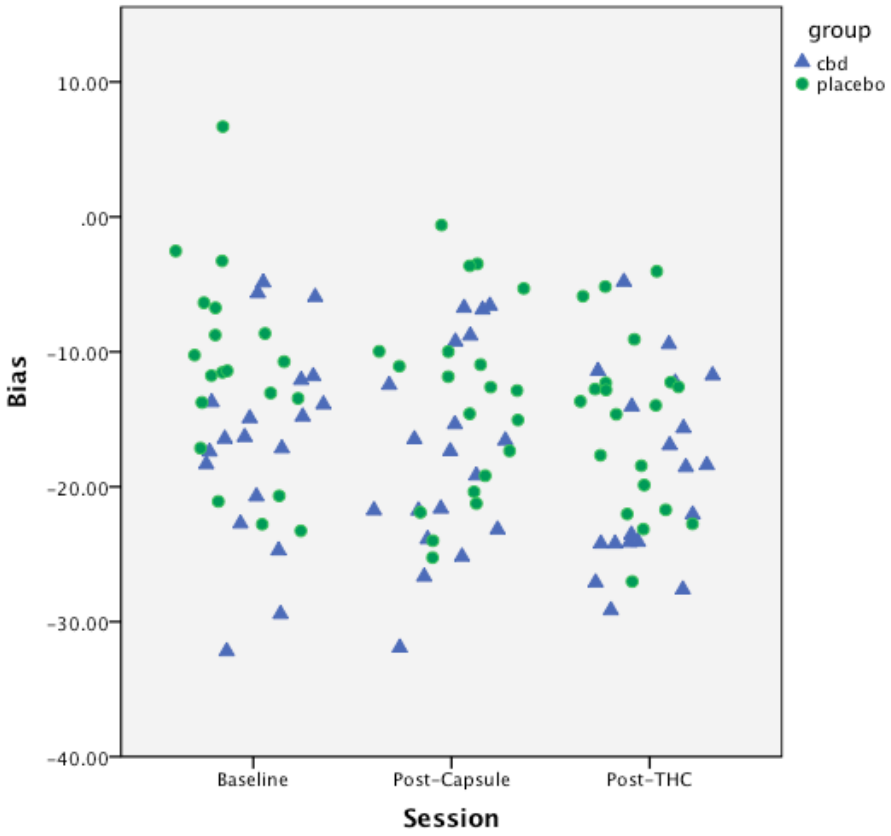
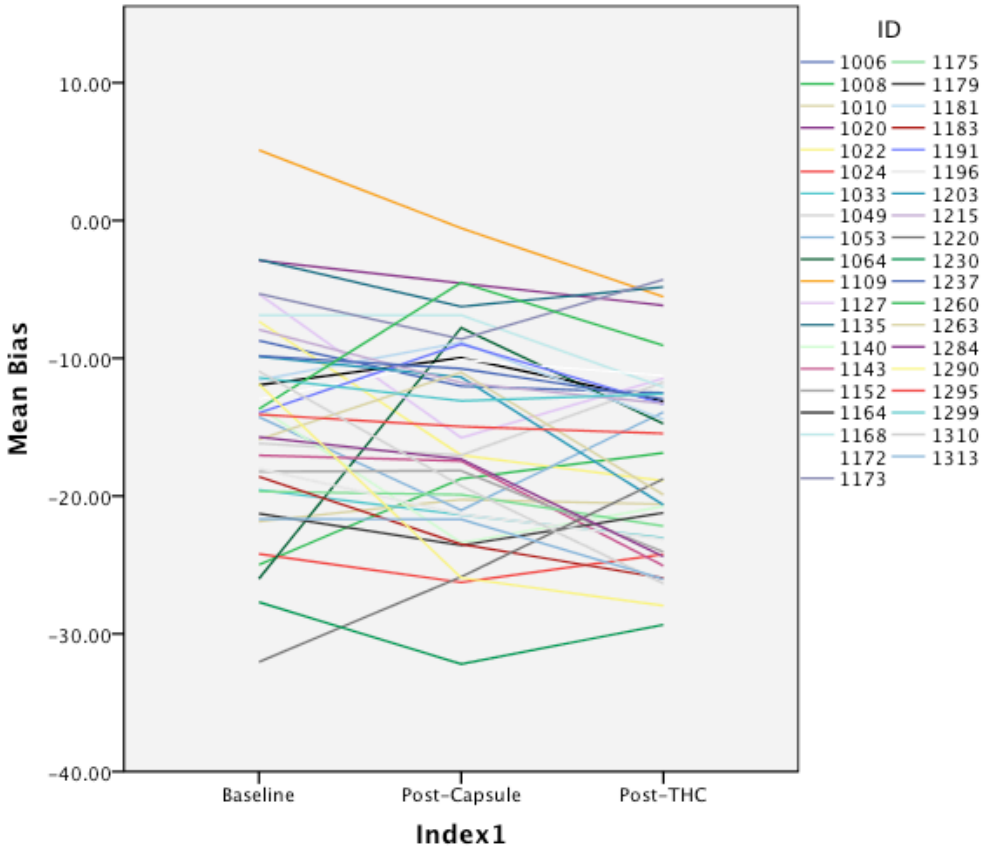


Figure 4.6 Chubb Bias By Group and Session





4.2.4 Hypothesis 2: Effect of THC and CBD Pre-Treatment On Psychosis Symptoms

Administration of THC will increase symptoms of psychosis as measured by PANSS (positive and negative) scores as well as by the State Social Paranoia Scale (SSPS).

a) The THC induced increase in symptom scores will be blocked by pre-treatment with CBD.

PANSS positive, PANSS negative and SSPS scores were not normally distributed according to the Kolmogorov-Smirnov test. Continuous data was thus tested using Friedman's test (FT, for analysis of SESSION effects) and Mann-Whitney (M-W, for independent group analysis of change scores). Fischer's exact test (FET) was used to test categorical data.

Symptom data is shown in Figure 4.7, Figure 4.8, Figure 4.9, Figure 4.10, Figure 4.11 and Figure 4.12.

4.2.4.1 PANSS Positive

There was a significant effect of SESSION on PANSS-positive scores, regardless of whether pre-treatment was with CBD (FT, $\chi 2=18$, $p<0.000$) or placebo (FT, $\chi 2=24$, $p<0.000$). From visual inspection of the data, it was clear that this SESSION effect was accounted for solely by change at post-THC. Thus THC, but not CBD, was associated with an increase in positive symptoms. There were no significant between-group differences in baseline-postTHC change scores (M-W, p=0.266).

An alternative approach to the data is to categorically define participants as 'responders' and 'non responders'. Following D'Souza (2005), participants were categorised according to a clinically significant change in score following THC (defined as an increase in PANSS positive scores of >=3 points). Such changes were more common, at trend level in the group treated with placebo (8 of 20 cases), compared to the group pre-treated with CBD (2 of 19 cases) (FET, p=0.065). Rerunning the analyses with previously removed outliers included resulted in a significant difference (FET, p=0.02, CBD responders = 2/21, Placebo responders = 10/24). This indicates that CBD counteracts the effect of THC on positive symptoms.

4.2.4.2 PANSS Negative

There was a significant effect of SESSION on PANSS-negative scores, regardless of whether pre-treatment was with CBD (FT, $\chi 2=8.4$, $p=0.015$) or placebo (FT, $\chi 2=6$, $p=0.050$). From visual inspection of the data, it was clear that this SESSION effect was accounted for solely by change at post-THC. There was no group difference in change scores (M-W, $p=0.574$).

4.2.4.3 SSPS

There was a significant effect of SESSION on SSPS persecution scores for placebo (FT, $\chi 2=14$, $p<0.001$), but not CBD (FT, $\chi 2=2$, $p<0.368$) groups. Inspection of the data shows that this effect is accounted for by change post-THC. Thus THC, but not CBD was associated with an increase in SSPS paranoia scores. Independent group analysis of change scores indicated that the group difference was not significant (M-W, $p=0.206$). Examination of scatter plots indicates that the response to THC was driven by relatively few participants (5 of 20 in placebo group, 2 of 19 in CBD group).

4.2.4.4 Conclusions

The data supported hypothesis 2, that THC would induce symptoms of psychosis. Furthermore, the data supported hypothesis 2a, that the degree of symptom induction would be reduced by pre-treatment with CBD.

Figure 4.7 Effect of THC on PANSS Positive (y axis truncated, 7 is baseline)

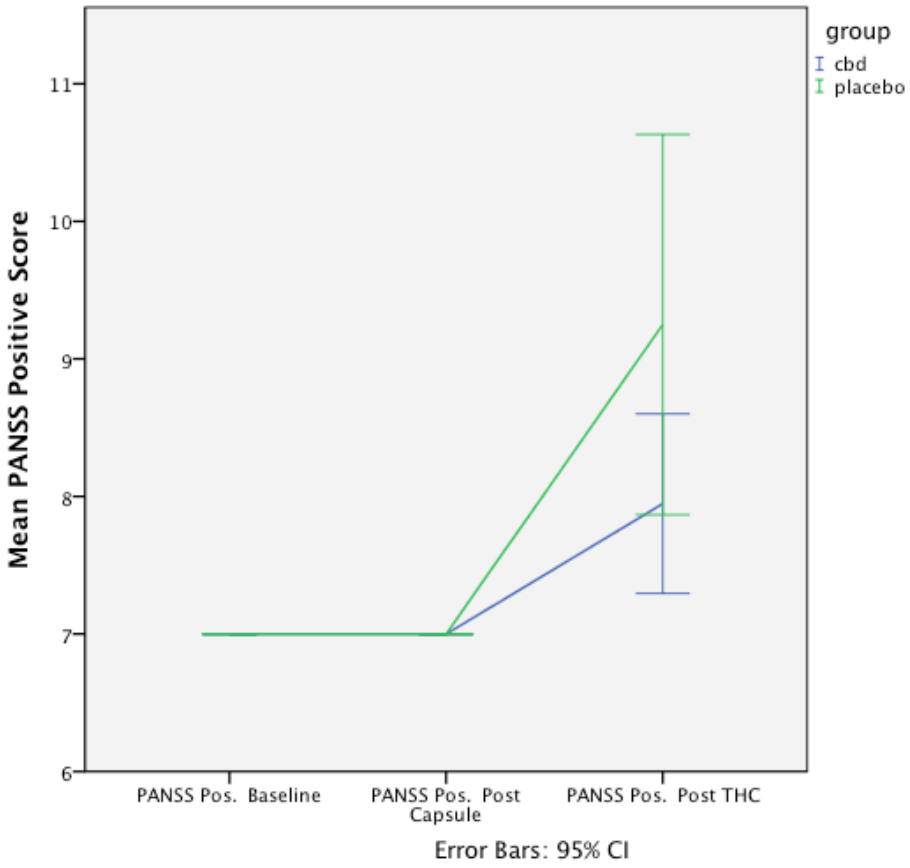
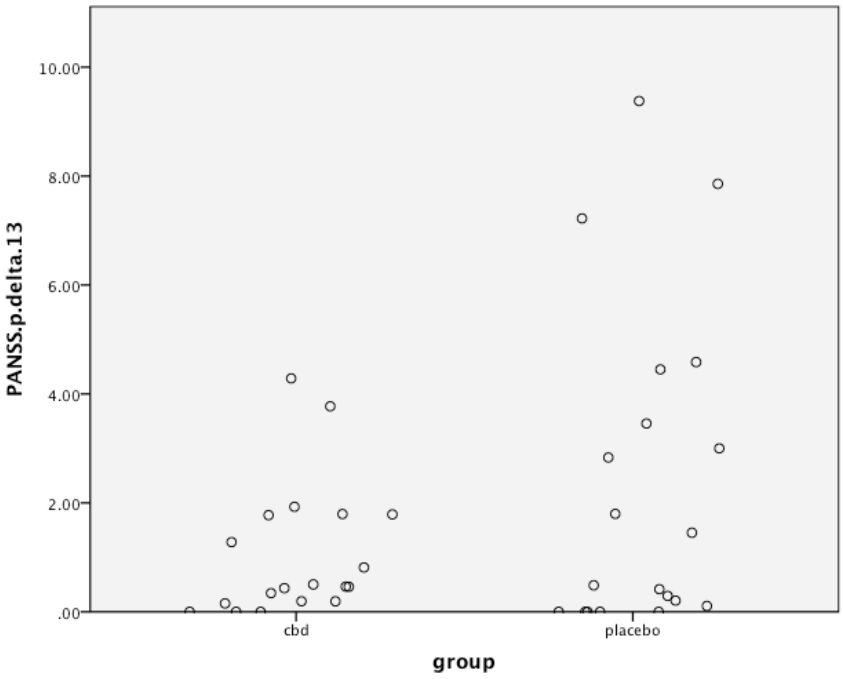


Figure 4.8 PANSS Positive. Baseline-Post THC Change Scores



(Data Jittered for clarity)

Figure 4.9 Effect of THC on PANSS Negative (y axis truncated, 7 is baseline)

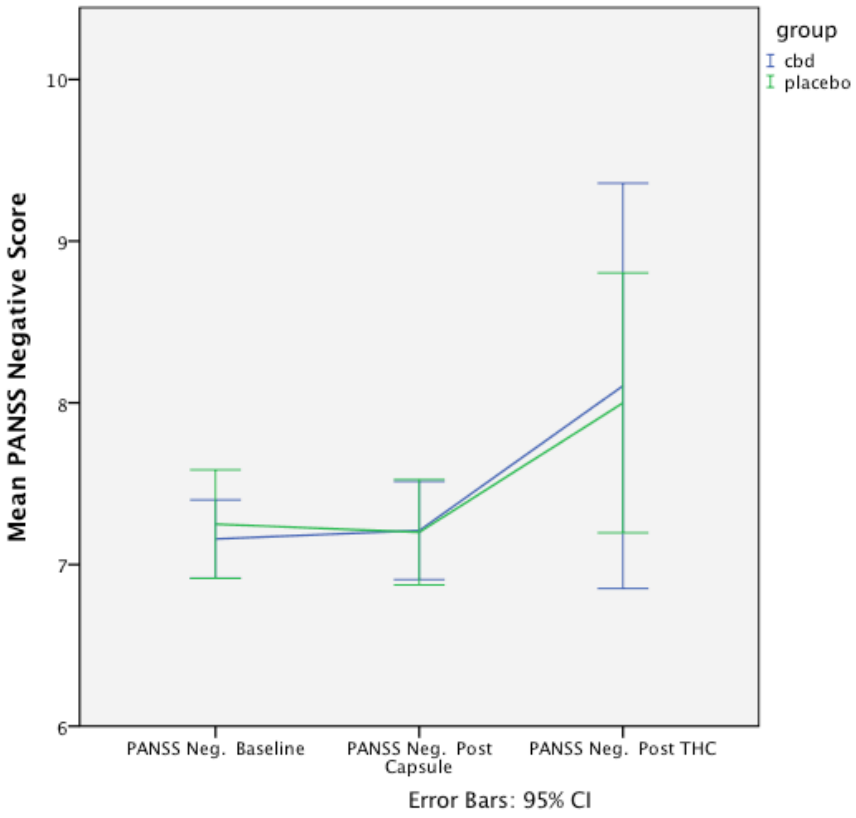
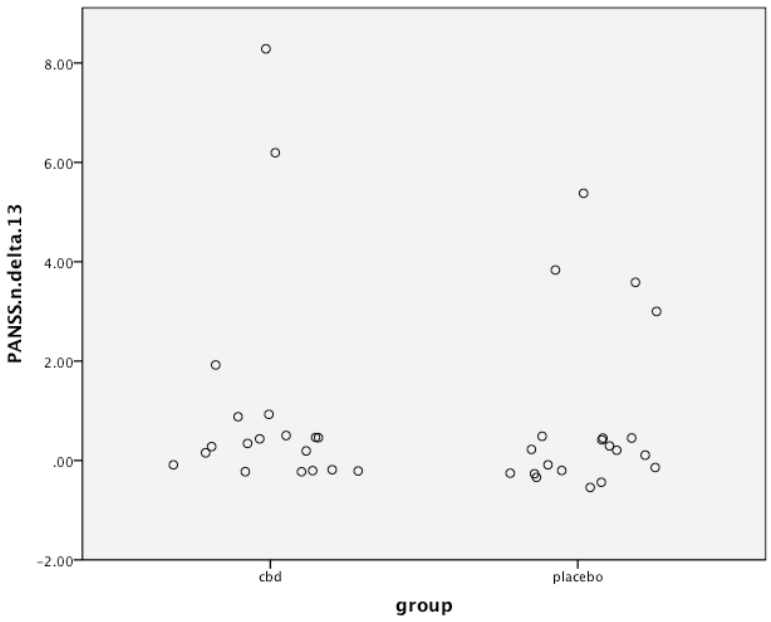


Figure 4.10 PANSS Negative. Baseline-Post THC Change Scores



(Data Jittered for clarity)

Figure 4.11 Effect of THC on SSPS Persecution(y axis truncated, 10 is baseline)

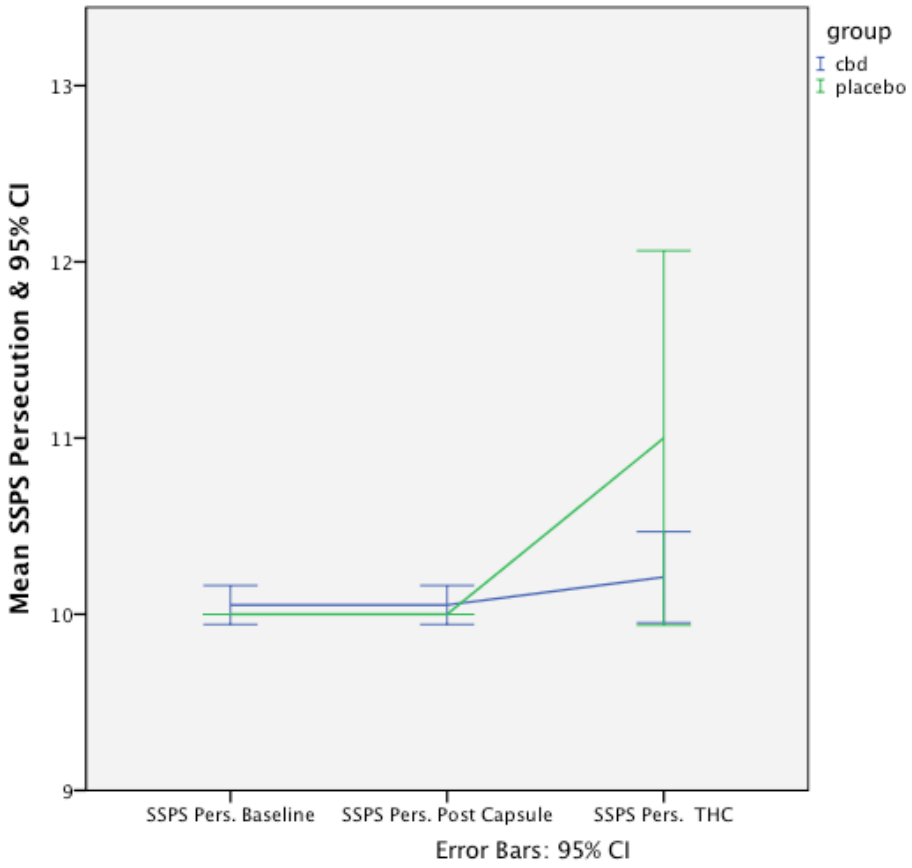
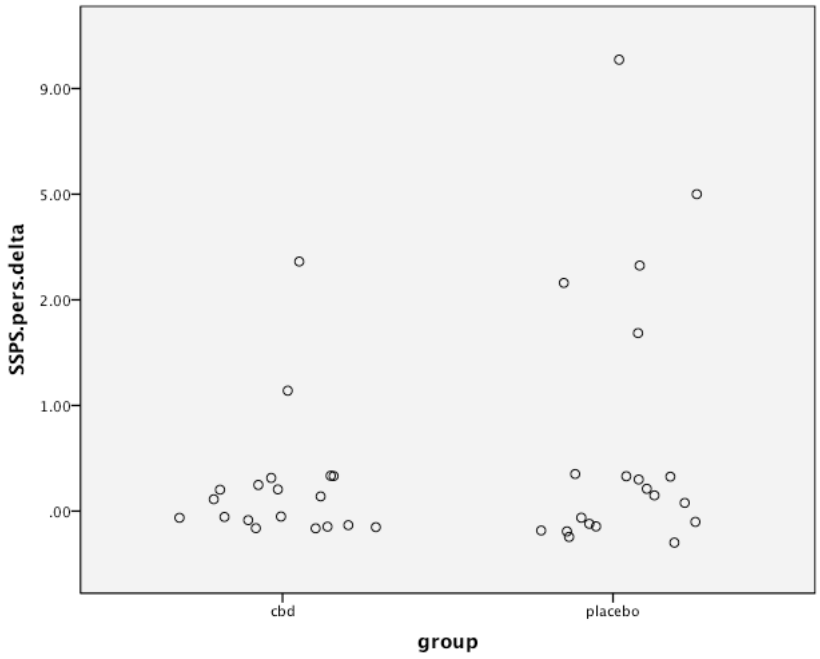


Figure 4.12. SSPS Persecution. Baseline-Post THC Change Scores



(Data Jittered for clarity)

4.2.5 Hypothesis 3. Relationship Between Baseline Symptoms and Bias.

Susceptibility to the Chubb illusion (bias) before THC administration will be negatively correlated with

a) Lifetime Anomalous Perceptions as measured on the Cardiff Anomalous Perceptions Scale (CAPS).
b) Psychotic-like reactions to cannabis as measured by the psychotic-like effects subscale of the Cannabis Experience Questionnaire (CEQ).
c) Scores on the Green Paranoid Thoughts Scale (GPTS).
d) Schizotypal Personality as measured by Scores on the Schizotypal Personality Questionnaire (SPQ). Specifically Total score, suspiciousness and unusual perceptual experiences.

Average scores for the CAPS (2.3 and 2.1 for CBD and Placebo groups) were lower than those reported by Bell (Bell et al., 2005), which were 7.3 (s.d. 5.8) in a non-clinical sample. There was no correlation between total CAPS score and bias.

Average scores for the psychotic-like effects subscale of the CEQ (43.1 and 43.5 for CBD and Placebo groups) were similar to those reported by Barkus (42.12) (Barkus et al., 2006), in their study of cannabis using controls. There was no significant relationship between this subscale and bias.

Average scores for the persecutory subscale of the GPTS (24.0 and 19.7 for CBD and Placebo groups) were similar to those reported by Green (22.1) for non-clinical samples (Green et al., 2007). There was no significant relationship between this subscale and bias.

Average scores for the total score of the SPQ (11.1 and 11.4 for CBD and Placebo groups) were more than a standard deviation lower than those reported by (Raine, 1991), which were 26.9 and 26.3 (s.d 11 & 11.4) for general population samples. There was no significant relationship between bias and: SPQ total, suspiciousness or unusual perceptual experiences.

4.2.5.1 Conclusions

Contrary to the hypotheses, the data did not support any correlations between bias on the Chubb illusion and trait measures of anomalous perceptions, reactions to cannabis, paranoid thoughts or schizotypal personality.

4.2.6 Post-Hoc Analyses

4.2.6.1 Test-Retest Reliability (Stability) For Chubb Task

From the protocol, the 'purest' test-retest data is obtained from comparing session1 and session2 in the placebo group. For this comparison test retest reliability was as below.

Bias:

Spearman's rho: 0.632

Pearson's r: 0.751. Both significant at $p<0.01$.

An alternative method for calculating reliability is Intra-Class Correlation. To confirm the first analysis, an intraclass correlation coefficient (ICC) was calculated using a two factor mixed effects model and type consistency (McGraw & Wong, 1996; Shrout & Fleiss, 1979). Single Measures ICC was 0.75 [95% CI 0.47-0.59). Relationships are shown in Figure 4.13.

Bias is therefore measured with adequate stability.

Threshhold:

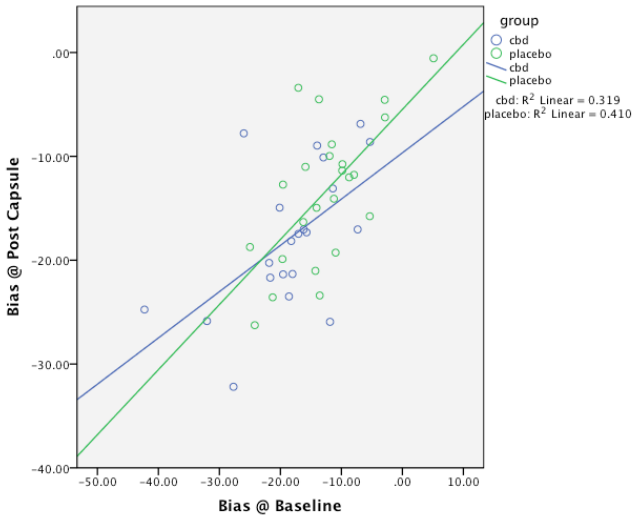
Comparing session1 and session 2 for the control group, there was a significant correlation with either Spearman's or Pearson's tests.

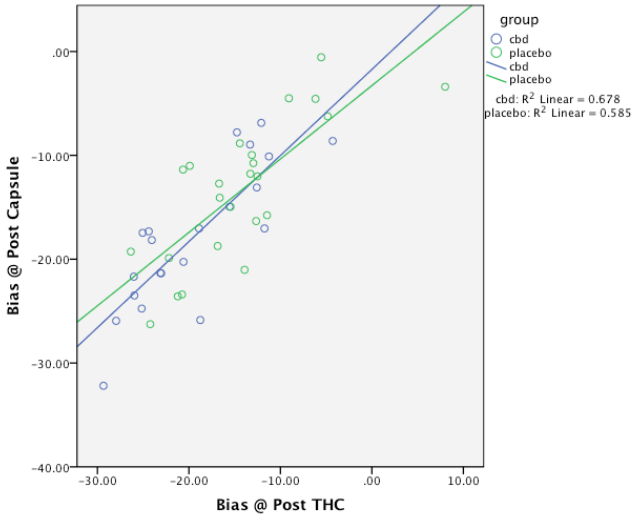
ICC using placebo group and sessions one and two only was: .0.31 (95% CI: -.14 – 0.63). Using all the available data, averaged measures ICC was: 0.20 (95% CI: 0.01 – 0.41). The results of standard correlation and ICC analyses therefore suggest that 'threshold' was not measured with good test-rested reliability. Given this, no further analyses were run on the 'threshold' variable.

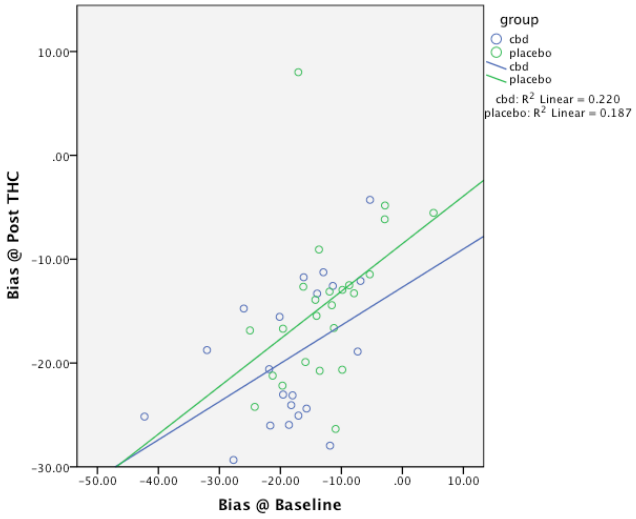
4.2.6.2 Relationship Between Previous Cannabis Use and Bias.

There was no relationship between the number of previous uses of cannabis and bias.

Figure 4.13. Relationships Between Bias At Different Sessions







4.2.6.3 Effect of Session Upon Accuracy.

The reported effect of SESSION upon bias might represent a practice effect. As participants did not know they had performed, and thus could not use such information to reduce their bias, a practice effect would most likely have been represented as increased response consistency or accuracy at the task. An estimate of accuracy for each subject was available from the 95% confidence interval obtained from the bootstrapping procedure (bias-range). Thus, a supplementary analysis was conducted to explore the effect of SESSION on accuracy. A 1X3 repeated measures GLM was conducted.

There was a significant effect of SESSION upon accuracy ($p=0.033$), shown in Figure 4.14. Further analysis revealed a significant quadratic ($p=0.019$), but not linear effect ($p=0.133$). There was a significant difference between baseline and post-capsule ($p=0.01$), but not between baseline and post-THC ($p=0.113$) nor between post-capsule and post-THC ($p=0.329$).

4.2.6.4 Relationship Between Bias and Accuracy

Correlations between bias and bias-range were significant ($p<0.05$) at each session and were as follows:

Session 1: -.369 Session 2: -.449 Session 3: -.495

Figure 4.15 shows the relationship between bias and accuracy (1/bias-range) at baseline. As bias range may be considered as the inverse of accuracy at a particular task, these correlations would indicate that as accuracy increases, estimates of bias decrease. These results would thus indicate that the change in bias was not due to an increase in accuracy, as this would be represented as a reduction in bias.

4.2.6.5 Conclusion

The results of the above analysis indicate that the effect of session was not due to accuracy, at least as measured by the bias-range.

Figure 4.14 Bias-Range by Session

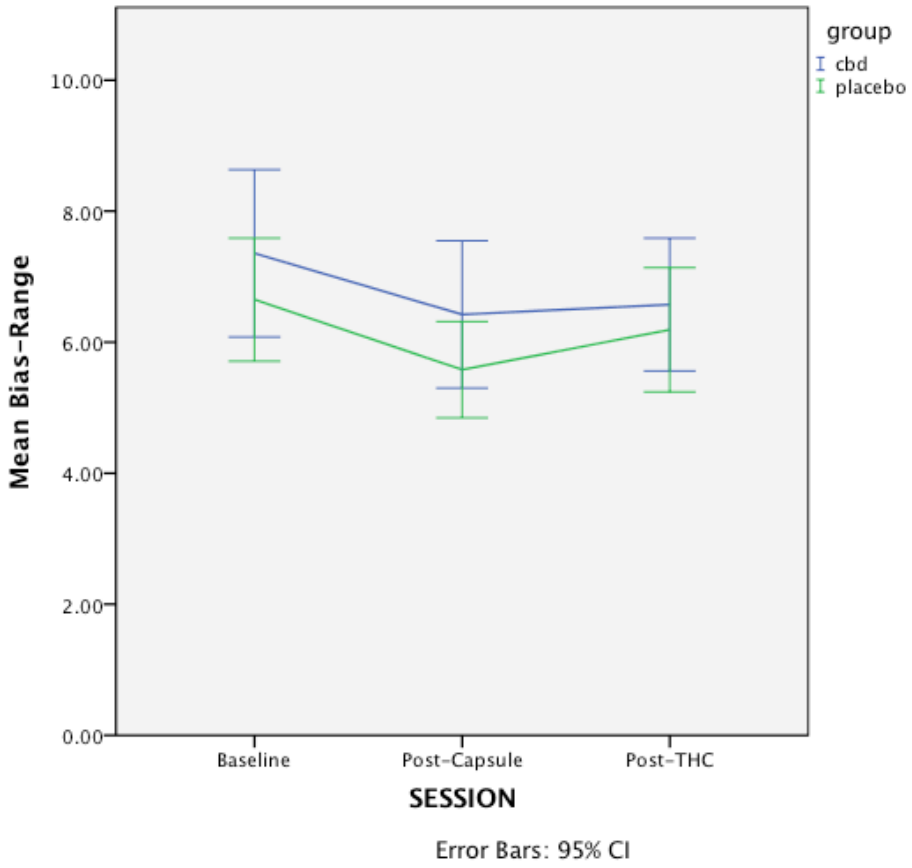
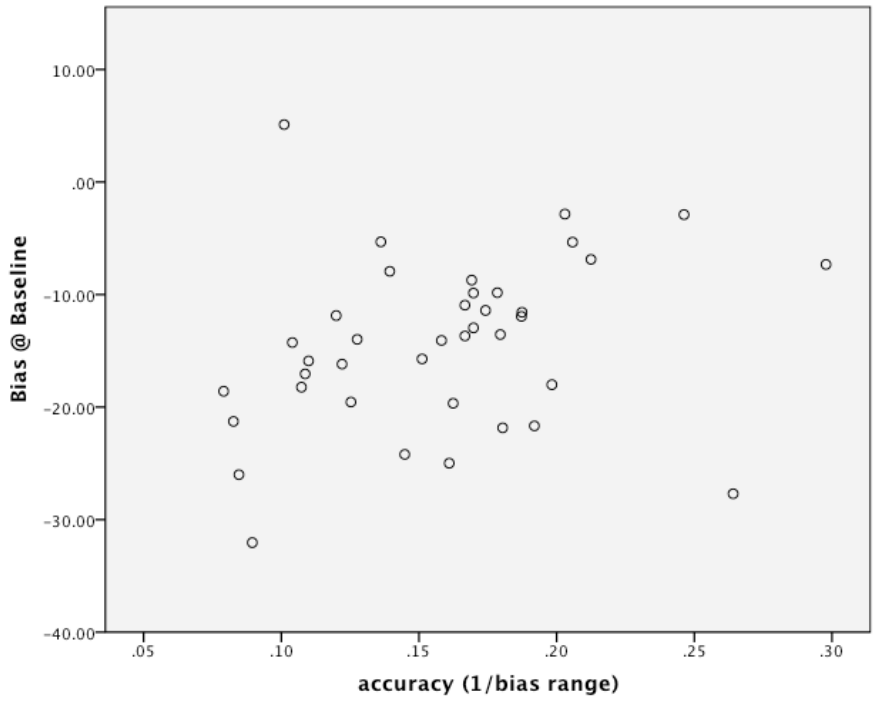


Figure 4.15. Relationship between Bias and Accuracy (Baseline)



4.3 Discussion

(Issues common to both Study One and Study Two will be discussed in the final chapter of the thesis. Thus discussion here will be limited to issues specific to Study One.)

This is the first study to investigate the effects of cannabinoids on performance on the Chubb visual illusion. It was predicted that THC would reduce normal levels of contrast-induced bias and that this reduction of bias would be offset by treatment with CBD. Contrary to this prediction, the results of the study demonstrate an increase in bias between baseline and post-THC conditions, and no effect of CBD. It was also predicted that performance on the Chubb illusion would be correlated with baseline schizotypy scores and THC induced change in symptom scores. No such correlations were identified. Thus the primary hypotheses of study one must be rejected

The study did, however replicate previous findings that THC can induce transient psychosis-like symptoms and that this symptom induction can be reduced by pre-treatment with CBD. The implications and interpretation of these findings are discussed below.

4.3.1 Effect of Session on Bias.

Regardless of treatment group, bias became significantly greater between baseline and post-THC timepoints. There was no interaction effect between groups. This is the opposite of what was predicted. The study was designed primarily to identify an interaction between THC and CBD, and did not have a THC-control component. It is therefore difficult to say conclusively whether this unexpected finding represents an effect of THC or a more general session effect (such as a practice effect). The analysis identified a linear effect of session on bias, indicating that bias became progressively greater from baseline to post-THC. This would suggest that the effect was not due to the administration of THC, as it was evident before THC administration.

It is possible that there was a practice effect of session on bias. This might arguably have been due to participants developing greater response accuracy over time. As we had estimates of the accuracy of each person's bias measurement at each session level, it was possible to analyse this by looking at whether the size of the confidence intervals decreased over time. This was found to be the case, with a significant effect of session on confidence interval range. It is not conceptually clear how bias and response accuracy are related, if at all. Correlation analysis indicated that there was a significant negative relationship between bias and bias-range (regardless of session), indicating that as

response accuracy increased, bias decreased. This result argues against increased accuracy being responsible for increased bias. It should however noted, that bias-range is a proxy measure of accuracy and thus these results do not represent a optimal analysis of participant accuracy on bias.

4.3.2 Test-Retest Reliability of Bias and Threshold Variables.

To my knowledge this is the first study to investigate test retest reliability of the two dependent variables from the Chubb paradigm: bias and threshold. To recap briefly, bias is a measure of the degree to which an individual's perception of a target stimulus is affected by the presence of a surround stimulus. Threshold is a measure of the smallest difference in stimulus that the observer can reliably distinguish.

From the results, it is clear that bias has reasonable test-retest reliability with an intra-class correlation (ICC) of 0.75. This means that it provides a relatively consistent and accurate measure of an individual's bias. By contrast, threshold did not have a significant ICC, indicating that it was very poorly measured in the current paradigm. This is likely due to the limited number of trials used in the task; accurate threshold estimation is difficult without collecting a full psychometric function.

4.3.3 Psychotomimetic Effects of THC and Protective Effects of CBD

The study provides clear evidence that THC increases both positive and negative symptoms of psychosis as measured by the PANSS scale. Furthermore for positive symptoms, pre-treatment with CBD dramatically reduced the number of people for whom THC induced clinically significant symptom change (only 10% of the CBD pre-treated participants had a clinically significant increase, compared to 42% of the placebo pre-treated participants). An important proviso to this conclusion is that clinically significant change was defined as a greater than 2 point change in PANSS-positive symptoms. Depending on how many items underlie this change, this may actually represent a fairly minor change. For instance, a person could achieve this score by moving from having no symptoms to minimal symptoms on three items, or by moving from no to moderate symptoms on one item, which would represent much more significant clinical change. Nonetheless, symptom change was observed and the CBD-THC interaction was observed under double blinded conditions and so remains an important result. The clinical implications of these findings are discussed in the final chapter.

4.3.4 Cannabis and Visual Illusions, What Does the Current Study Tell Us?

The present study indicates that neither THC nor CBD result in any reduction of bias on the Chubb Illusion. This is in contrast to the finding that THC reduces susceptibility to the Binocular Depth Inversion Illusion (BDII). Cannabis resin (Emrich et al., 1991), dronabinol[3] (Leweke et al., 1999) and nabilone[4] have been shown to decrease susceptibility to the BD-II and this decrease was attenuated when nabilone was administered with cannabidiol (Leweke et al., 2000). Furthermore, cannabis users have been shown to have reduced susceptibility to the BDII relative to matched controls (Semple et al., 2003). Also of interest is that sleep deprivation has been shown to result in a reduction of the illusion (Sternemann et al., 1997).

Although the BDII and the Chubb illusion share some conceptual similarities, especially in that they may be considered as examples of top-down processing, their underlying mechanisms are likely to be quite different. The Chubb illusion is primarily explained by mechanisms early in the visual system. Evidence for this comes both from early experiments by Chubb involving direct measurement of visual system cells in the cat, and from the observation that if the illusion is presented dichoptically (to different eyes) the illusion disappears (Chubb et al., 1989). This suggests that the mechanism of the illusion is primarily at a level before the information from both eyes is integrated (either pre-cortical or cortical), possibly in V1 of the human visual cortex. It has been suggested that surround interactions in V1 provide contextual priors that help disambiguate information based on the statistics of natural scenes. Higher areas (V2 and above) may also provide feedback contextual suppression, although the extent to which this happens is not clear (Seriès et al., 2003). Lotto and Purves's data (2001) suggests that higher levels may be involved in providing necessary feedback for interpretation of even these relatively basic stimuli. However, it is possible that their explanation overlooks the possibility that classical surround mechanisms in V1 may explain their data.

What is certain is that in the visual system, feedback mechanisms (which may specify priors) are more numerous than feed-forward mechanisms. Area V1 sends more projections back to the Lateral Geniculate Nucleus (LGN) than it receives from the LGN – and receives more connections from V2 than it sends upwards (Felleman & Van Essen, 1991). The brain thus invests a lot of biologically expensive wiring in these processes,

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[3] A pure isomer of THC

[4] A synthetic THC equivalent

supporting the idea that the 'heavy lifting' in perception is carried out by processes encoding contextual (or prior) knowledge. The literature is not clear on this point, but it is possible that the 'top-down', contextual processes in the Chubb illusion are entirely encoded in V1. Equally, it is possible that higher levels may be drawn upon. In keeping with the principles of evolution, Occam's razor and indeed Bayesian theory, it seems likely that the brain will use the least complex mechanism it can to process data at this level. At the same time, feedback projections would not be in place, unless they were necessary.

The BDII by contrast, depends on dichoptic presentation, indicating that it must involve higher level processing. Furthermore, the BDII is likely a more complex example of top-down processing. For instance, the illusion is stronger for more familiar objects, such as faces, than it is for unfamiliar objects (Hill & Johnston, 2007). Object recognition thus plays an important role in the illusion; this may indicate the influence of context (past experience) on perception of objects. This evidence fits with Bayesian interpretation of illusions as Bayes optimal perception. In this interpretation, the brain perceives the most likely interpretation of ambiguous data based on statistical probability, thus the BDII effect is stronger for familiar objects. The effect of familiarity makes it likely that the BDII involves processing in the ventral stream of the visual pathway and perhaps higher areas. The ventral stream (the "what pathway") is involved in identifying objects, while the dorsal stream (the "where pathway") is involved in spatial awareness (Milner & Goodale, 2006). In particular it is likely that the BDII, when using face stimuli will engage the fusiform face area. This area, which is part of the ventral stream, has been directly linked to processing of facial stimui, but has also been linked to recognition of other familiar stimuli (Gauthier et al., 2000). Another area which has been linked to the BDII is the hippocampus, which has been suggested as a comparator mechanism, involved in determining the ultimate conscious experience of the outer world (Gregory & Langton, 1966). This area is particularly dense in cannabinoid receptors (Abush & Akirav, 2010) and presents a possible location for the effect of THC on the BDII. Furthermore, in the hippocampus, cannabinoids act presynaptically to inhibit Ca2+-induced release of glutamate and acetylcholine, neurotransmitters that Corlett et al (Corlett et al., 2009) have argued are responsible for the specification of priors. Inhibition of these neurotransmitters may thus reduce the top-down input on the system, thus weakening the BDII illusion.

Given the above, is possible that THC affects visual perception at higher brain areas than V1 and thus alters performance on the BD-II but not on the Chubb illusion. However, significant further work would be necessary to confirm this hypothesis. Studies exploring the effect of THC on illusions similar to the Chubb illusion (such as the Ebbinghaus size illusion) would be a step in this direction. A battery of such illusions would help further characterise any effects of THC on visual perception.

4.3.5 Limitations

Use of PANSS scale. The PANSS scale is not designed for use in non-clinical populations. It was chosen for the current study based on its use in previous studies of cannabis compounds (Bhattacharyya et al., 2010; D'Souza et al., 2005). Further it was used for its comparability with clinical samples, as the research is interested in the similarities between psychiatric psychosis and drug induced psychotic symptoms.

Although the PANSS was sufficient to detect THC induced psychopathology and its reduction by CBD pre-treatment, other scales such as the CAPE (Stefanis et al., 2002), may be more sensitive to cannabis induced symptoms. This scale is a stable, reliable and valid measure of self reported dimensions of psychotic experiences in the general population, which captures both positive and negative symptoms (Konings et al., 2006). The 42-item scale is based on items from the PDI-21 (which is designed to measure symptom levels in the general population) with additional items to measure auditory hallucinations, negative symptoms and depressive symptoms. The scale has three main dimensions: positive, negative and depressive. A disadvantage of self-report measures such as the CAPE is that transient symptoms may not be clear to the person experiencing them, and clinician delivered tools might be more suitable in acute drug administration. However, to my knowledge, no study has compared available measures of psychosis symptoms with regards to their sensitivity to cannabis-induced change and thus choosing a particular scale is not straightforward. It may therefore be useful in future to design and test a scale to measure such symptoms. Further research investigating the subjective experience of cannabis use may be a good place to begin this process.

4.3.5.1 Environment, Dose and Administration

Testing took part in an old building, in a space that used to house an MRI scanner. The environment was somewhat run down, characterised by loose cabling and peeling paint. Beyond this, the environment was plain, with white walls, white Formica surfaces, plain

carpet and no decoration. A variety of equipment was in place, including a number of computers and EEG machines. How this compares to each individual's normal drug using environments is an open question, but it was certainly not akin to a comfortable living room. Although there is a lack of systematic research, informal reports of cannabis use fairly consistently report that initial mood and environment play a large part in the subjective experiences of using cannabis (Booth, 2005; Ludlow, 1857). Thus the effects of the THC and CBD in the current study may not be readily generalizable to the full range of situations in which cannabis may be used. Although there is a lack of evidence to support firm conclusions, it seems plausible that certain environments would be more likely to induce paranoia than others, for instance being around strangers is presumably more anxiogenic/pro-psychotic than being around friends.

The dose and administration methods used for CBD and THC were based on previous studies and chosen so as to provide reliable levels of the drugs and a measurable CBD-THC interaction effect. Intravenous THC was chosen instead of smoking, as smoking is a very unreliable method (differing lung capacities and smoking styles mean that it is impossible to ensure that all participants have the same dose). The three most typical methods of cannabis use are smoking, eating and drinking. In the UK currently, smoking is almost certainly the normal method (as a cigarette, although pipes and vaporisers are also used). Intravenous THC works on a similar time scale to smoking. However, with smoking, the user can regulate their dose according to their subjective experience, thus to some extent receiving the effect that they are looking for. In the present study, this was not possible and therefore individual's experiences may not have represented their typical experience of cannabis use. Equally, in normal use, THC and CBD are delivered simultaneously through the same method and thus the interaction may be different. Another issue here is the dose of CBD chosen, as there is limited evidence as to what a 'therapeutic' does might be. It is possible that higher doses, or doses administered over several days would have stronger 'protective effects'.

4.3.6 Conclusions.

The findings here indicate that neither THC nor CBD have significant effects on contextual visual processing as measured by the Chubb illusion. This indicates that the effects of cannabis on visual perception may have their mechanisms in higher brain areas.

Previous experimental and epidemiological studies have suggested that cannabis preparations low in CBD are more psychogenic than those with higher levels. The present findings, under controlled experimental conditions, provide support for this view.

5 Study Two: Visual Context Processing in Recent Onset Psychosis

5.1 Methods

Recruitment and data collection for this study was conducted in conjunction with another researcher, Dr Oliver Suendemann. Only those measures directly relevant to the current study will be described in full. Control participants were recruited as part of Study One and details can be found in the corresponding methods section. Methods below are therefore restricted to the clinical sample.

5.1.1 Ethical approval and Consent.

The study was approved by the local research ethics committee (South East London Research Ethics Committee, Ethics reference: 11/LO/0573). Individuals provided informed consent and were free to stop the study at any stage.

5.1.2 Study Design

The study was of cross-sectional, case-control design.

5.1.3 Procedure

The session consisted of three stages:

1. In the first stage, participants first read the study information sheet and, after all questions had been clarified with the investigator, provided written informed consent. Following this, participants were interviewed to assess both positive and negative symptoms of psychosis. Positive symptoms were assessed for both current state and retrospective recall of the most severe symptoms of psychosis, typically by identifying a most severe fortnight. Negative symptoms were only assessed for current state. Participants then completed the CES Depression measure.

   During this stage, participants were also interviewed using the time budget measure, completed the Social Support Scale and filled in visual analogue scales (VAS) assessing baseline loneliness, anxiety, distress, happiness, paranoia, and sadness. These measures are not directly relevant to this thesis and will be discussed elsewhere.

2. The second stage of the session consisted an experimental task in which participants were shown two sets of pictures (one with negative and one with neutral valance). Repeated visual analogue scales were used to assess the impact of these interventions. Presentation was randomised and counterbalanced, and a distractor task was completed in between (FAS verbal fluency task). Results of this experiment will be reported elsewhere.

3. In the third stage, participants first completed the Cardiff Anomalous Perception Scale (CAPS), they then completed the Chubb task. This was completed once by default. If time allowed, the task was repeated.

5.1.3.1 Participants and Recruitment

The clinical sample consisted of 38 individuals with a recent onset in psychosis. In line with other studies, "recent onset" was defined as illness onset within the last five years (e.g. Baldwin et al., 2005). Individuals were recruited from outpatient services and psychosis teams within the South London and Maudsley NHS Foundation Trust (SLaM). Of these participants, 29 were able to come to the Institute of Psychiatry for the full battery of tests.

This study collaborated with Dr. Craig Morgan's psychosis research team who at the start of this project was running a large multi-centred trial attempting to recruit all first onset psychosis clients who presented within any of the SLAM services. The aim of this collaboration was twofold, namely: (1) facilitating recruitment and (2) reduce unnecessary duplication of data collection and participant fatigue (3) sharing some of the data.

- Patients who had completed Dr. Morgan's study were asked whether they would be interested in taking part in some further research. If participants expressed an interest and provided consent, Dr. Morgan's team passed on their contact details to the author of this study who made arrangements to contact the participant. Participants were initially contacted by telephone and provided with details about the study. They were subsequently sent written information in the post or by electronic mail. Participants were then either booked in for an appointment or in case they required more information or contacted again one week later. sent the information sheet via email/mail and contacted.
- In order to avoid over-fatiguing and over-researching of clients by asking the same questions multiple times, some of the relevant client information that had

already been collected was provided by Dr. Morgan's team (demographic information).

5.1.3.2 Eligibility Criteria

Inclusion criteria were:

- Recent episode of psychosis (within 5 years)
- Age 18-65
- Sufficient comprehension of English
- Absence of history of brain injury, known organic cause of psychosis or primary diagnosis of drug or alcohol dependency.

5.1.4 Materials and Measures

5.1.4.1 Assessment of Symptoms

Psychosis symptoms and functioning were assessed using the following measures:

- **Scale for the Assessment of Positive Symptoms (SAPS).**
  The SAPS is a widely used semi-structured interview for assessment of positive psychosis symptoms (Andreasen & Olsen, 1982)**.** The scale consists of 35 items and is divided into four subscales: hallucinations, delusions, bizarre behaviour, and formal thought disorder. Items are rated on 6-point scale from 0 (no abnormality) to 5 (severe). The SAPS was carried out twice. First with regards to the patient's worst episode and second with regards to current positive symptoms. Total scores were calculated as sums of the symptom cluster subscores.

- **Scale for the Assessment of Negative Symptoms SANS.**
  The SANS a widely used semi-structured interview to assess negative symptoms of psychosis in the past month (Andreasen & Olsen, 1982). It consists of 25 items which are divided into 5 subscales: affective flattening or blunting, alogia, apathy, asociality, and inattention. Items are rated on a 6-point scale from 0 (no abnormality) to 5 (severe). The SANS was carried out with regards to current symptoms. Total scores were calculated as sums of the symptom cluster subscores.

- **Center for Epidemiologic Studies Depression Scale (CES-D).**
  The *CES-D* is a widely used 20-item self-report questionnaire to measure depressive symptomatology in adults (Radloff, 1977).

5.1.4.2 Medication

Current medication was recorded for all participants. Where participants were taking antipsychotic drugs, the Defined Daily Dose (DDD) was used to calculate an equivalency. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDD data for antipsychotics is available from the World Health Organisation (Word Health Organisation, 2012), thus for each participant, it is possible to calculate an antipsychotic equivalence variable as follows:

$$Equivalence = \frac{(Participant\ Daily\ Dose)}{DDD} * 100$$

5.1.5 Chubb Illusion Task.

The Chubb Illusion Task is a modified version of that used by Dakin, Carlin and Hemsley (Dakin et al., 2005). Full details of the task can be found in the methods for Study 1.

5.2 Data Analysis:

All analyses were performed in SPSS 19.0 (SPSS inc., Chicago). Data were assessed for normality using Kolmogorov-Smirnov test statistics. Baseline group differences were assessed using Pearson's Chi-square and independent t-tests, for categorical and ratio data respectively.

Normally distributed data were analysed using Student's T-Test.

Relationships between psychosis scores and bias/cognitive data were analysed with Spearman's rank correlation coefficient. This was chosen to account for the possible distorting effect of outlier data. Significance was accepted at $p<0.05$, all comparisons were two tailed.

5.3 Results

5.3.1 Participants

29 participants from the clinical group completed test battery. Of these, one participant was excluded for clearly incorrect responses. This participant appeared to give opposite responses for high contrast target patches, even after the task had been explained several times.

45 control participants were available from Study One.

5.3.1.1 Identification of Outliers.

The first step in the analysis was to identify possible outliers (as detailed in the methods of Study 1) on the basis of performance on the Chubb task, either with respect to bias or threshold. One participant, from the clinical group, was identified as representing outlier data. The final dataset thus included 45 control participants and 27 clinical participants.

5.3.2 Demographics and Symptom Scores

Demographics and symptom scores are shown in

Table 5.1. Ethnicity and education data were collapsed into binary outcomes (White European/other and non-university/university respectively in order to facilitate statistical analysis).

Clinical and control groups were matched for gender but were significantly different for ethnicity and education. The clinical group has significantly a lower proportion of participants reaching university education and significantly more participants of non-White-European background. The control group was also significantly younger than the clinical group (25.6 vs 32 years).

Duration of untreated psychosis (DUP) ranged from 0 to 2652 weeks, with a mean of 208 and a median of 6 weeks. The highest DUPs may be explained by a late onset, combined with early experience of subclinical symptoms.

5.3.2.1 Psychosis Symptoms

For symptoms of psychosis, group could not be directly compared as they were assessed using different scales. However, control participants did not have any positive symptoms as assessed by the PANSS. For PANSS negative symptoms, 42 of 45 participants were without symptoms. 3 participants had mild negative symptoms.

For clinical participants, scores for current state were generally low. 16 of 27 participants had no positive symptoms (SAPS), while 6 of 27 had no negative symptoms (SANS). Mean scores were 2.6 and 4.8 respectively.

5.3.2.2 Anomalous Experiences

Scores on the CAPS measure of anomalous experiences were not normally distributed, thus data was analysed using Mann Whitney. Clinical participants had significantly greater scores on CAPS total score than control participants ($p=0.000$). These differences were also significant for distress, distraction and frequency of experience subscales (all $p<0.000$).

5.3.3 Hypothesis 1: Reduced Bias in First Episode Psychosis

1st Episode Patients will show a reduced influence of context, indicated by reduced bias on the Chubb illusion.

Bias data were normally distributed in both groups according to Kolmogorov-Smirnov test. Group differences were tested with an independent groups T-test. There was no significant difference between case and control group for bias. However, there was a trend level difference between groups, with bias being greater in the control than in the case group (p=0.089, mean difference 4.1, 95% CI of difference: -0.6 – 8.8).

Model fitting of individual subject data provides a 95% estimate of confidence in the bias estimate (bias-range). This may be considered as a proxy measure of participant response accuracy. A further analysis was thus conducted to analyse whether bias-range was different between groups. Bias-range was significantly greater in the case than control groups (p=0.008).

Controlling for bias-range using univarate GLM with bias as dependent variable, group as fixed factor and bias-range as a covariate resulted in the group difference becoming significant (p=0.023). This result should be treated with caution as controlling for variables on which groups differ significantly and non-randomly risks issues of co-linearity.

5.3.3.1 Conclusion

Although a significant difference was not demonstrated between groups, there was evidence of a difference in the expected direction at trend level. The effect size (Cohen's d, pooled s.d.) was 0.4. Thus there was limited evidence to support hypothesis one.

Table 5.1 Demographics

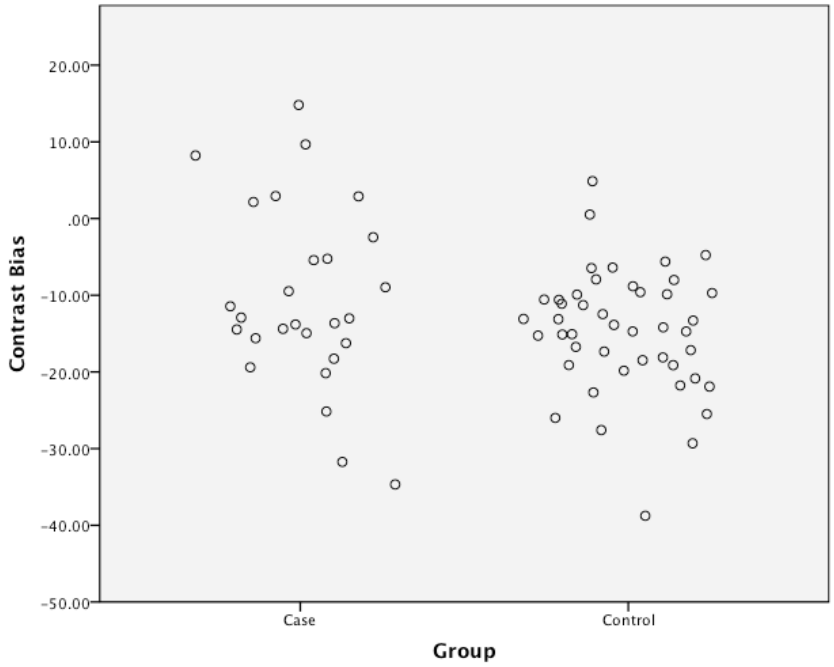
	Control			Psychosis			p
Demographics							
N	45			27			-
Sex (m:f)	26:19			15:12			ns
Ethnicity (White European/other)	37:8			13:14			0.002
Education (Non-university, University)	7:38			16:10			0.000
	mean	med	s.d.	mean	med	sd	
Age	25.6	25	4.13	32	30	8	0.001
DUP (weeks)*	-	-	-	165	4	531	-
Symptom Scores							
CAPS (total)	2.0	1	2.6	9.7	8.5	7.6	0.000
Distress	3.6	2	5.5	25.2	22	23.7	-
Distraction	4.2	2	6.3	21.6	20.5	14.4	-
Frequency	2.9	1	7.9	17.1	17	11.2	-
SAPS Current				2.6	0	4.4	-
Episode				9.1	10	4.1	-
SANS Current				4.8	4	4.7	-
PANSS Positive	7	7	0	-	-	-	-
PANSS Negative	7.18	7	.576	-	-	-	-

*Duration of Untreated Psychosis (First symptoms to first formal psychiatric contact)

Table 5.2 Bias by Group

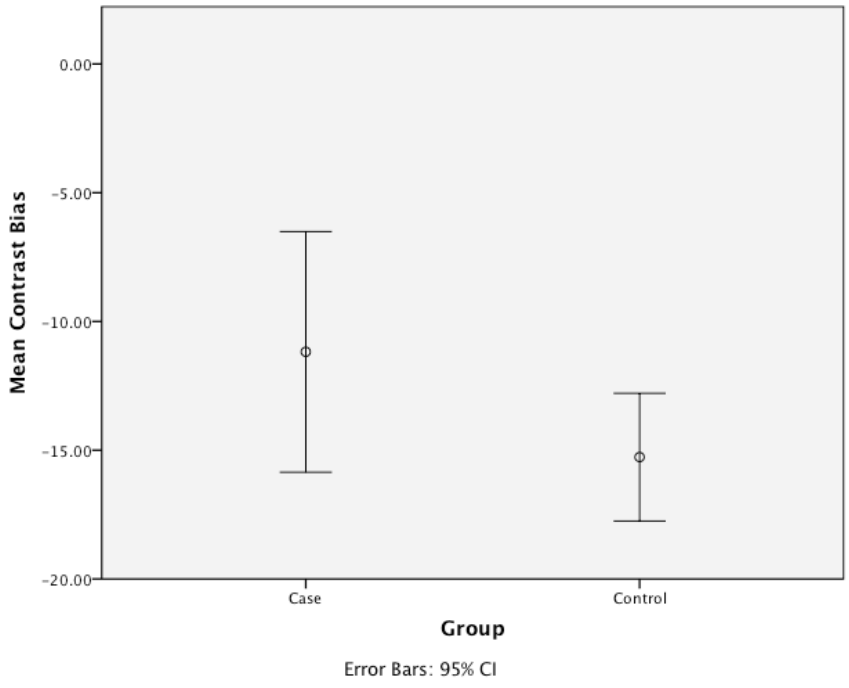
	Control			Psychosis			Sig	d
	mean	med	sd	mean	med	sd		
Chubb								
Bias	-15.3	-14.2	8.3	-11.2	-12.9	11.8	0.089	0.40
Threshold	11.8	11.2	3	12.9	11.6	4.1	-	
Bias Range	7.3	6.3	2.6	9.8	8.9	4.2	0.008	0.46

Figure 5.1. Bias Data By Group. Scatter Plot



(Data jittered for clarity)

Figure 5.2 Bias Data By Group, Means and 95% CI.



5.3.5 Hypothesis 2: Correlations Between Bias, Symptoms and Demographics

Bias on the Chubb illusion will be negatively correlated with:

a) Negative symptoms as measured by the SANS
b) Positive symptoms as measured by the SAPS

Due to the number of tests, correlations were only reported if they were significant at $p<0.05$.

5.3.5.1 Correlations with Bias

Symptoms

In the clinical group, there were no significant correlations between bias and SAPS (current or worst episode) or SANS scores. There were also no significant correlations between bias and CAPS scores. Symptom correlations for the control group have already been reported in Study One.

Demographics

As groups differed on age, ethnicity and education variables, relationships between these variables and bias were investigated. No significant correlations were identified.

Medication

There was no significant correlation between participant's dose of antipsychotic (calculated as percentage of Daily Dose Equivalence) and bias.

5.3.5.2 Post Hoc: Correlations with Bias-Range

Model fitting of individual subject data provides a 95% estimate of confidence in the bias estimate (bias-range). This may be considered as a proxy measure of participant response accuracy. It was therefore of interest to know if symptom scores might affect bias range. Correlations were thus run between bias range and SAPS and SANS scores.

In the patient group, there was a significant correlation between bias range and SANS scores (Pearson: $r=0.496$, $p=0.009$). The was no significant relationship between bias-range and SAPS (rho=.349, $p=0.075$).

5.3.5.3 Correlations

Given this relationship between bias-range and symptom scores, further analyses were run investigating the relationship between bias-range and CAPS scores. Correlations were run separately for each group and were not significant.

5.3.5.4 Conclusion

There was no support for a relationship between bias and symptoms, as measured by the SAPS, SANS and CAPS. There was however an unpredicted relationship between negative symptoms and a measure of confidence in the bias estimate.

Figure 5.3. Correlation between Bias Range and SANS scores.

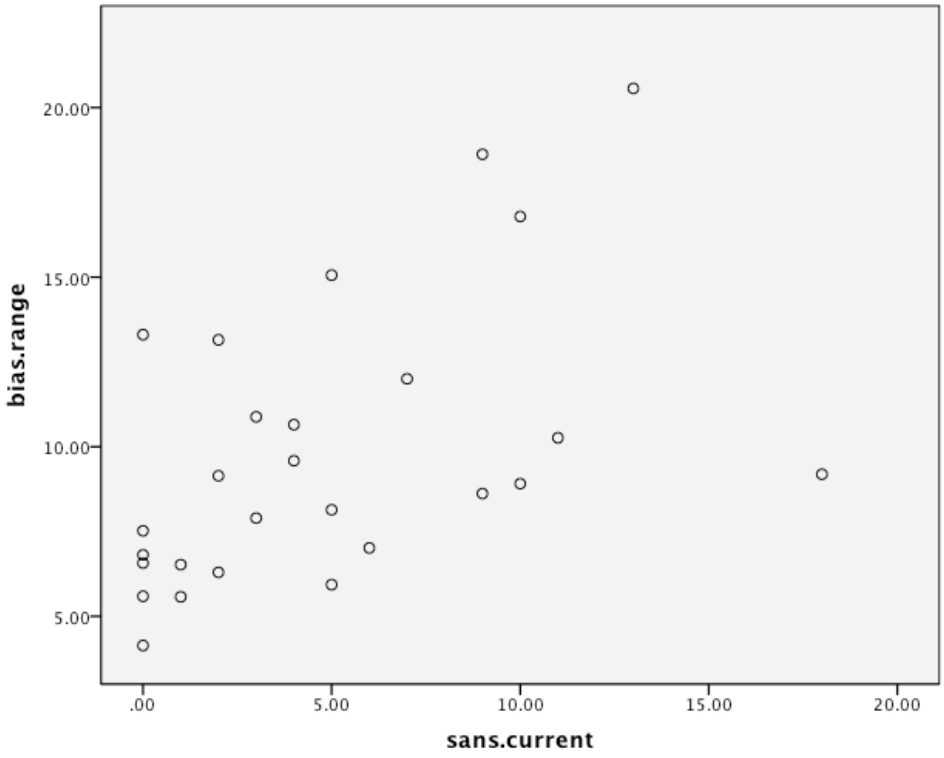
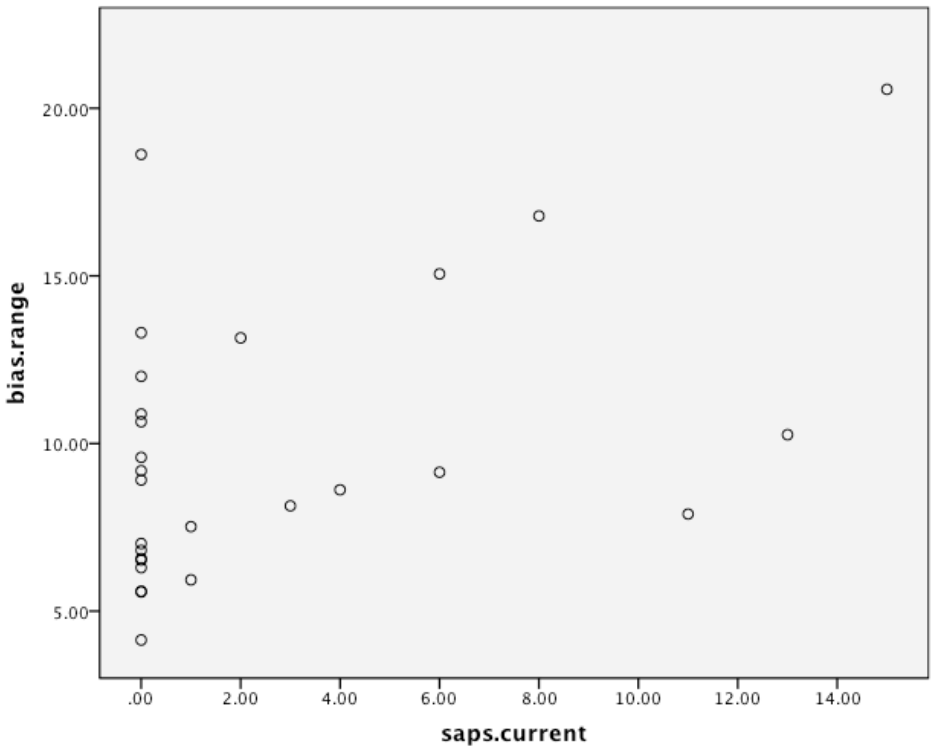


Figure 5.4. Correlation between Bias Range and SAPS (current)



5.4 Discussion

(Issues common to both Study One and Study Two will be discussed in the final chapter of the thesis. Thus discussion here will be limited to issues specific to Study Two.)

Previous studies have reported that psychosis is associated with differences in contextual visual processing – specifically reduced levels of suppression. These differences have been found in the Chubb illusion and analogues of the Chubb illusion (Barch et al., 2012; Dakin et al., 2005; Tadin et al., 2006; Tibber et al., In Preperation; Uhlhaas et al., 2004; Yoon et al., 2009, 2010). None of these studies however, looked at whether such differences were present early in the development of psychosis. This study thus set out to expand on these findings by investigating whether such differences were present in recent onset psychosis.

The study found limited evidence to support the idea that differences in visual context processing are present even in recent onset psychosis. Although the main finding of the study, that contextual visual suppression (as measured by bias) was reduced in people with recent onset psychosis, was not statistically significant at $p<0.05$, it was consistent with previous findings. The study did not however find any evidence of predicted associations between symptom measures and bias.

5.5 Interpretation

The data are consistent with an association between reduced levels of suppression and thus abnormal cortical gain in psychosis. Although the results are not statistically strong, they indicate that the reduced suppression effects seen in psychosis may be present from onset if not before. Reduced suppression may therefore represent a vulnerability factor for the development of psychosis. The pattern of data in the literature indicates that these suppression effects may be stronger in people with a longer duration of psychotic disorder (effect sizes appear greatest in the chronic forensic sample of Dakin, with other studies of less chronic samples showing smaller effect sizes (Barch et al., 2012; Tibber et al., In Preperation). However, the data is insufficient to view this as more than speculation at this point. Further replications, and preferably longitudinal studies would be necessary to draw stronger conclusions.

Virtually all neurotransmitter systems have been in some way linked to psychotic experience. Of these dopamine is perhaps the most prominent (Howes & Kapur, 2009), with glutamate also increasingly studied (Javitt, 2010). However, as Tibber et al (In Preperation) argues, another neurotransmitter that has been linked to psychosis (Javitt,

2010), GABA, may be particularly relevant to visual suppression. GABA has been linked to reduced surround suppression in schizophrenia(Yoon et al., 2010) and GABA also mediates inhibition in a number of other tasks reported to be affected in psychosis, such as contour integration (Silverstein et al., 2000, 2006), and orientation discrimination (Edden et al., 2009). Thus, it is possible that GABA neurotransmission abnormalities may underlie the altered surround suppression effects seen in psychosis. It is however, not clear how such putative visual system neurotransmitter differences might relate to the more general psychopathology in psychosis. Certainly, benzodiazepines, which enhance GABAergic activity, have no clear utility as an antipsychotic agent (Volz et al., 2007). If GABA deficits are related to visual dysfunction in psychosis, it is virtually certain that interactions with other neurotransmitter systems will be involved.

The clinical implications of these findings are discussed in the final chapter.

5.5.1 Limitations

The study had a number of important limitations, which are discussed below.

5.5.1.1 Group Selection

This study adopted a pragmatic approach, using available data from Study One, combined with new data from an on-going study of participants with recent onset psychosis. A number of issues arise from this approach. Perhaps the most important of these issues is that the groups were poorly matched, the control group having significantly higher levels of education and being predominantly white European (whereas the case group were of mixed ethnicity, with an equal mixture of white European and other ethnicities). However, none of these demographic variables were correlated with the outcome measure, and as such, the poor matching of groups is of limited concern. A secondary difficulty with this approach was that the symptoms measures chosen in each case were not directly comparable (PANSS in the control group and SAPS/SANS in the case group). Although this was not ideal, the control group were essentially asymptomatic as measured on the PANSS and it is likely that they would not have scored significantly on the SAPS/SANS.

Finally, the control group were somewhat unusual, in that they all had experience of cannabis use (although they were not classified as dependent). Although Study One did not demonstrate any clear effect of THC or CBD on bias scores, it is possible that chronic, rather than acute use of cannabis might affect bias. Chronic cannabis smokers have been shown to exhibit reduced susceptibility to the BDII (Semple et al., 2003), thus it is possible the control group may not be representative of the general population with regard

to their performance on the Chubb Illusion. If a history of cannabis use also reduced susceptibility to the Chubb effect, this would reduce the power of the present study to detect a group difference. Arguing against this possibility however is the fact that in the control group there was no relationship between lifetime use of cannabis and bias.

Further, given that cannabis use is considered a risk factor for the development of psychosis (Murray et al., 2007), and that cannabis use is common in people ages 16-40 (with a lifetime prevalence of between 30-50% according to the British Crime Survey (Roe, 2005)), a control group with no experience of cannabis would likely be equally unmatched. Unfortunately cannabis use data was not available for the clinical group and so a group comparison of cannabis use was not possible.

5.5.1.2 Medication

The majority of the clinical group were taking antipsychotic medication. It is possible that medication may affect surround-suppression. However, there was no significant correlation between percentage of Defined Daily Dose and bias. This indicates that medication was unlikely to be responsible for the between group difference in surround-suppression effects. This conclusion is supported by data from Dakin et al (2005), in which reduced suppression was not seen in a group of patients with a diagnosis of bipolar disorder, several of whom were taking antipsychotics. Finally, Tibber (In Preperation) found that while contrast surround-suppression was reduced in patients with schizophrenia, a matched analogous task (luminance surround-suppression) was robust to diagnosis.

5.5.1.3 Other Cognitive Confounds

General cognitive, attentional or motivational factors that differ between groups may represent confounds in the present study. This is discussed in more detail in the next chapter.

5.5.2 Summary

In summary, the data from this study provide further support for a reduction of surround suppression in psychosis. Furthermore, they demonstrate that this reduction may be present even in people with recent onset of psychosis. However, the evidence from this study is relatively weak and replication with larger samples will be necessary in order to draw stronger conclusions.

6 Overall Discussion and Conclusions

This thesis aimed to extend research into context processing, hypothesised to be the basic cognitive difference in psychosis, by examining the performance of non-clinical controls who had completed measures of psychotic symptoms and a first episode psychosis group on a visual context processing task; and to further investigate context processing as a candidate mechanism linking psychosis and cannabis use, by comparing the effects of two consituents of cannabis on the same task. Specifically, it has investigated: A. The effect on of cannabinoids on suppression of visual context and B. The relationship between recent onset psychosis and suppression of visual context. In both cases, the Chubb Illusion was used as a measure of suppression of visual context.

In Study One, it was predicted that THC, an important component of cannabis, would reduce context based visual suppression (bias) and that this reduction would be attenuated by pre-treatment with CBD, another key component of cannabis. It was also predicted that THC would induce transient psychotic symptoms, and that this induction would be attenuated by pre-treatment with THC. No evidence was found to support the first prediction of an effect on bias, while the second prediction was supported by the data.

In Study Two it was predicted that a clinical group consisting of participants who had experienced a recent onset of psychosis would show a reduction in context based visual suppression (bias) relative to a control group. Although not statistically significant, the results of the study supported this prediction, with the clinical group showing reduced bias relative to the control group. In both studies, it was predicted that bias would be correlated with symptom scores. No evidence was found to support this prediction.

Issues specific to the individual studies have been discussed previously. I shall now consider a number of issues common to both studies as well, before considering the clinical implications of the findings.

6.1.1 Relationships Between Bias and Symptom Scores

Conceptually, one might expect that altered visual context processing, which may be considered non-optimal in an adaptive sense, would predispose an individual to anomalous visual experiences. If this processing difference was not limited to the visual domain, but representative of a general context processing difference, one might expect anomalous experiences in other domains. At the same time, reduced contextual suppression, as demonstrated by a reduction in Chubb bias, has been interpreted as

reflecting an overall reduction in top-down processing in psychosis. According to the models of Hemsley (Hemsley, 2005b) and Corlett (Corlett et al., 2009), such reductions in top-down processing are predicted to result in increased relative influence of bottom-up signalling, leading to anomalous experiences and thus increasing the likelihood of delusion formation. Put another way, the brain normally engages top-down processes as a way of using past experience to make sense of the present. A reduction in the use of such contextual knowledge makes it more likely that novel, but unlikely explanations of experience will be formed (delusions).

Based on the above, if altered perceptual processing was indeed a vulnerability factor for psychosis, it might be expected that there would be a correlation between measures of this process and symptom scores. It was therefore predicted that bias (as measured by the Chubb illusion) would be correlated with symptom scores, in particular anomalous experiences (as measured by the CAPS), and also positive and negative symptoms (as measured by the PANSS, SAPS and SANS) and paranoid ideation (as measured by the GPTS). However, neither study in this thesis found any evidence of a relationship between bias and symptoms measures.

Clearly, there are two possible general interpretations of these results: (1) that no such relationships exist and (2) that such relationships exist, but that the current study was unable to confirm them. With regard to the first possibility, it could be that differences in visual context processing are associated with psychosis but not with symptom scores. Such differences could predispose a person to psychotic experience generally, but not predict symptom levels. Alternatively, it could be, as has been suggested by others, that the reported difference on the Chubb illusion are an artefact of another aspect of psychosis, in particular inattention (discussed below).

With regard to the second possibility, it is possible that a lack of sensitively of the scales used meant that there was not enough variability to detect a significant relationship. Certainly, in Study One, there was negligible variance in PANSS scores at baseline (this floor effect was not surprising given the non-clinical sample). In Study Two, the clinical participants were generally quite well, with many being asymptomatic on SAPS scores (just 16 of the 27 participants had any current symptoms). Partly this is to do with the sampling method, as participants who were currently too unwell to come to the testing lab could not be assessed on the Chubb task. The study may therefore have been underpowered to detect significant relationships. This lack of variability and relatively

small sample size also precluded more fine-grained, and potentially more informative analyses looking at individual symptoms.

Given the above, it is interesting to note that in the clinical sample, bias-range (a measure of confidence in the bias estimate, used here as a proxy measure of response accuracy) was significantly correlated with both negative and positive symptom scores. This would indicate that although bias was not systematically influenced by symptom levels, participants' response accuracy was affected. This is perhaps not surprising as the presence of positive symptoms may reduce a person's cognitive capacity available to concentrate on a task, while negative symptoms may result in a lack of motivation or energy to concentrate on a task. This is perhaps particularly relevant to the Chubb task as unfortunately many participants find the Chubb paradigm used here to be somewhat tedious.

6.1.1.1 The Chubb Task: Some Behavioural Observations and Suggestions.

In both studies, a number of participants reported finding the Chubb task tedious and in a few cases quite aversive (although a few participants also reported enjoying it). I propose that a number of factors contribute to this response. For the participant, the task is repetitive and lacks a obvious purpose, performance feedback and reward. The participant must complete 64 trials, all of which are essentially the same and is never told if their response is correct or incorrect (given that a veridical response is not 'normal', it not meaningful to talk of correct responses). It is possible that this ambiguity is part of what makes the task aversive for some people. Evidence from Freeman et al (2006). suggests that this may be especially true of people with psychosis. Indeed, while some participants responded quickly on each trial, others appeared to find it much more difficult to commit to a decision (response latency was not recorded). Such participants were given prompts such as to 'go with their hunch', yet often still struggled. An obvious consequence of such an approach is that the task takes significantly longer, which may compound a participant's frustration. Other participants found it difficult to focus on the computer monitor for the full duration of the testing. Although many scientific tasks are less than enjoyable, in future it may be worth trying to develop more user-friendly tasks that measure similar constructs. Apart from making tasks less aversive, such an approach could lessen the attentional confounds that are a common problem in psychological assessment.

In designing such tasks, researchers could follow the example of computer games. Like the Chubb task, many computer games can be repetitive, yet are better tolerated (or even enjoyed!). Perhaps the key difference between the Chubb task and simple, repetitive games such as the classic Pong (a very basic tennis game) is that Pong provides feedback (there are points, sounds and visual feedback) on performance, which also removes ambiguity and provides reward. Although providing contingent feedback may not always be appropriate, making tasks more interesting by providing goals, breaks, non-contingent feedback or varying the point of fixation might all help. One clear example of a task that draws on the computer game industry is Daniel Freeman's virtual reality assessment of tendency to paranoia (Freeman et al., 2005); this provides an interesting, immersive environment, and indeed is currently being used to investigate the effects of cannabis use (personal communication).

An alternative, and much simpler solution, is not to obtain a full psychometric response function (the relationship between varying stimulus and an individual's response), but to simply obtain an estimate of bias alone. This could be done in a simple matching task. Here the participant would be shown both target and reference patches simultaneously. The participant would simply have to change (with a slider) the contrast of the target patch, so that it matched that of the reference patch. Running this several times while varying the contrast of the reference patch would provide an average estimate of bias. Although this matching approach is less rigorous, and potentially subject to experimenter bias, it is an order of magnitude faster and thus perhaps appropriate for incorporating into larger test batteries.

6.1.2 The Problem of Attention

It has been argued that psychosis is accompanied by a general cognitive disturbance may be responsible for many of the more specific findings of cognitive differences in psychosis. An early candidate for such a disturbance was selective attention (McGhie & Chapman, 1961). The more veridical performance of patients with psychosis in the Chubb task is a compelling finding in that it represents objectively (but not adaptively) better performance in psychosis, something rarely reported in the literature. Nevertheless, Barch et al (2012) have argued that impaired attentional mechanisms may account for the patient-control differences in bias on the Chubb illusion in their own study. They measured attention by incorporating a number of 'catch trials' in which there was a very

high contrast target stimulus, for which the correct response was clear. It is possible that the same applies in this study; however unlike Barch et al, the paradigm used here does not have the necessary catch trials to analyse the data in this way. A potential problem with the approach of Barch et al is that the two groups differed in their performance on catch trials. One might presume (although the authors do not provide details) that those participants with greater psychiatric impairment would also have poorer attention. Thus Barch et al face a problem of collinearity, in that either removing those participants with attention impairment, or covarying for attentional performance (both approaches were used), may remove a real group difference from the study (see Miller & Chapman, 2001).

Previously it was not thought that attention would have any systematic effect on measures of bias. There is no clear mechanism by which this would occur. Although if all responses were random (all noise, no data), bias would become zero, if random responses were added into a normal response pattern, it should have a random and thus unbiasing effect on bias (the noise should not systematically change the data). In the control sample there was unexpectedly a significant negative relationship between bias and bias-range indicating that at least in this proxy measure, as accuracy increased, estimates of bias decreased. This is the opposite of what would be expected if accuracy systematically affected bias estimates. There was no significant relationship between bias and bias-range in the clinical sample, which may perhaps cast doubt on the relationship found in the control sample. One way to clarify this issue would be to run a simulation study, discussed later.

Finally, Tibber et al (in preparation, discussed in more detail in the introduction), have shown patient-control difference in bias in the Chubb illusion, but not in a luminance-contrast analogue, further indicating that reduced bias is not an artefact of attention, but represents a real difference in psychosis.

6.2 Clinical Implications

6.2.1 Cannabis

The results of Study One are consistent with previous experimental and epidemiological studies that suggest that cannabis may induce symptoms of psychosis. Of course, the development of transient psychotic symptoms is not in itself a matter of serious concern. However, considered together with evidence that cannabis use is associated with increased risk of developing a chronic psychotic disorder, these findings may play a role in informing public health policy. What role they should play is however, unclear. The relative harms of cannabis, and indeed other illegal drugs have been compared to both legal drugs such as alcohol and tobacco, as well as to other recreational pursuits (perhaps most famously Professor David Nutt's comments comparing the dangers of horse riding to those of ecstasy). Additionally the relative costs and benefits of prohibition and legalisation policies are controversial.

Perhaps of more significance is the finding that CBD and THC play very different roles in the effects of cannabis. This finding joins a growing body of evidence that suggests that treating 'cannabis' as if it were one homogenous substance is an approach that fails to consider complexity and variability of the substance. Cannabis plants can vary significantly in their proportion of THC, CBD and other cannabinoids. Thus from a public health perspective, treating all cannabis alike is akin to considering vintage Bordeaux and Moonshine as the same substance. Although it has long been known that cannabis consists of many active compounds, only recently has significant effort gone into characterising their various effects and mechanisms. The present study addresses just two of these components, Δ9-THC and cannabidiol and provides clear support to the notion that not only do these components have different effects, but also that cannabidiol moderates the effect of Δ9-THC.

Clinically, some cannabis using clients with psychosis report both positive and negative effects of cannabis. There may be a tendency for concerned clinicians, in their attempts to dissuade clients from using cannabis, to dismiss the positive effects and focus on the negative effects. There are two clear problems with this. The first is a problem of engagement and motivation; such approaches tend to leave the client feeling like they are not being listened to and indeed may result in the client taking a defensive posture that entrenches their position on cannabis. A strong denial of a substance's positive aspects may also lead to a loss of the clinician's credibility in the client's eyes. Thus, the client

and clinician enter into an adversarial debate rather than a Socratic process of learning from each other. Motivational Interviewing approaches (Rollnick & Miller, 1995), which have been shown to be important in working with substance use require that among other things, in trying to help a client, the clinician must first try to understand the client's frame of reference - and this means understanding their subjective experience.

The second problem is that the 'cannabis is bad for you' approach ignores not only the subjective experience but also complex nature of cannabis itself. The same cannabis preparation may have different effects in different people, and may also have multiple effects in the same person. Thus, it is quite conceivable that smoking a joint may lead to concurrent anxiolytic, anti-psychotic and pro-psychotic effects. The pharmacokinetics and pharmacodynamics of cannabis compounds are complex and varied, thus these effects may operate over different time-scales. These effects may also present differently depending on the environment and the person's pre-drug presentation.

The finding that CBD reduces the pro-psychotic effects of THC leads also to the intriguing idea that 'cannabis' may be useful as an anti-psychotic. Cannabis itself has long been used as a medicinal drug; indeed in the 19th century it was a widely prescribed in the UK and elsewhere as a tonic for a wide variety of presentations. In other regions of the world, especially in the Middle and Far East, it has a long history as a medical and spiritual aid. In India, cannabis was used as a tranquiliser in the treatment of anxiety, mania and hysteria over 3000 years ago (Crippa et al., 2010). The twentieth century led to a demonization and prohibition of cannabis that meant that doctors were forced to abandon it as a medical aid (Booth, 2005). In common with other traditional treatments, belief in many of cannabis' uses may prove to be unfounded. Nevertheless, cannabis as a medicine is in the midst of something of a renaissance and is a now an important therapeutic drug for many with multiple sclerosis (Zajicek & Apostu, 2011).

A recent review by Crippa et al (Crippa et al., 2010) details a wide range of investigations into the potential psychiatric effects of CBD and report that its anxiolytic effects are now well established. In terms of its use as an antipsychotic, a number of studies are of particular interest. Trials in humans began in 1995 with a case report of a 19 year old who had experienced severe side effects in response to antipsychotic medication (Zuardi et al., 1995). CBD reduced psychotic symptoms as well as did haloperidol and did so without side effects. This was followed by a treatment trial of three patients with a diagnosis of treatment resistant schizophrenia (Zuardi et al., 2006); of these two had a

mild improvement with CBD. However, clearly, given their diagnosis, the prognosis for a strong response was poor. More recently Leweke at al (2012) published the results of a randomised controlled trial comparing the effects of CBD and amisulpiride. They found that both treatments led to a comparable clinical improvement, but that CBD had a better side-effect profile. This is quite a remarkable result, and indeed may pave the way for cheaper, and less aversive treatments for psychosis. One might also imagine that many clients would be rather more accepting of a 'natural', cannabis-based drug than of existing antipsychotics. Finally, to muddy the waters a little, it has been reported that in clients who report that cannabis reduces their psychotic symptoms, treatment with synthetic THC (dronabinol) has been shown to do exactly that (Schwarcz et al., 2009). Thus when a client says that cannabis helps their symptoms, we should listen.

6.2.2 Reduced Contextual Processing in Psychosis

The study provides further evidence of an association between psychosis and reduced surround suppression in psychosis. Assuming that this may be considered as evidence of reduced influence of contextual/top-down processing in psychosis, what might the clinical implications be?

Let us first reconsider the possible effects of reduced top-down processing, before moving on to the clinical implications. As has already been discussed in detail in the introduction, top-down processing is the mechanism whereby contextual information guides stimulus-response functions. To put it another way, the influence of top-down processing is why we jump at a loud crash when we are alone in a house, but not when we know someone else (or the cat) is in. If we are alone, having jumped, we may worry about who has just broken into the house. Or even if we are not alone, but have previously experienced a traumatic break-in, we may fear for our lives (the image we form in our mind is a prediction). Our prior experiences, evolution and our knowledge of our present circumstances all affect how we process new stimuli.

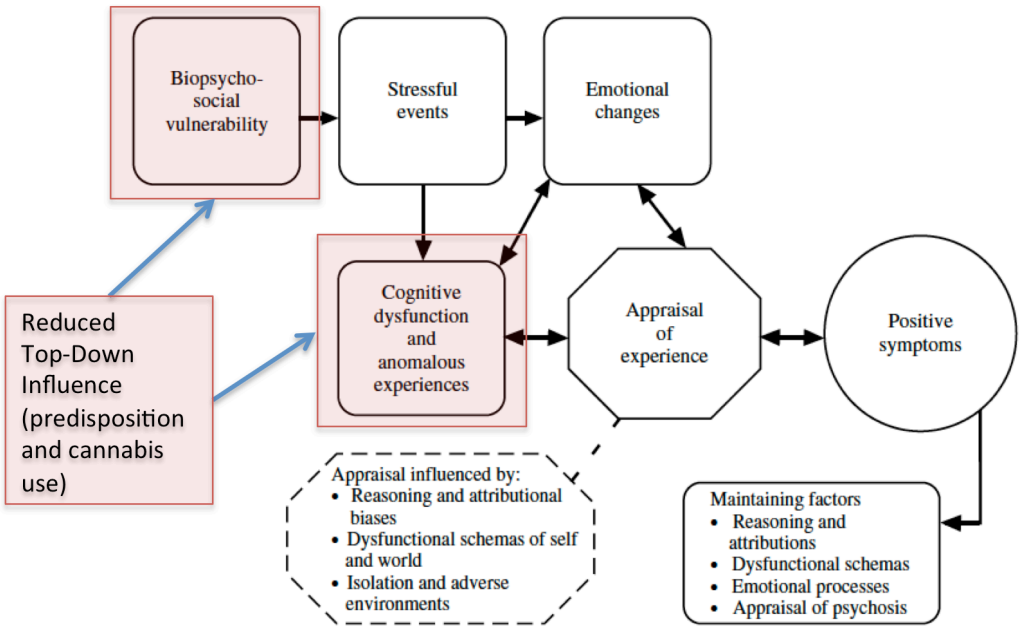
A reduction in top-down processing will theoretically increase the relative influence of bottom-up signalling (the loud crash becomes more important). Such a change may also reduce our confidence in our prior beliefs, allowing other belief to form more easily. Drawing on the cannabis literature, the effects of putative reduced top-down processing clearly include changed to the salience of internal and external stimuli. Sounds and colours may appear louder and more vivid, previously meaningless patterns become meaningful, and sensations of touch taste and smell are altered and so on (Tart, 1970). As noted before, there are clear similarities between drug use experiences and those of psychosis. Patients with psychosis, even those who don't use cannabis, report very similar experiences. Although there may also be both qualitative and quantitative difference in the experience one clear difference is the person's belief about the experiences. The cannabis user generally knows why they are having unusual experience and also knows that the experiences will stop. The patient, by contrast, may have no explanation for their experiences and has no idea of when they will recede; the patient thus needs to try and explain their experiences. In Bayesian terms, the patient needs to minimise the disparity between their experiences and their predictions (prior beliefs). Carl Sagan has said that "extraordinary claims require extraordinary evidence"; the patient may have extraordinary evidence, they just need to invent the extraordinary claim. As discussed earlier, cannabis can also cause paranoia; perhaps (and this fits with the

anecdotal literature) this also happens primarily when the user fails to see the connection between their drug use and their experiences. There is now considerable evidence to suggest that the unusual experiences are not in themselves pathological, and that a person's beliefs about their experiences mediate their distress (Perez-Alvarez et al., 2008).

Cognitive models of psychosis invoke the idea of 'confirmation bias' and argue that following the development of delusional ideas, an individual may actively seek out evidence to support their ideas (Cameron, 1951; Woodward et al., 2006). A bias against non-confirmatory evidence has also been reported to be associated with psychosis proneness in non-clinical samples (Woodward et al., 2007). Thus once beliefs have formed, they may contain mechanisms to maintain themselves. Indeed, at the risk of tautological argument, beliefs that persist must contain such mechanisms (they are competing against other beliefs). Interestingly, this fits with the idea that Bayesian priors guide not only perception but also action; indeed, it is argued that in order to minimise prediction error, we will move to minimise the disparity between our predictions and perception. Reduced top-down processing may also fit with the well-replicated finding that patients with psychosis jump to conclusions more quickly that controls (the 'jumping to conclusions' bias), which has been interpreted as a possible failure to engage Bayesian decision-making processes(Moutoussis et al., 2011) , perhaps translating 'abnormal experiences directly into belief statements with no intervening stage of considering evidence which might be relevant to the related hypothesis' (Hemsley & Garety, 1986).

In order to consider the clinical implications, we may fit these arguments within Garety et al's cognitive model of psychosis (e.g. Garety et al., 2001), which has more recently been considered with reference to the neurobiological literature (Garety et al., 2007). The model is shown in Figure 6.1.

Figure 6.1. Cognitive Model Of Psychosis. Adapted From Garety et al 2001.



In this model, a biopsycho-social vulnerability, combined with stressful events leads to emotional changes, which combined with cognitive dysfunction and anomalous experiences and mediated by appraisals of experience, lead to positive symptoms such as delusions. Appraisals are themselves affected by cognitive biases, dysfunctional schemas, isolation and adverse environments. Positive symptoms are maintained by cognitive biases, dysfunctional schemas, emotional processes and appraisal of experience.

Within the model, reduction of top down processes fits most clearly into the vulnerability factors and cognitive dysfunction/anomalous experience boxes. Evidence from the current thesis indicates that weakened contextual processing may be present early in psychosis and may represent a risk factor for the development of psychosis. These ideas are complemented by research suggesting that schizoptypy, in particular a history of anomalous experiences, is a risk factor for traumatic intrusions (Holmes & Steel, 2004) and that these intrusions are more intrusive, vivid and affective in people reporting anomalous experiences than in 'low-scoring schizotypes' (Marks et al., 2012). These findings add weight to the idea that weak contextual integration increases the risk of intrusive memories/experiences. A history of trauma, recent stressful events and perhaps cannabis use may further increase the likelihood of anomalous experiences. Furthermore, loosening of the influence of prior beliefs may make dysfunctional appraisals of experience more likely, increasing the probability of delusion formation.

The model suggests a number of loci for intervention. Intervention may start prior to the development of psychosis, in populations at risk of developing psychosis (e.g. Power et al., 2007), or may take place after the development of clinical symptoms. Ideally, early intervention takes place before delusional beliefs have become well established, with the early stages of psychosis seen as a "critical period" (Birchwood et al., 1998) in which the "blueprint" for long term trajectories may be laid down (Harrison et al., 2001). This "blueprint" may perhaps be seen as a mixture of helpful and unhelpful beliefs about the world as well as the development of unhelpful behavioural patterns. The clinician's job at this stage is perhaps to aid the client in strengthening their helpful beliefs, increasing their cognitive flexibility and expanding their behavioural repertoire.

There may also be a role here for explicitly addressing cognitive processing dysfunction. Cognitive Remediation Therapy (CRT) aims to help patients improve cognitive function and thus everyday functioning. Evidence suggests that it may be effective in this aim (Bowie et al., 2012; Wykes & Reeder, 2005).. However, it has also been argued that despite many years of research, CRT has not increased in its effectiveness(McGurk et al., 2007). As CRT is guided primarily by the research evidence of cognitive dysfunction in psychosis, the more that is understood of the basis of such dysfunction, the better-targeted CRT can be.

With regard to the reported differences in contextual processing as measured in the BDII and Chubb Illusion, without longitudinal data, it is not possible to say to what degree such differences are state or trait in nature. Thus, it is not clear if any psychological intervention would be able to directly address these differences. Nevertheless, even if these differences represent a trait like tendency to weaker influence of context, this may be counteracted by work targeted at helping clients to alter the relationships between their thoughts, perceptions, beliefs and actions. Increasingly evidence suggests that interventions (such as person based CBT and ACT (Bach, 2005; Chadwick, 2006)) targeted towards increasing meta-cognitive awareness and development of a different relationship with experience, may be effective in reducing the distress associated with psychosis, as well as reducing symptom levels (Chadwick, 2006; White et al., 2011). Increasing meta-cognitive awareness may also help clients to more carefully consider the psychological and environmental context within which they are viewing the world, perhaps restraining the tendency to jump to unlikely conclusions. Equally, an awareness of the cognitive biases as promoted by traditional CBT for psychosis may help the client realise when they are applying (for instance) confirmatory biases to their experience.

Further, given that the way we relate to our experiences may be conceptualised as contextual processing, mindfulness training might be conceptualised as a CRT intervention for contextual processing.

Environmental factors in psychosis have often been overlooked in favour of biological factors. However, there is strong support for the theory that our environment alters our predisposition to psychotic beliefs, both clinical and subclinical (Bentall et al., 2007). A striking example of this is the finding that immigrants are at increased risk of psychosis and that this risk varies in a dose dependent fashion with the proportion of immigrants in the destination area – perhaps indicating that real and perceived discrimination play a role in the development of psychosis (Boydell et al., 2001). Other identified risk factors for psychosis include adverse life events, childhood trauma, isolation and family environment (Garety et al., 2007). Our environment, of course, is the context within which we learn. Our prior experiences determine how we see the world now. Thus even in the absence of weakened top-down processing, traumatic past events are likely to predispose us to negative appraisals of future events (unusually salient events mays also be judged to occur more frequently than is the case (Hemsley & Garety, 1986)). Thus, in order to address the effect of these negative past events, it may be necessary to work on them in therapy, in effect changing a person's prior beliefs. Finally, therapy may not be enough; following from the argument that people will try to find evidence to fit their existing beliefs, it seems logical that if such evidence is readily available then our beliefs will be more easily reinforced. Thus, although helping people to develop a different way of relating to their experiences may be useful, helping the client to change their current environment may also be necessary in many cases.

With regard to the treatment of pre-existing delusions, Corlett at al (Corlett et al., 2010) have suggested a novel approach that involves 'involves engaging the prior belief and administering a drug that destabilizes it, preventing its reconsolidation'. They have suggested the use of propranolol, which has been shown to attenuate learned fear responses in humans, may be useful for this purpose. Interestingly, propranolol has been used before in the treatment of psychosis, with research dating back to the 1970s (Yorkston et al., 1974). However, propranolol has also been reported to cause psychosis, both with acute treatment and in withdrawal (Ananth & Lin, 1986), which may explain why it has largely remained unused as an anti-psychotic agent. Perhaps with better understanding of how psychological therapy and pharmacotherapy may be integrated, such agents may prove to be more useful in future.

This suggested synergistic combination of psychological and pharmacological interventions is not a new idea. Kapur (2003) and others suggest that current antipsychotics may work by dampening the salience of stimuli and thus reducing the impact of bottom up perception on the maintenance of delusions. This process may be effective by itself; however, the process of belief change may be accelerated via cognitive therapies (van der Gaag, 2006). Given that medication remains the primary treatment for psychosis, considering how current and novel medications (including cannabis compounds such as CBD) may be most effectively combined with psychological intervention is an obvious direction for future research.

6.3 Future Work

The results of the present study suggest a number of directions for future research, these are briefly discussed below.

6.3.1 Simulation Study of Poor Attention to Task

Given concerns about the effect of poor attention to task on bias estimates, a future study might wish to formally simulate the effect of random responses on bias estimates. This should be relatively straightforward. A suggested method would be to programme a virtual respondent with (e.g.) 15% bias. Multiple simulation runs could be generated, each with a varying number of random responses (thus modelling inattention) varying from 0/64 to 64/64 trials. In this way a function could be generated showing the effect of random responding on the bias estimate.

6.3.2 Further Investigation of the Effects of Cannabinoids on Context Processing.

Study One did not find any evidence that the cannabinoids THC and CBD reduce contextual suppression as measured on the Chubb task. This was in contrast to evidence from another illusion the BDII. It was hypothesized that this difference was due to the two illusions working at different levels. The use of a battery of different illusions, involving a variety of different neural processes would help to be more specific about the areas of the brain implicated in the effects of cannabis on context processing. Functional neuroimaging techniques would provide another way of characterising the effect of cannabinoids on processing during illusion perception.

6.3.3 Replication of Study Two

To my knowledge, Study Two represents the only study to investigate contextual suppression in recent onset psychosis. As the results of the study were consistent with previous research, but not statistically significant, they require replication. A future study could be conducted with a number of adaptations. As discussed above, an estimate of bias on the Chubb illusion could be obtained significantly faster using a matching to sample method. By using such a method, it would be possible to also incorporate other illusions in the study (as in Tibber et al (in preparation). Other measures of context based processing believed to be altered in psychosis (such as Latent Inhibition (Gray et al., 2001)) might also be incorporated so that the relationship between different aspects of contextual processing could be investigated. Finally, based on the current study, a larger sample would be necessary to detect significant effects.

6.4 Final Thoughts

Distinguishing between real and perceived risks is a difficult task for us all (and arguably, evolutionary processes may not have kept pace with the way in which we have changed out environments). Witness the young male client in London who is convinced that straying into the wrong postcode will cost him his life – sadly, for the clinician, deciding whether this represents a delusion is a remarkably hard task. A predisposition to reduced contextual processing may increase the client's tendency to unusual experiences and unusual explanations of events. Cannabis use may further reduce the influence of context on the client's perception of the world. Combine this with media coverage of gang warfare and real personal experiences and it is perhaps unsurprising that the client develops 'paranoid' thoughts. Considering this example also demonstrates some of the difficulties with the model. For this client, experience may well have led to the belief that the world is a dangerous place, thus for appropriate caution to develop into excessive paranoia does not represent a reduction in prior beliefs, but a selective strengthening of the influence of particular priors at the expense of others. Thus in psychosis, the modification of prior beliefs is likely to be a dynamic process, whereby the conditions are first set for the development of unusual beliefs, followed by a process in which such beliefs become relatively established. Finally, of course, the response (internal and external) to such beliefs is key to how they affect the person who holds them.

The essence of clinical research is the iterative development and testing of models that provide ever-closer approximations to real life experience. The data presented in this thesis, is intended to inform our thinking about the processes by which psychosis is developed and maintained. These experiments were inspired by convergent evidence that indicates that alterations of contextual processing may underlie the experiences commonly associated with both psychosis and cannabis use. The results, although certainly not clear-cut, provide further information within which to develop these models and design future research. To put it another way, the results of this thesis provide evidence with which to test our prior beliefs, which are in turn, the consequence of past personal, cultural and evolutionary experiences. Where these data fit with our predictions, our beliefs may be strengthened, where they don't, we may change our beliefs. We must thus be mindful of the context within which we fit our evidence; our prior beliefs inevitably affect how we react to new evidence, and we may resist evidence that does not fit our beliefs.

In research there are inevitably trade offs to be made between ecological validity and experimental feasibility, and the current study is no exception. The experiments presented here, while useful for testing our models, bear limited resemblance to the complexity and heterogeneity of real life experience. Equally, when we report average differences between groups of people, we risk overlooking the similarities. At the same time, it is important to remember that models are just models. A bit like illusions, the important question is not so much whether they are 'true' but whether they are useful – and a bit like thoughts, it is what we do with them that counts.

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Service Project

An Audit of Neuropsychological and Psychometric Measures in South London and Maudsley National and Specialist Child Services

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Abstract

Neuropsychological assessment requires the use of tools that sometimes have very high upfront costs, and which may appear expensive. At the same time, due to initiatives such as Payment by Results and the Health and Social Care Act, there is increasing pressure for individual services to be fully costed. Prior to this audit, there were no figures either for usage or costs of psychological measures in South London and Maudsley's (SLAM) National and Specialist (N&S) child units. The aim of the current audit was thus to assess the real world usage and costs associated with such tools within SLAM N&S child services.

Estimates of measure usage and related expenditure were calculated based on a 3-month sample between from October 2010 through to December 2010. This was used to estimate yearly usage within each individual service and for the N&S services as a whole. The results of the audit are considered within the context of current service pressures and a putative move to devolve costs to individual teams. Possible strategies for reducing the costs associated with neuropsychological and psychometric assessment are discussed.

Table of Contents

1 Introduction

1.1 Aim

Neuropsychological assessment requires the use of tools that sometimes have very high upfront costs, and which may appear expensive. The aim of the current audit was to assess the real world usage and costs associated with such tools within South London and Maudsley's (SLAM) National and Specialist child services.

More specifically, the current audit set out to:

- Assess the current usage of neuropsychological and psychometric tests, both within each service and overall for all services.
- Determine whether there was significant scope for financial savings.
- Determine whether there was any broader scope for systems change to make the service more efficient.

1.2 Background

This service evaluation is, in part, as response to the demands of Payment By Results, a Department of Health initiative from 2002. However, more recent proposed changes to the NHS and the severe cuts to local government funding are also of significance to the current audit.

The NHS was set up by Clement Attlee's Labour government in the 1940s, being formally launched by health minister Aneurin Bevan, on July 5, 1948. The three guiding principles of the NHS were: A. That it meet the needs of everyone, B. That it be free at the point of delivery and C. That it be based on clinical need, not ability to pay.

Since its inception, the NHS has been under pressure to improve its services and reduce its costs (Rivett, 1998). This pressure has arguably increased dramatically over the last few decades. Politicians who, when in opposition have decried constant change, have found it impossible to resist major change when in government (e.g. HM Government, 2010, p. 24). Among the most significant of the initiatives put in place over the last two decades is Payment by Results (PbR). PbR was intended to provide a "transparent, rules-based system for paying

trusts" and to "reward efficiency, support patient choice and diversity and encourage activity for sustainable waiting time reductions". This was contrasted to a putative existing model in which the money a service received was "reliant principally on historic budgets and the negotiating skills of individual managers" (Department of Health, 2006).

The basis of PbR is that price X activity = income; essentially, a service gets paid for how much of a certain activity they are carrying out. Although this sounds simple, the reality is more complex and controversial; in particular there are fears that quality of work will be sacrificed for quantity (Oyebode, 2007) – however this is beyond the scope of the present discussion. In order to implement PbR, it has thus been necessary for services to fully cost all of their activities. This process is difficult and labour intensive, but without going through the process, a service will not be able to effectively apply for funding. Beyond the controversy, it is undeniably good practice for any service to audit and understand the underlying costs of its activities.

In 2012, service providers within the NHS arguably face greater uncertainty than at any time since its inception. The NHS Health and Social Care Act, which received royal ascent on the 27th March 2012, proposes to fundamentally change the way the NHS in England works, with 80% of the NHS budget being transferred to GP led commissioning bodies. The Health and Social Care Bill was highly controversial and faced strong opposition from within the NHS, parliament and the House of Lords. Nevertheless, the government prevailed and the bill was passed into law. It is therefore more important than ever that services within the NHS prepare themselves for further disruptive change. The current evaluation, both as part of such preparation and as good practice, aims to provide an accurate measure of the material costs involved in the provision of neuropsychological tests and psychometric measures, within Maudsley Child and Adolescent Mental Health Services (CAMHS).

1.3 Neuropsychological and Psychometric Assessment.

Neuropsychological testing and psychometric assessment tools are essential to both research and clinical practice. Without neuropsychological testing, our ability to assess and help people with disorders that affect brain function would be vastly impaired. The use of neuropsychology to collect valid and reliable

information from multiple sources enhances diagnostic precision and clinical management (Braun et al., 2011). Among other things, combined use of neuropsychology and psychometric assessment allows us to objectively assess current function, identify specific difficulties or disorders, track change over time and measure response to treatment. Early identification of a person's specific difficulties may allow services to provide appropriately matched support to maximise their developmental potential (Silver et al., 2006). Conversely, failure to identify such difficulties may mean that no or inappropriate support is provided. For instance, difficulties that are neurodevelopmental in origin may be misattributed as behavioural, while difficulties due to mood disorders may be missed. Adequate provision of neuropsychological assessment is therefore an imperative in a modern National Health Service, and this is especially important in child services.

Despite this, neuropsychology is sometimes viewed as an expensive luxury, especially in stretched health care systems. Neuropsychological assessments are time consuming, and they need to be administered by highly trained clinicians if they are to be delivered and interpreted correctly. To add to this, the upfront costs of purchasing measures may seem high, with neuropsychological batteries costing anywhere between £100 and £1600.

The current audit does not extend to the cost of clinician time and training. Instead, it is, by design, limited to provide a picture of the levels of resource use within National and Specialist Child Services and the related monetary costs of such use.

1.3.1 Costs of Assessment: Upfront Vs Running Costs

Many assessment tools involve both an upfront cost and on-going running costs. The upfront cost is typically for buying a 'test kit', which generally includes manuals, equipment and assessment forms. Once the kit has been bought, additional assessment forms may be purchased separately. An example would be the Wechsler Intelligence Scale for Children, version 4 (WISC-IV). The upfront cost of the WISC-IV is £948.00, which includes: administration, scoring and technical manuals, 25 record forms, 25 response booklets, scoring keys and physical test equipment. The kit therefore provides all a psychologist needs to test 25 participants. After this, it is necessary to buy more response booklets

and record forms; in total these cost £177 for 25 assessment or £7.08 per participant. Thus, the upfront cost of a kit is equivalent to the running costs of testing over 130 participants. The balance between upfront costs and on-going costs thus depends on how often a particular tool is used and its useful lifespan.

Assessment tools are also updated on a semi-regular basis, in order to update normative datasets and to incorporate scientific advances. These updates also provide a part of the publisher's revenue stream. The WISC was first published in 1949, and was updated in 1974, 1991 and 2003 (Flanagan & Kaufman, 2009). The original adult form, the WAIS, was first published in 1939, and was updated in 1946, 1955, 1981, 1997 and 2008 (Lichtenberger & Kaufman, 2009). Thus based on recent publication history, updates can be expected every 10-15 years. Clinicians and researchers are typically encouraged to use the latest versions. Thus, practitioners and services will typically have to budget for purchasing updated kits.

There is no easy way to identify how many kits a service needs to purchase. This will clearly vary depending on how many assessments the service needs to carry out and how many psychologists will be carrying out the assessments. Many psychologists can share the same kit, but clearly a kit may only be used by one psychologist at a time. Thus good organisational practice and resource management is needed to maximise the efficient use of psychological measures.

1.4 The Audit Process.

Audit in the NHS is a process designed to ultimately improve the quality and efficiency of patient care. It does this via a process of systematically reviewing current practice and identifying current strengths, weaknesses and areas for improvement. According to NICE, 'The time has come for everyone in the NHS to take clinical audit very seriously. Anything less would miss the opportunity we now have to re-establish the confidence and trust on which the NHS is founded' (Rawlins, 2002).

NICE guidance describes the audit process as a cycle (Figure 1), within which are a number of stages that lead to the establishment of best practice. The essential point of this cycle is to iteratively improve practice. It is essential to this process that the outcome of each stage of the audit be taken forward; where improvements are indicated, they must be followed though and further evaluated.

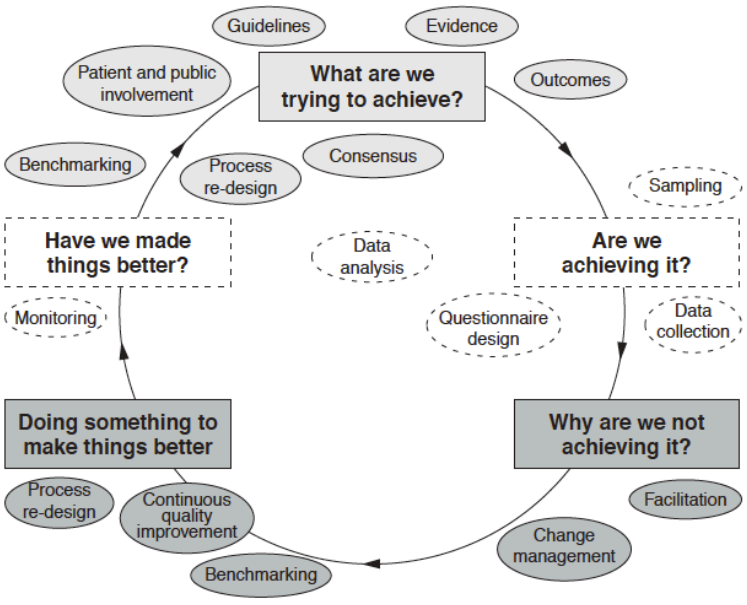

Figure 1 The Clinical Audit Cycle According to NICE

The audit cycle pictured in Figure 1, must begin with the question "what are we trying to achieve?" The context to this question is an overall goal to accurately cost CAMHS services. Within this context, the primary aim of the current audit is to identify the level and cost of psychological audit use. Currently there is no specific budget for psychological equipment. Further, it is envisaged that this

information will be used to help devolve costs to individual teams. It is hoped that the audit will provide information to help achieve an efficient, cost-effective use of psychological measures within CAMHS services.

The first step in the audit is thus to collect data on what the current levels of measure use are and what the associated costs are. The second step is to use this data to draw conclusions about whether current usage is efficient and cost effective. The third step is to identify ways in which the system could be made more efficient. To close the audit cycle, recommendations must be communicated, acted upon and levels of progress identified ("have we made things better?").

1.5 The Structure of South London And Maudsley CAMHS.

South London and Maudsley NHS Trust encompasses many different CAMHS services. For the purposes of the current audit, only National and Specialist CAMHS teams based at the Maudsley and Bethlem hospitals were considered.

At the Bethlem Hospital the following services were considered: Acorn Lodge Children's Unit, Bethlem Adolescent Unit, Bill Yule Adolescent Unit

At the Maudsley Hospital the following services were considered: Conduct Adoption and Fostering Service, Autism and Related Disorders Service, Challenging Behaviour Service, Forensic Service, Mood Disorder Service, Neuropsychiatry and Neuropsychology Service, Child Anxiety and PTSD Team, Child Care Assessment Team, Dielectical Behavioural Therapy Service, Snowsfield Adolescent Service, Obsessive Compulsive Behaviour Service, Learning Disability Service and Eating Disorders Service.

To provide context, brief descriptions of each unit are provided below (information is primarily sourced from the document 'CAMHS National and Specialist Services Directory', published by South London and Maudsley NHS Trust). All services are based at the Maudsley hospital unless otherwise indicated.

1.5.1 Inpatient Care

1.5.1.1 Acorn Lodge Children's Unit

Provides inpatient (10 beds) and outpatient services for children (4 to 13 years old) with a wide range of emotional and/or behavioural disorders, the only exclusion criterion being a primary difficulty of conduct disorder. Work is conducted within a flexible model designed to help families understand their children's' needs and provide support for both families and children.

1.5.1.2 Bethlem Adolescent Unit (BAU)

Provides inpatient (12 beds) and outpatient assessment and treatment for adolescents (12-18) with serious mental illnesses. About half of the young people have psychosis, the remainder include young people with mood disorders, who pose a risk to themselves or for whom there is diagnostic uncertainty. The primary exclusion criterion is a need for a secure environment. The unit also has a limited number of day patients.

1.5.1.3 Bill Yule Adolescent Unit

Provides medium secure inpatient care (10 beds) for young people, between 12 and 18 years old, with severe behavioural and psychiatric problems. The unit caters for male clients who are under a Mental Health Act detention order and who cannot be cared for by local services. Exclusion criteria are need for a high security setting, severe learning disabilities preventing basic self care and admissions under a secure care order.

1.5.1.4 Snowsfield Adolescent Unit

Has essentially the same rationale, inclusion and eligibility/exclusion criteria as the BAU; it has 11 inpatients beds and four day-patient beds. The service is currently piloting a supported discharge element to the team that comprises a further small caseload.

1.5.2 Outpatient Care

1.5.2.1 Developmental Neuropsychiatry and Neuropsychology Service

Acquired Brain Injury Service

Provides neuropsychological and neuropsychiatric assessment and treatment to children and adolescents with acquired brain injury.

Autism and Related Disorder Service (ARD)

Provides assessment and treatment for young people with autism and pervasive developmental disorders. The service has specialist experience in a variety of rare disorders such as Cri Du Chat syndrome. Consultation and support are also offered to the family or carers of young people with autism or related disorders.

Behavioural Phenotype Learning Disability Service

Provides assessment, consultation, advice, support and counselling for young people with intellectual and other disabilities.

Challenging Behaviour Service

This service provides support for young people with intellectual disability or neurodevelopment for whom challenging behaviour is the primary concern.

Neuropsychiatry and Neuropsychology Service

This service provides assessment and interventions for young people presenting with neuropsychiatric difficulties including ADHD, epilepsy and cello-cardio-facial syndrome.

Mental Health of Learning Disability Service

Provides assessment and management for young people with a learning disability and behavioural or mental health problems, including autism, ADHD, obsessive compulsive disorder, psychosis, depression, feeding disorders, offending behaviours and sleep disorders.

1.5.2.2 Conduct Adoption and Fostering Service.

A specialist outpatient service of young people who have been fostered or adopted and who are experiencing difficulties. These difficulties may be general emotional or behavioural difficulties or more specific placement related issues.

1.5.2.3 Anxiety Service (incorporating the Child Traumatic Stress Service)

A specialist outpatient service for young people (up to 18) suffering from anxiety disorders including posttraumatic stress disorder (PTSD). Exclusion criterion: requirement for urgent assessment or treatment for another, overriding problem. This service now includes the Child Traumatic Stress Service, which was previously separate.

1.5.2.4 Mood Disorder Service

This service provides assessment and treatment for young people suffering from mood disorders. Exclusion criteria: emergency referrals, self harm as a primary difficulty, another primary psychiatric disorder.

1.5.2.5 Child Care Assessment Service

This service provides assessments and court reports for children and their parents or carers, where they are undergoing care proceedings in public or private courts.

1.5.2.6 Conduct Problems Service

This service provides assessment and treatment for children (aged 3 to 8) who are presenting with behaviours considered to be disruptive, difficult or antisocial and who persistently behave in an aggressive or defiant way.

1.5.2.7 Dialectical Behaviour Therapy Service

This service provides assessment and treatment for young people who have a history of self-harm and symptoms associated with borderline personality disorder.

1.5.2.8 Eating Disorders Service

This service provides individual and family therapy for clients suffering from eating disorder and their carers.

1.5.2.9 Forensic Service

This service provides assessment and treatment for young people who are engaged in or are at risk of offending behaviour.

1.5.2.10 Obsessive Compulsive Disorder Service

This service provides assessment and treatment for young people with a diagnosis of obsessive-compulsive disorder (OCD) and related disorders.

2 METHOD.

2.1 Data Collection

A key contact was identified for each team via Dr Maxine Sinclair. The contact was then emailed and asked to provide detailed information of which and how many neuropsychological and psychometric measures they had used over a representative set period. The representative period was chosen following consultation with the contact member from each team that responded to the initial consultation e-mail. A period of 3 months was decided upon as a compromise method, which would provide a fair representation of each team's workload, while not placing undue strain on the resources available to carry out the audit. The period chosen was from 1 October 2010 until 31 December 2010.

The majority of services provided their own summary data of the number of measures used. Where this was not possible two alternative methods were used:

1. A list of clients seen during the period was requested and the number of measures used was established by cross-referencing against ePJS (electronic Patient Journey System), SLAM's electronic patient notes database. Information was gathered from two sources within ePJS: A: 'events', which consists of general clinical notes and B: 'correspondence', which consists of reports and letters attached to the system as documents.
2. In the case of the OCD and ARD teams, data was calculated from details of the teams' standard assessment procedures and client throughput.

2.2 Acquisition of Costing Information for Measures

SLAM's supplies department was contacted to ascertain what, if any specific contracts existed for the purchase of psychometric or neuropsychological measures. Laura Hurst of the supplies department was liaison for the purpose of the audit. According to the supplies department, supplies are ordered on a requirement basis and no bulk orders are placed, there are therefore neither formal contracts nor negotiated discounts. However, discounts are negotiated on an individual basis by the ordering department and these negotiated

discounts are communicated to the supplies department. Detailed information on such discounts was unavailable and therefore prices for measures were sourced from publically available pricing information from publishers' websites. Where the only source was from the US (E.g. Pearson Assessments US for the Mullen Scales of Early Learning), a dollar/sterling conversation rate of 1.6 was used. Prices are all provided *exclusive of VAT*.

2.3 Calculation of Per Use Costs

Costs for psychological measures have been calculated in two ways.

- **Ongoing Cost.** The on-going costs of each measure have been calculated based on the costs of ordering extra materials. This is straightforward and calculated as the price of a consumable pack (or packs) divided by the number of assessments in the pack.
- **Overall Cost.** An estimated measure of total cost has been calculated, including both kit cost and on-going costs. This is more complex and involves a key assumption. The primary assumption is that each kit ordered will be used 200 times. Most kits come with 25 sets of forms, thus for such a kit, the overall costs would be:

$$Overall\ Cost = \frac{KitCost + (SupplyCost * 175)}{200}$$

It is likely that some kits will be used more than 200 times and some less than 200 times. However, if a kit life of 10 years is assumed, 20 assessments per year is likely a conservative estimate for usage.

3 RESULTS.

3.1 Response from Services/Units.

Data was collected from the following units/services:

Inpatient Care:

Acorn Lodge and Snowsfield

Outpatient Care:

Neuropsychiatry and Neuropsychology, Challenging Behaviour, Forensic Service, Adoption and Fostering Service, Mood Disorder Team, Anxiety and PTSD Team, Child Care Assessment Service, Dielectical Behaviour Therapy Service, Learning Disability Service, OCD Team.

Data was not acquired from the following unit/services: Bill Yule, Bethlem Adolescent Unit and Eating Disorders. Usage by these teams could therefore not be accounted for. The figures quoted below thus represent an underestimation of the overall usage by Maudsley and Bethlem CAMHS services.

3.1.1 Measures and Tests

A list of 55 different assessment measures were identified across the teams. Of these measures, 27 measures were copyrighted, paid measures. The remaining 28 measures were a mixture of freely available scales and measures, as well as service specific idiosyncratic measures. For the purposes of clarity in the current discussion, freely available and idiosyncratic measures have been removed from the tables; however, details are available in the appendix.

3.2 Measures Used From 1 October 2010 until 31 December 2010

3.2.1 Paid Measures

All paid measures are listed in Table 1, along with the number used over the audit period and the cost to the service of each measure. Costs per team are shown in Table 2. Costs per publisher are shown in Table 3.

The total cost to the service of all paid measures, including the cost of initial kit purchase was £2532 for the quarter year between 1st October 2010 and 31st

December 2010. Assuming equal usage over the year, the yearly cost was therefore £10,128.

The most used measures were (from most to least used, with quarterly usage in brackets): Conners' ADHD Scales (82), Beck Depression Inventory (60), Social Communications Questionnaire (39), Wechsler Individual Achievement Test (38), Beck Youth Inventory (33), Anxiety Disorders Interview Schedule (33), Wechsler Intelligence Scale for Children (29), NEPSY (20).

3.3 Overall SLAM Spending on Neuropsychological Measures

SLAM supplies department were able to provide figures for overall purchasing from the major suppliers of measures for the year from 21st March 2011 until 21st March 2012. Total spending for the year was £52,257.63. A breakdown of this cost by publisher is provided in the appendices. A full breakdown by publisher and order is available on request.

Table 1. Measures. Number Used and Cost To Service. 1st October 2010 until 31st December 2010.

Measure	Full Name	Publisher	No. Used	Kit Cost	Running Costs (All costs exclude VAT)	Reorder cost Per Person	Unit cost adjusted for Kit	Total Reorder Cost	Total Adjusted Cost
AARS	Adolescent Anger Rating Scale	Ann Arbour	3	£155.00	£61.75 for 25 forms	£2.47	£2.94	£7.41	£8.81
ABAS	Adaptive Behavior Assessment System	Pearson Assessment	11	£190.00	£62 for 25 forms	£2.48	£3.12	£27.28	£34.32
ADI	Autism Diagnostic Interview	Pearson Assessment	5	£190.00	£72 for 10 forms	£7.20	£7.25	£122.40	£123.25
ADIS	Anxiety Disorders Interview Schedule	OUP	33	£40.00	£40 for pack 10	£4.00	£4.00	£132.00	£132.00
ADOS	Autism Diagnostic Observation Schedule	Hogrefe	11	£1,538.00	£42 for 10 forms	£4.20	£11.68	£96.60	£268.64
BAI	Beck Anxiety Inventory	Pearson Assessment	2	£83.00	£44: 25 forms	£1.76	£1.96	£3.52	£3.91
BDI	Beck Depression Inventory	Pearson Assessment	60	£82.00	£43.50: 25 forms	£1.74	£1.93	£104.40	£115.95
BYI	Beck Youth Inventory	Pearson Assessment	33	£182.00	£87: 25 forms	£3.48	£3.96	£114.84	£130.52
CELF IV	Clinical Evaluation of Language Fundamentals	Pearson Assessment	2	£565.00	£69 for record forms, £26.50 for rating forms	£3.82	£6.17	£7.64	£12.34
Connors	Conners' Rating Scales–Revised / Connors-3	Pearson Assessment	82	£294.50	£42.50 each for parent/teacher forms	£3.40	£4.45	£479.40	£557.89
DKEFS	Delis-Kaplan Executive Function System	Pearson Assessment	2	£568.00	£48.50: 25 forms	£1.94	£4.54	£3.88	£9.08
Family Relations Test	Bene-Anthony Family Relations Test.	GL Assessment	3	£280.00	£20: 25 forms	£2.08	£3.22	£6.24	£9.66
MULLEN	Mullen Scales of Early Learning	Pearson Assessments US	6	£581.09	$43.30: 25 forms	£1.08	£3.85	£6.50	£23.12
NEPSY	NEPSY	Pearson Assessment	20	£775.00	£51 each: response form and record books X25	£4.08	£7.45	£81.60	£148.90
PSI	Parenting Stress Index	Hogrefe	3	£160.00	£58: 25 forms	£2.32	£2.83	£6.96	£8.49
RCMAS	Revised Children's Manifest Anxiety Scale	Hogrefe	5	£98.00	£46: 25 forms	£1.84	£2.10	£9.20	£10.50
SCQ	Social Communications Questionnaire	Hogrefe	27	£108.00	£34: 20 forms	£1.70	£2.03	£66.30	£79.07
SIQ	Suicidal Ideation Questionnaire	PAR (parinc.com)	6	£107.50	$54: 25 forms	1.35	£1.72	£8.10	£10.31
STAXI	State-Trait Anger Inventory	AnnArbour	9	£228.00	£75 : 50 rating forms, £65 : 50 profile forms	£2.80	£3.59	£25.20	£32.31
TEACH	Test of Everyday Attention for Children	Pearson Assessment	4	£454.00	£47.50: 50 forms	£1.90	£3.70	£7.60	£14.78
TVPS	Test of Visual-Perceptual Skills	AnnArbour	1	£199.00	£36: 25 forms	£1.44	£2.26	£1.44	£2.26
WAIS	Wechsler Adult Intelligence Scale	Pearson Assessment	9	£1,150.00	£111.50, £68.50, £41.50 for forms, response book 1 and 2 X 25	£8.86	£13.50	£79.74	£121.52
WASI	Weschler Abreviated Scale of Intelligence	Pearson Assessment	4	£282.00	44: 25 forms	1.76	£2.95	£28.16	£47.20
WIAT	Wechsler Individual Achievement Test	Pearson Assessment	26	£437.00	£63.00 and £63.00 for record forms and response booklets X25	£5.04	£6.60	£191.52	£250.61
WISC	Wechsler Intelligence Scale for Children	Pearson Assessment	29	£948.00	£50.50, 50.50, £76.00 for Response book 1+2 and record forms. X25	£7.08	£10.94	£205.32	£317.12
WPPSI	Wechsler Preschool and Primary Scale of Intelligence	Pearson Assessment	7	£915.00	£65.50 for 25 record forms, £46.50 for 25 response booklets	£4.46	£8.48	£31.22	£59.34
							TOTAL	**£1,854.47**	**£2,531.88**

Table 2. Cost of Measures. Per Team. Per Quarter.

	Service	Team	Quarterly Cost, consumables only	Quarterly cost, with kit.	Yearly Cost, with kit
Inpatient Care		Acorn Lodge	£123	£184	£737
		Snowsfield	£127	£203	£811
		BAU	unknown	unknown	unknown
		Bill Yule	unknown	unknown	unknown
Outpatient Care	Developmental Neuropsychology and Neuropsychiatry	Neuropsychiatry	£310	£394	£1,578
		ARD	£300	£437	unknown
		Challenging Behaviour	£24	£46	£185
		Learning Disability	£159	£207	£827
		Forensic	£224	£326	£1,306
		CAFT	£88	£123	£492
	Mood/Anxiety	Mood Disorders Team	£27	£41	£162
		Anxiety/PTSD Team	£24	£35	£140
		CCAT	£185	£253	£1,010
		DBT	£25	£32	£127
		Eating Disorders	unknown	unknown	
	OCD Team	TCBT	£115	£119	£475
		DCS	£61	£63	£250
		Clinic	£63	£70	£278
		OCD Total	£239	£251	£1,003
		Total	**£1,854**	**£2,532**	**£10,128**

Table 3. Spend By Publisher

Publisher	Total Adjusted for Kit / Quarter	Total Adjusted for Kit / Year	Putative 15% Discount
Pearson Assessment	£1,946.72	£7,786.86	£1,168.03
Hogrefe	£366.70	£1,466.81	£220.02
PAR (parinc.com)	£10.31	£41.25	£6.19
AnnArbour	£43.37	£173.50	£26.02
GL Assessment	£9.66	£38.64	£5.80
OUP	£132.00	£528.00	£79.20
Peason Assessments US	£23.12	£92.46	£13.87
Total	**£2,531.88**	**£10,127.52**	**£1,519.13**

4 Discussion

The aim of the current audit was to provide a representative picture of the level of use of neuropsychological and psychometric resources within South London and Maudsley National and Specialist Services. Towards this aim, data was collected from the majority of team within the Maudsley and Bethlem CAMHS services.

Taking into account the initial costs of buying testing kits, the total estimated yearly spend on psychological measures was £10,128. Annual spending on consumables alone was estimated at £7,418. The later figure is more reliable as it is not dependent on assumptions about the number of times each kit is used during its lifetime. Both figures are also based only on those teams that responded to the audit and therefore represent an underestimate of total usage/costs.

Usage varied considerably by team (total yearly costs estimated from £127 to £1749), with the highest usage in Autism and Related Disorders (ARD). At this stage, it is not possible to comment on whether each service's individual usage represents optimal use of resources. It may, however, be considered unlikely that clinicians will carry out significantly more testing that is necessary; there being little incentive to do so within the current system. Discussion shall therefore focus on possible ways in which costs may be reduced without reduction in the actual level of assessment.

4.1 Strategies For Reduction of Costs

There are a number of potential strategies by which costs may be reduced. These include: reduction of neuropsychological testing, better usage of economies of scale, research collaboration and the use of open-source or limited copyright measures.

4.1.1 Reduction of Use of Neuropsychological Testing Measures

Clearly the costs incurred by neuropsychological testing could be reduced, but restricting the frequency and range of the measures used by psychologists. However, neuropsychological testing is a core part of both the assessment and monitoring of the type of conditions seen by National and Specialist units. Psychologists are trained in the judicious use of tests and are unlikely to use any measures unless they are likely to be useful in assessing or treating clients

4.1.2 Economies of Scale

The NHS employs approximately 1.7 million people, making it one of the world's largest employers (NHS Choices, 2011) and has a budget of over £100 billion annually (Department of Health, 2010). It therefore has huge spending power and theoretical purchasing leverage, which should enable it to get the very best deals from suppliers. However, this can only work if purchasing is to some extent centralised. SLAM National and Specialist Child Services currently have a centralised store of measures, which in turn orders these measures from SLAM supplies department. The supplies department purchases measures for the whole of SLAM on an as needed basis and has no specific contracts with suppliers.

Two potential options for reducing the cost of measures to SLAM would be:

1. SLAM Supplies Department to negotiate further discounts for bulk orders of measures from publishers.
2. SLAM to use a company such as 'NHS Supply Chain' (http://www.supplychain.nhs.uk/) to source measures. According to its website, NHS Supply Chain acts to provide coordinated purchasing for NHS trusts.

These options are certainly worth exploring. For instance, Maria Priestly, at the Institute of Psychiatry has negotiated a 15% discount for orders from Pearson assessment. Thus despite publishers' apparent monopoly on most, if not all, of the available measures, there is clearly scope for negotiation. Dr Sinclair, on behalf of N&S CAMHS services, also negotiates various discounts with Pearson, ranging from between 5 and 10%.

Over the last year, SLAM has an overall spend at Pearson Assessment of £33,977, a 15% discount on this spend would represent an actual saving of £5,097 per year. Spend at Pearson Assessment by the CAMHS services included in this audit at Pearson Assessment is estimated at £7787 per year. A 15% discount on this would represent £1168 per year. Factoring VAT into account, savings would be 20% higher. Potential savings however, will be lower than this as discounts are already negotiated on a case-by-case basis.

4.1.3 Research Collaboration

Where clinical and research work overlap, there is potential to share costs and to save on VAT. If assessments are being provided both for research and clinical purposes, the research grant may include provision for assessment tools. In addition research costs from a project conducted by a registered charity (such as a University) do not attract VAT and thus there is potential for savings here. There may also be potential for discounts where research or clinical work contributes to the further development of measures. For instance Pearson Assessment US's Research Assistance Programme offers a 50% discount on measures in such circumstances, with a maximum discount of $5000 (Pearson Assessments, 2012).

4.1.4 Use of Alternative Measures

Not all psychological measures attract a charge. There are a variety of measures that are available either for free use or for free use with permission from the authors. For some measures there are clear alternatives available, while for others there are either no alternatives, or the alternative are less attractive (for instance, a service might want to use the most widespread or validated scale for research purposes). A list of paid measures and possible free alternatives can be found in Table 5.

With regard to the paid measures identified in the current audit, for the majority, no viable alternatives were identified. However, for measures of mood, there are a number of possible publically available measures including the Self-Report for Childhood Anxiety Related Disorders (SCARED), Spence Children's Anxiety Scale (SCAS), Depression Anxiety Stress Scale (DASS) and the Center for Epidemiological Studies Depression scale (CES-D). These measures have the extra attraction of essentially always being in stock, as they may be photocopied or printed. The estimated annual spend on mood measures (BAI, BDI and BYI) is £1,111, which would represent the maximum possible saving from a switch to publically available measures.

Choice of measures though, depends on more than cost. A good NHS service involves clinical, research and teaching roles, and the measures it uses must fit these roles. Thus in selecting a measure, concerns such as reliability, validity, ease of use, research applicability and transferability must be considered. As an example we may consider the CED-D and the BDI. The CES-D and the BDI are reported to be equally useful for screening for depression across a variety of settings, with no clear

differences in terms of sensitivity and specificity, reliability or validity (Andriushchenko et al., 2003; Fountoulakis et al., 2007; Tandon et al., 2012). The CES-D may provide more information where severity is low, with the opposite applying for the BDI (Olino et al., 2012). The CES-D has been reported to be more sensitive to change than the BDI (Santor et al., 1995). Patient preference for the CES-D has also been reported (Wilcox et al., 1998), with patients reporting the CES-D to be 'less depressing and quicker than the BDI. Given the results of these studies, there seems to be little compelling reason to stick with the BDI over the CES-D. A possible reason is that the BDI has been more widely used in research; however, such self-fulfilling concerns should be carefully considered – especially given that the above studies provide information on relative cut-offs for the two scales, allowing results to be compared.

4.2 Purchasing Process.

The ordering process for measures appears rather convoluted. New stock and new measures are ordered via Dr Maxine Sinclair. Individual psychology staff identify when stock is running low, or new measures are required. This information is passed to Dr Sinclair, who then places an order with the Business Manager. Orders are then authorised by the Service Manager (Patricia O'Neil) and Deputy Director (Jo Fletcher). Once authorised, orders go to SLAM supplies. Consumables and replacements are authorised automatically. Purchase of new equipment needs to be justified; such requests are therefore taken to the two-monthly National and Specialist psychology meeting and must be agreed by the professional group and the lead psychologist (previously Dr Troy Tranah, now Dr Sinclair).

While checks on purchasing are important in any system, it is unclear why so many steps are involved in this process. Having multiple steps in purchasing has two clear disadvantages. Firstly, with each extra step, additional staff time, and therefore costs are involved. Secondly, each step provides the potential for delay and thus inefficiency. This may impact on both staff efficiency and quality of clinical care, in terms of delays in assessment. Given these disadvantages, a convincing case should be made for every step in a process.

4.3 Devolution of Costs to Individual Services

As part of the adjustment of services to the demands of PbR and more recent NHS reform, devolution of costs to individual services is being considered. Advantages and disadvantages of this process with regard to assessment measures are discussed below.

4.3.1 Advantages

The primary advantage of devolving costs to individual services is that it can facilitate more accurate costing of each service. At the same time, the burden of costs may fall more appropriately to each service, with services paying for only the measures that they use. Service level costing could also arguably incentivise staff to reduce any unnecessary use of psychological measures. However, as previously noted, due to the effort required in administering such measures, it is unlikely that they would be employed without good reason. Another advantage is that each service would have direct responsibility for their own measures, thus reducing the potential for any abuse of resources.

4.3.2 Disadvantages

Although devolution is envisaged as a route to increased efficiency, all devolution approaches carry with them a risk that desired efficiencies would be offset by extra bureaucracy. To some extent this depends on how devolution is managed.

At the extreme, all services would have to order, maintain and store their own measures. This would potentially result in a loss of efficiency of resource use. For instance, a WISC assessment takes approximately 3 hours to conduct and score, meaning that with one kit, two can be conducted in a day and thus hundreds in a year. With a fairly basic booking system[1] tests can be shared between multiple teams. By contrast, if measures are owned by individual services, they will likely be underused. For instance, the CAFT service used the WISC assessment once in a three-month period, compared to 29 uses for all N&S CAMHS services. If CAFT had to purchase its own WISC, this would represent an inefficient use of the measure. Additionally, it is important to consider the potential penalty in terms of staff time

[1] Booking systems. This may be an area for further investigation. The current system is paper based. Moving to an electronic system could make it easier to see when and which resources were available and make booking of resources quicker.

involved in having multiple staff individually auditing and ordering measures. Further, it is arguably better to have one member of staff who knows the procurement system intimately, than many with vague and intermittent experience, although this approach carries the risk of reliance on one staff member.

4.3.3 A Compromise Solution

A possible compromise solution would be for N&S CAMHS services to retain a central storage and ordering system, but to charge services according to their use of measures. Costs could be based on calculations such as those in this audit. Thus it would be possible to reduce the burden of ordering tests and maintain efficient use of resources, whilst at the same time allowing for accurate costing of resource use. If devolution of costs is the intended outcome, then this might be the most appropriate solution. Even so, the cost of additional bureaucracy (include setting up such a system, raising internal invoices and getting them paid) involved in such a solution need to be outweighed by the benefits, and it is not immediately clear that this would be the case.

4.4 Keeping Perspective

When considering the costs of psychological assessment measures to services, it is important to compare the material costs to other pertinent costs of assessment. Many cognitive assessments will be conducted by trainee and band 7 psychologists. Specialist neuropsychological assessments will often be conducted by neuropsychologists at band 8 or above. Furthermore, psychologists not familiar with neuropsychological testing require considerable supervision and training, in order that results are reliable and comparable. Band 6 and 7 staff will attract an annual salary of between £25k and £40k, which equates to an hourly pay of between approximately £12.5 and £20 per hour, with band 8 salaries of up to £40 per hour. The costs to the NHS will be higher. A full assessment might take 3-8 hours, with considerable extra time necessary for scoring and report writing. Time for both assessment and report writing varies considerably with case complexity.

An assessment for an individual client by the Neuropsychiatry Service is priced at £1485.00. A typical assessment might use the following measures: Beck Youth inventory for mood assessment, Connors ADHD assessment form (parent, teacher and self-report), WISC-IV for IQ assessment, plus a NEPSY-II. The total cost of these assessments is £28.27 excluding VAT. Thus, for comparison the purchase cost of

measures is 2% of the total assessment cost or about two hours of trainee salary. It should also be noted that insufficient supplies of kits and consumables inevitably reduces the efficiency of a service.

4.5 Overall Conclusion.

The costs of neuropsychological assessment to SLAM National and Specialist units are not negligible, at over £11,000 per annum. There may be limited scope for reducing this cost though alternative buying practices or the use of publically available measures. Overall however, the comparative cost of purchasing neuropsychological measures remains a small component of the overall costs of assessment and treatment. Devolution of costs to individual teams carries a number of benefits, but these have to be weighed against the potential inefficiencies of such a move.

As a final comment, the impact of such changes on the culture of a service should also be considered. Services may wish to think twice before implementing a system in which resource competition risks taking priority over cooperation.

4.5.1 Specific Feedback From Teams

Only one team gave specific feedback. The Child Care Assessment Team reported that the Beck Anxiety and Depression scales were not always available. They also reported that they use the Family Relations Test in a qualitative fashion, but that the most up to date versions are not available in store.

4.5.2 Feedback to Service

Feedback has been provided to the lead psychologist, Dr Maxine Sinclair. Further feedback is scheduled be provided to the relevant committees within SLAM N&S services.

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6 Appendix

Table 4. SLAM Total Spend on Measures and Related Items (21/3/11 until 21/3/12).

Supplier	Value
Pearsons	33,977.63
Hogrefe	15,430.11
Ann Arbour	849.00
OUP	563.00
GL Assessment	99.35
PAR (parinc.com)	0.00
MHS	1,338.54
Total	52,257.63

Table 5 Alternative Free Measures

Measure	Abreviation	Possible Free Alternatives
Adolescent Anger Rating Scale	AARS	None identified
Adaptive Behavior Assessment System	ABAS	None identified
Autism Diagnostic Interview	ADI	None identified
Anxiety Disorders Interview Schedule	ADIS	None identified
Autism Diagnostic Observation Schedule	ADOS	None identified
Beck Anxiety Inventory	BAI	Self-Report for Childhood Anxiety Related Disorders (SCARED), Spence Children's Anxiety Scale (SCAS), Depression Anxiety Stress Scale (DASS)
Beck Depression Inventory	BDI	Center for Epidemiological Studies Depression scale (CES-D), DASS
Beck Youth Inventory	BYI	SCARED, SCAS, CES-D, DASS
Clinical Evaluation of Language Fundamentals	CELF IV	None identified
Conners' Rating Scales–Revised / Connors-3	Connors	None identified
Delis-Kaplan Executive Function System	DKEFS	None identified
Bene-Anthony Family Relations Test.	Family Relations Test	None identified
Mullen Scales of Early Learning	MULLEN	None identified
A Developmental NEuroPSYchological Assessment	NEPSY	None identified
Parenting Stress Index	PSI	None identified
Revised Children's Manifest Anxiety Scale	RCMAS	None identified
Social Communications Questionnaire	SCQ	None identified
Suicidal Ideation Questionnaire	SIQ	Many available, but costs not clear.
State-Trait Anger Inventory	STAXI	None identified
Test of Everyday Attention for Children	TEACH	None identified
Test of Visual-Perceptual Skills	TVPS	None identified
Wechsler Adult Intelligence Scale	WAIS	None identified
Weschler Abreviated Scale of Intelligence	WASI	None identified
Wechsler Individual Achievement Test	WIAT	None identified
Wechsler Intelligence Scale for Children	WISC	None identified
Wechsler Preschool and Primary Scale of Intelligence	WPPSI	None identified

Table 6. List of Freely Available / Licenced Measures Identified in Audit

Acronymn	Name
CGAS	Children's Global Assessment Scale
CHOCI	Children's Obsessional Compulsive Inventory
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
DASS	Depression Anxiety Stress Scales
DBT-WCCL	Ways of Coping Checklist
DERS	Difficulties in Emotion Regulation Scale
FAS	Verbal Fluency FAS
FFMQ	Five Facet Mindfulness Questionnaire
IES-R	Impact of Event Scale - Revised
MacLean	MacLean Questionnaire
MFQ	Mood and Feelings Questionnaire
NIMH OCD	NIMH OCD
PEAS	Physical Education Activities Scale
RLQ	Reasons for Living Questionnaire
SCARED	Screen for Child Anxiety Related Disorders
SDQ	Strenths and Difficulties Questionnaire
TASC-r	Therapeutic Alliance Scale for Children
BAT	Behavioural Avoidance Task
CARBBQ	Cognitive and Avoidant Response Bias Questionnaire
CARER-SUS	Carer Service Use Schedule
CASUS	Child and adolescent service user schedule
COIS-RP/C	The Child Obsessive Compulsive Impact Scale, revised-parent report / child report
EQ-5D	Euroquol-5D