Biopsychosocial Predictors of Paranoia in the Attenuated Psychosis Syndrome

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Abstract

Despite a consensus that psychosocial adversity plays a role in the onset of psychosis, the nature of this role and the underlying neurobiological mechanisms remain unclear. This study examined the complex relationship between perceived ethnic discrimination (PED) and paranoid ideation and its mediating factors, in individuals with Attenuated Psychotic Syndrome (APS) using a virtual reality paradigm to objectively quantify paranoia. Secondly, a sensory gating deficit, indexed by P50 Event Related Potential (ERP) abnormalities was examined, and the combined effect of electrophysiological sensory gating deficits and psycho-social adversity on the development of psychosis was explored. Results showed that perceived maternal neglect and antipathy in childhood, PED and perceived social support were key factors in young adults with APS. Also PED was positively correlated with persecutory paranoia. Furthermore, individuals with APS displayed sensory gating impairments. Therefore, perceived exposure to adverse experiences and sensory gating deficits observed in individuals with APS are present before the first episode and are consistent with current biopsychosocial models in which early psychosocial stress, later psychosocial adversity and neurocognitive functioning plays a key role in the development of psychosis.

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1. INTRODUCTION

This chapter contains a review of the literature relating to the three main areas of this thesis: firstly, psychosis and the attenuated psychosis syndrome; secondly, psychosocial adversity in psychosis; and thirdly, biomarkers for psychosis.

1.1. Introduction to Psychosis

Psychotic disorders, including schizophrenia and psychotic bipolar disorder, are amongst the most severe and enduring mental illnesses, resulting in great psycho-social and economic burden on patients, their relatives, and the community (Knapp, Mangalore, & Simon, 2004; Saunders, 2003). The diagnosis of schizophrenia and other psychotic disorders is largely based on descriptive clinical criteria, as commonly recognised by the International Classification of Disease, Tenth Edition (ICD-10) (WHO, 1992) and the Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (APA, 2013). Both non-affective and affective psychotic disorders are complex phenotypes, characterised by abnormalities in thought content and process; perception; speech; affect and behaviour; cognition; and insight. The symptoms of schizophrenia can be broadly classified into Type I and Type II symptoms (Crow, 1980). Type I are positive symptoms that generally include features of delusions, hallucinations, psychomotor over-activity and behavioural disturbance, whereas Type II are negative symptoms that comprise features such as blunted affect, reduced speech, slowness of activity, apathy and social withdrawal.

Positive symptoms such as paranoid thought content can be either delusional or overvalued in presentation, depending often on the nature, intensity and conviction

of symptoms, and the level of insight into such features. Common paranoid symptoms include perceived anxiety, fear, threats, apprehension, mistrust, ideas of persecution and conspiracy, accompanied by subjective distress and behavioural changes. Research based on surveys and formal assessments indicates that paranoid thinking occurs regularly in 15–20% of the general population (Eaton, Romanoski, Anthony, & Nestadt, 1991; Freeman et al., 2005; Olfson et al., 2002) on a continuum of severity (van Os, Verdoux, & 2003). This continuum extends from trait-like suspiciousness to non-psychotic clinical manifestations to full-blown paranoid delusions. The relationship between anxiety and psychosis has attracted considerable attention in the literature. Freeman et al, (Freeman, Garety, & Kuipers, 2001) examining the role of anxiety in the development of persecutory delusions, propose that similar themes and processes underlie both (Gilbert et al, 2005). Anxiety is a defensive reaction to the anticipation of threat and danger (physical, social or psychological); persecutory delusions are characterised by similar themes referring to perceived danger or harm from another. Paranoia also shares features with social anxiety (Freeman et al, 2005), such as social discomfort and fear of humiliation in social situations; however, paranoia is differentiated from social anxiety by the belief that other's motives are malevolent. Freeman et al (Freeman et al., 2001) argue that anxiety is inherent in paranoia and is likely to play an important role in the formation and maintenance of persecutory delusions. At the extreme end of the anxiety-paranoia continuum are well formed persecutory delusions, as commonly seen in psychotic disorders such as schizophrenia. Consistent with this continuum view, sub-threshold and clinical paranoid experiences are associated with the same risk factors (Freeman, 2007; Myin-Germeys, Krabbendam, & van Os, 2003). The presence of sub-threshold symptoms increases the likelihood of subsequent diagnosis of psychotic disorder (Poulton et al., 2000).

1.2. The Neurodevelopmental Basis of Psychosis

In spite of advances and extensive efforts in neurobiological research, the aetiology of psychosis is still far from understood as a result of problems with heterogeneity of clinical presentation, and often compounded by long term medication usage and cognitive decline, associated with the illness. There has also been a lack of conclusive and consistent findings from first episode psychosis research, which tend to mirror those of established schizophrenia. The heterogeneous clinical presentation of psychosis is more plausibly explained by models of increased complexity, taking into account a multitude of genetic and environmental factors predisposing to the development of a psychotic disorder (Bramon et al., 2013; Schmitt, Malchow, Hasan, & Falkai, 2014; Svrakic, Zorumski, Svrakic, Zwir, & Cloninger, 2013).

The neurodevelopmental theory of psychosis posits that the illness arises from the interaction of a wide range of factors at various stages of life. It is believed that susceptible individuals appear to inherit a number of at-risk genetic traits, which interact with early developmental factors, psychological impairments, chronic social adversity, ultimately making an individual susceptible to developing psychosis (Murray, Lappin, & Di Forti, 2008). Multiple factors, including the interaction of gene and environment, with cumulative effects, possibly contribute to liability to develop psychosis, as certain individuals who exceed a critical threshold, manifest the disorder, as explained by the multi-factorial liability-threshold model for psychosis (Gottesman, 1991a; Gottesman & Shields, 1967). It has been observed that close relatives of affected probands, at a genetic high risk of developing the illness, tend to have a higher mean liability of developing the disorder than the general population (Gottesman & Shields, 1967; McGue, Gottesman, & Rao, 1983). It is also

possible to adapt the model to include several thresholds, corresponding to broader versus narrower definitions of psychosis (Reich, 1975).

1.3. Clinical High Risk for Psychosis

Individuals at clinical high risk of developing psychosis are known to experience attenuated psychotic symptoms, which are below the severity, intensity and frequency of clinical symptoms, between one and five years prior to the first psychotic episode, (Beiser, Erickson, Fleming, & Iacono, 1993). Individuals presenting with sub-threshold clinical features such as attenuated or brief intermittent psychotic symptoms or even significant decline in global functioning in the presence of genetic risk factors, are clinically grouped under prodrome or 'at-risk mental states (ARMS)', although other terms such as 'clinical high risk (CHR)' or 'ultra-high risk (UHR)' are also used interchangeably (Yung et al., 2003). Recently, the 5th Edition of Diagnostic and Statistical Manual of Mental Disorders (APA, 2013) has proposed the term 'Attenuated Psychosis Syndrome (APS)' for this at-risk phase. This contemporary term has been adopted for this thesis, and the broad clinical high risk for psychosis group will be referred to as APS.

Individuals with APS appear to be at elevated risk of developing psychosis, although only a proportion of such individuals would actually make a transition to first episode psychosis. A recent meta-analysis found that a substantial proportion (20-35%) of those engaged at this stage will develop a first episode of psychosis within three years of presentation (Fusar-Poli et al., 2012), mostly schizophrenia spectrum psychoses (Fusar-Poli et al., 2013). It still remains unclear why only a small proportion of those who are highly vulnerable to psychosis actually proceed to the

illness stage. Over the last one decade there has been an interest in the exploration of factors that predict transition to psychosis.

Investigating APS has the advantage of having fewer confounders such as prescribed medication, and chronic effects of the illness itself. As previously mentioned, individuals with APS are likely to have biological vulnerabilities which interact with early developmental factors and psycho-social stressors making them susceptible to developing the disorder (Murray et al., 2008). Evidence suggests that environmental factors such as substance misuse and other psychosocial stressors, such as trauma, often trigger the onset of the illness, manifested by biological factors such as dopamine dysregulation that underlies the onset of clinical features of psychosis (Howes & Kapur, 2009). Individuals with low levels of maternal care in early childhood have showed increased striatal dopaminergic response to stressful events, providing support for the complex interaction between biological and psycho-social factors (Pruessner, Champagne, Meaney, & Dagher, 2004).

There is increasing evidence that aetiological models of psychosis need to incorporate the role of social, psychological and biological factors, and to clarify how these interact (Broome et al., 2005; Cooper, 2005; Garety, Bebbington, Fowler, Freeman, & Kuipers, 2007; Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). There is evidence for the existence of a hereditary component to psychosis from studies which reported risk of developing such schizophrenia spectrum disorders increasing with proximity of relationship to a proband (Cardno et al., 1999; Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002; Gottesman, 1991b). However, at best the risk for schizophrenia in the unaffected concordant monozygotic twin is 50% (Gottesman, 1991b). Hence, a substantial proportion of the aetiological aspects should be explained by the environmental factors. This thesis will primarily

investigate environmental factors, specifically psycho-social aspects as well as neurophysiological markers that contribute to our understanding of psychosis.

1.4. Environmental factors- Psychosocial Indices

1.4.1. Defining Stress

Stress is an ambiguous concept and its definition varies in different contexts. Early and rudimentary conceptualisations of stress define it simply as the physiological reaction of an organism to a threatening stimulus (the 'stressor'). The physiological stress response is similar across mammalian species, involving activation of two key systems: the HPA axis and the sympathetic (adrenergic) branch of the autonomic nervous system. Activation of these systems allows the organism to respond to the threat in an adaptive way. Stress is also defined as a psychological concept, in which cognitive appraisal of threatening stimuli occurs, resulting in the activation of a coping response (Lazarus, DeLongis, Folkman, & Gruen, 1985; Lazarus & Folkman, 1984). Furthermore, the term stress is commonly used in everyday language to indicate a variety of subjective mental states, including feelings of anxiety, frustration, and inability to cope with demands, in addition to its use as a euphemism for more serious mental health problems. Given that stress is such a broadly defined concept and that there is considerable inter- and intra-individual variability in the subjective experience, there are inevitable methodological limitations in its accurate assessment, and the variety of methods used to measure stress make comparison of findings across studies problematic (Lazarus & Folkman, 1984; Norman & Malla, 1993; Phillips, Francey, Edwards, & McMurray, 2007).

There is also considerable variation in the definition of different types of psychosocial stress, with some instruments focusing on 'objective' measures of exposure to specific events, for example, being assaulted, assuming that such events would indeed be stressful to all respondents, while others concentrating on the more personal, subjective experience of stress, for example, feeling unable to cope, which is likely influenced by a variety of factors like personality, mental states, and current occupational/social circumstances. Other relevant issues are the timing, frequency, and duration of stressful events, as well as previous experience of psychosocial stress, which are thought to moderate the impact of the subsequent stressful experiences. Most measures of psychosocial stress rely primarily on retrospective self-reports, and are thus susceptible to recall and other forms of bias, which becomes even more problematic if it occurs differentially across participant groups.

In this thesis, the term stress will encompass experiences encountered in the psychosocial domain that provoke feelings of distress. These experiences specifically include subjective feelings of stress related to discrimination and early childhood experiences including attachment. The following sections will focus primarily on those aspects of psycho-social stress most relevant to this thesis: (i) early adverse experiences such as perceived parental neglect; (ii) perceived stressful experiences such as discrimination. The main findings of this research will be discussed and their contributions to the current understanding of psychosocial factors in psychosis will be probed with consideration to future research and development.

1.4.1.1. Stress Vulnerability and Psychosis

Stress or emotional reactivity has been widely investigated as a possible predictor for psychosis. Cohen, Kessler and Gordon (1997) define stress as “the process in which environmental demands exceed the adaptive capacity of an organism, resulting in psychological changes that may place the person at risk to disease”. Lazarus, DeLongis, Folkman, and Gruen (1985) upheld the importance of an individual’s appraisal of his/her environment and their ability to cope with these demands. Rabkin (1980) stated, “those who become schizophrenic are believed to be exceptionally sensitive to perceived or actual threats to self-esteem” (p441).

Myin-Germeys, van Os, Schwartz, Stone and Delespaul (2001) investigated the relationship between emotional response and daily life stress in people with psychosis and their first-degree relatives. They measured subjective stress and emotional reactivity (in particular, positive and negative affect) at regular intervals in the natural flow of their daily life. As predicted, the participants with psychosis and their first-degree relatives showed more intense emotional responses to subjective appraisals of stress than control participants. They also showed increased negative affect and decreased positive affect in response to these events. These findings provide evidence that perceived stress and emotional reactivity are experienced to a greater extent in individuals with psychosis and their relatives, who are at an increased genetic risk of developing the disorder. Hence, it also would be meaningful to explore stress vulnerability in individuals with APS to determine the contribution of stress on clinical risk factors and transition to psychosis.

Research by Myin-Germeys and van Os (2007) builds on the vulnerability-stress model for schizophrenia (Zubin & Spring, 1977). In this model, vulnerability to stress

(perceived or otherwise) is viewed as a genetic predisposition, which can be mediated by certain early adverse life events, such as high levels of family stress, birth complications, childhood trauma or social adversities such as discrimination. 'Adaptation' comprises 'coping effort', 'coping competence' and the resultant 'coping ability' and these factors should be considered alongside an individual's tolerance threshold. Zubin and Spring (1977) hypothesised that an individual with a low level of coping ability will be at greater risk of developing mental illness, and their model described how individuals have differing levels of vulnerability to schizophrenia and that the illness could be controlled with preventative interventions targeting the reduction of stress and increasing coping abilities.

Nuechterlein and Dawson (1984) looked to build upon the 'stress-reactivity' model with their Dynamic Vulnerability Formulation, which emerged from similar assumptions about genetic predisposition, but used a broader framework to incorporate the interaction of appraisals, coping, stressors and symptoms. Underlying these factors is the issue of subjective interpretation, which was identified as pivotal in understanding how stress can influence schizophrenia. The individual's perception of the subjective stress is of more relevance when investigating adversity and psychotic symptoms. However, investigating objective measures, such as significant life events, can help evaluate increased risk of illness onset or exacerbation (Cohen, Kamarck, & Mermelstein, 1983). There could still be a level of unpredictability in addressing objective measures of stress alone.

To apply the stress-vulnerability model or the dynamic vulnerability formulation, an individual could experience many adverse life events and may have strong resilience to these, for example, helpful coping mechanisms and good social resources. This approach seeks to understand the development of psychosis as

resultant of biological predispositions, social climate, interpersonal relationships and the individual's psychological processes. Interpretation of events and the interplay between these factors within the individual suggests that social defeat and psychological processing are paramount in the understanding of the development of psychosis.

1.4.2. Early Adversity and Psychosis

A number of studies have investigated exposure to early adverse or traumatic experiences in people with psychosis, with sample sizes ranging from less than ten (Cohen et al., 1996) to more than three thousand individuals (Oltman & Friedman, 1965). However, differences in the methods employed by studies make direct comparison across studies difficult. The most commonly investigated adverse or traumatic experiences were sexual abuse, physical abuse, and the death of a parent or separation from a parent (Briere, Woo, McRae, Foltz, & Sitzman, 1997; Coons, Bowman, Pellow, & Schneider, 1989; Hlastala & McClellan, 2005; Rubino, Nanni, Pozzi, & Siracusano, 2009; Schofield & Balian, 1959).

A high prevalence of trauma and early adverse experiences, including physical and sexual abuse, is commonly reported in people with psychotic disorders (Read, van Os, Morrison, & Ross, 2005) and exposure to trauma or adversity is associated with both sub-clinical psychosis and psychotic disorder in adults and adolescent general population samples (Bebbington et al., 2004; Campbell & Morrison, 2007; Giesbrecht, Merckelbach, Kater, & Sluis, 2007; Gracie et al., 2007; Kelleher et al., 2008; Lataster et al., 2006; Scott et al., 2009; Shevlin, Dorahy, & Adamson, 2007a; Shevlin, Dorahy, & Adamson, 2007b; Whitfield, Dube, Felitti, & Anda, 2005; Wicks,

Hjern, Gunnell, Lewis, & Dalman, 2005). Of those studies which addressed comparisons of the prevalence of adverse or traumatic experiences with healthy control participants, most found that the rate of exposure to various early adverse or traumatic experiences was greater in individuals with psychosis (Agid et al., 1999; Friedman & Harrison, 1984; Miller & Finnerty, 1996; Morgan et al., 2007; Nettelbladt, Svensson, & Serin, 1996; Rubino et al., 2009), although this was not true for all adversities investigated within the studies, such as paternal maltreatment, sexual abuse and parental death (Fisher et al., 2010; Rubino et al., 2009). Fewer studies have investigated perceived exposure to emotional abuse/antipathy and neglect (Compton, Furman, & Kaslow, 2004; Coons et al., 1989).

Bebbington et al. (2004) found that people who experienced trauma had a fifteen times greater risk of developing psychosis, and a recent meta-analysis (Varese et al., 2012), which included studies in the general population, and those with experience of psychosis, found that an estimated attributable risk of psychosis due to adversity was 33%. Those with psychosis were found to be almost 3 times more likely to have experienced adversity than control participants (Varese et al., 2012).

Not all studies, however, observed such a relationship between early adverse experiences and psychosis measures (Colins et al., 2009; Houston, Murphy, Adamson, Stringer, & Shevlin, 2008; Minnes et al., 2008; Pribor & Dinwiddie, 1992; Rossler et al., 2007). A prospective study of a large cohort (n=1612) of children who had experienced sexual abuse found that there was no increased risk of later psychotic disorders (Spataro, Mullen, Burgess, Wells, & Moss, 2004); however, the sample consisted of abused children that had been recognised by services and

hence the findings were not necessarily representative of all children in the population who have experienced abuse, and the contact with services and any subsequent intervention could potentially have reduced any risk for psychosis associated with the abuse (Read et al., 2005).

Several studies have found that parental separation and other measures of social adversity at birth were associated with an increased risk of subsequent hospitalisation for psychotic disorders and the presence of psychotic symptoms or disorder (Higgins et al., 1997; Morgan et al., 2009; Scott et al., 2009; Whitfield et al., 2005; Wicks et al., 2005). However, two large longitudinal studies of children who were raised in a single-parent family; or were temporarily separated from their parents during the first year of life found no increased risk of subsequent development of psychosis compared with those who had not (Maki et al., 2003; Makikyro et al., 1998).

Nonetheless, there is evidence to suggest a relationship between adversity and psychosis, but whether or not such experiences constitute a causal risk factor for psychosis is still a matter of debate (Bendall, Jackson, Hulbert, & McGorry, 2008; Morgan & Fisher, 2007). It is possible that early adversity mediates the relationship between biological and other psycho-social factors and subsequent psychosis.

1.4.3. Attachment and Psychosis

One prominent area of adversity research has focussed on attachment relationships. According to Bowlby (1977), experiences of important relationships, beginning with the main carers in infancy and childhood, shape an individual's

longstanding perspective of him/her and others around. Bowlby (1982) described the experiences as internalised concepts through which the expectations for future relationships operate. Insecure attachment style, indicating that the individual lacked a consistent and comforting 'secure base' from their closest relationships has been found to be more prevalent in people with psychosis than amongst controls (Ainsworth, Blehar, Waters, & Wall, 1978; Dozier, 1990). Mickelson et al. (1997) in a national co-morbidity survey found that psychosis predicted insecure attachment. Research in large student samples also suggests insecure attachment style predicts paranoid thinking (Pickering, Simpson, & Bentall, 2008), and both paranoia and social anhedonia (Berry, Wearden, Barrowclough, & Liversidge, 2006). Insecure attachment is also found to be a predictor of paranoia, regardless of diagnosis (Read, Agar, Argyle, & Aderhold, 2003; Ross, Anderson, & Clark, 1994; Shevlin et al., 2007b), supporting the view that early adversity increases vulnerability to attenuated psychotic features.

Specific aspects of family relationships or behaviours have also been found to indicate likelihood of developing psychosis, and may also be an indication of the attachment problems observed alongside the diagnosis of psychosis. Growing up and living within a disruptive family environment with high expressed emotions is believed to increase risk and clinical outcomes and prognosis in psychosis (Docherty, Cutting, & Bers, 1998; Lim, Chong, & Keefe, 2009).

While a considerable proportion of the studies described above provided support for an association between adverse or traumatic experiences and psychosis, the design of the majority of these studies was cross-sectional and retrospective. Thus so the occurrence of the relevant adverse or traumatic event in relation to the onset of full

blown psychotic symptoms could not always be established. Recall bias is also a factor that potentially impacts on retrospective perceptions. Thus, it cannot be assumed that the adverse or traumatic experiences occurred before the onset of psychotic symptoms; hence it is not possible to draw definitive conclusions regarding causality and predictive factors.

However, people with psychosis have been shown to be at greater risk of subsequent victimisation than those without psychosis (Goodman, Rosenberg, Mueser, & Drake, 1997), and social maladjustment has been observed during childhood in people who later go on to develop psychosis (Done, Crow, Johnstone, & Sacker, 1994) so it remains possible that psychosis risk might manifest as increased vulnerability to psychosocial stress. Another possibility is that the associations reported between psychosis and adversity might be due to other latent factors, for example, poverty, familial genetic risk or cognitive and emotional processing. Indeed, parental mental health problems have been found to be associated with an increased risk of abuse in the children (Walsh, MacMillan, & Jamieson, 2002), possibly due to both genetic and psycho-social factors. Nevertheless, compelling support for a causal association comes from the results of the NEMESIS study (n=4045) (Janssen et al., 2004) in The Netherlands and the EDSP study in Germany (n=2024) (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006). These prospective population-based studies found that exposure to childhood adversity (emotional, physical, and sexual; NEMESIS) and lifetime trauma (including sexual and physical abuse; EDSP) at baseline significantly increased the risk of subsequent development of psychosis assessed at follow up (Janssen, et al., 2004; Spauwen, et al., 2006). The dose-response nature of the association between baseline adversity and subsequent psychosis, such that risk increases linearly with

number of adversities, suggests a possible causal role for adversity in the onset of the illness.

1.4.4. Early Adversity in the Context of APS

The development of criteria to identify people at high risk of developing psychosis has provided the opportunity to explore prospectively whether early adverse or traumatic experiences are present in at-risk populations who might go on to make a transition to psychosis in the future. Studies with relatively small samples, employing the clinical high risk criteria, have examined the prevalence of traumatic experiences and found higher rates of exposure to trauma in those with APS (Bechdolf et al., 2010; Thompson et al., 2009; Tikka et al., 2013). Out of 30 participants at clinical high risk, 27 had experienced at least one traumatic event (Thompson et al., 2009). Physical, sexual, and emotional abuse were reported by 83, 27, and 67 per cent of the sample, respectively. While the rates of reported trauma appear high, it was not clear whether or not this was exceptional for an inner-city area, as no information was collected from a geographically matched control sample, although an association between trauma history and presenting symptoms was reported (Thompson et al., 2009). However, this high rate of exposure to trauma was replicated in a more recent study by Bechdolf et al. (2010), in which traumatic experiences were assessed in a sample of 92 people at clinical high risk for psychosis. Sixty-four (69.7%) of these participants had a history of trauma, as assessed by their care manager, with 26, 28, and 24 percent reporting physical abuse, sexual abuse, and neglect, respectively. Exposure to childhood sexual abuse was found to be associated with transition to psychosis over a mean 615 day follow up, after controlling for other clinical factors related to transition (OR=2.96, 95% CI: 1.16-7.57). Tikka et al (2013) also reported more childhood

trauma experiences and poorer premorbid adjustment in individuals at-risk for psychosis than controls. In individuals at-risk, emotional abuse was associated with poor general premorbid adjustment (Tikka et al., 2013). Addington et al (2013) found that individuals with APS reported significantly more trauma and bullying than healthy controls, and trauma was observed to be highly correlated with perceived discrimination. Those who had experienced past trauma were more likely to have increased levels of depression, anxiety and a poorer sense of self (Addington, Stowkowy et al., 2013).

Furthermore, Falukozi and Addington (2012) investigated the relationship between trauma and the content of attenuated psychotic symptoms in individuals with APS. They found significant positive relationships between increased trauma and feeling watched or followed. At face value these findings suggest that those with a history of increased trauma may feel the need to be more aware of their surroundings. Although this was a small sample (n= 45), these findings support the possibility of a meaningful relationship between experiences of trauma and the content of attenuated positive symptoms. These studies provide further support for trauma and adversity as risk factors for the onset of psychosis.

Nonetheless, not all individuals exposed to adversity and childhood abuse go on to develop psychotic experiences or a psychotic disorder. Identifying the intervening factors that modify these relationships is an important next step in elucidating the mechanisms by which negative experiences in childhood might contribute to risk. A number of possibilities have been proposed. For example, exposure to adversity and abuse in childhood may confer an enduring vulnerability to psychosis (and

indeed other disorders) via deleterious effects on biological (van Winkel, Stefanis, & Myin-Germeys, 2008) (such as hypothalamic–pituitary–adrenal axis function (Borges, Gayer-Anderson, & Mondelli, 2013) and psychological (Bentall & Fernyhough, 2008) (such as affect and emotion (Fisher et al., 2013)) processes. This vulnerability might then manifest as low-level psychotic experiences and, more rarely, psychotic disorders, in the event of exposure to further risk factors over time, such as, for example, subsequent life events (Beards et al., 2013) and cannabis use (Moore et al., 2007). Both life events and cannabis use to varying degrees have been linked with psychosis and, as such, are strong candidate exposures that may have more pronounced effects in those with a pre-existing vulnerability (Harley et al., 2010; Lataster, Myin-Germeys, Lieb, Wittchen, & van Os, 2012; Morgan et al., 2014). However, research on combined or synergistic effects of childhood adversity and other environmental exposures in psychosis remains underdeveloped (Morgan et al., 2014). By studying the APS sample, it may be possible to study the content of attenuated or sub-threshold symptoms in the context of past experiences and synergistic effects of adversity and other environmental exposures, shedding light on the development of symptoms in the early stages of psychosis.

1.5. Social defeat

Selten and Cantor-Graae (2005) and later Veling (2007) identified an individual's perception of 'social defeat' as a mechanism facilitating the link between aversive psychosocial events and the potential for developing psychosis. The social defeat hypothesis proposes that defeat is a subjective interpretation, and that if an individual appraises the circumstances as uncontrollable, it would leave them prone to developing mental disorders. Social factors such as belonging to a minority

ethnic group, bullying, childhood separation, discrimination, migration and living in an urban area can be viewed as stressors linked to an increased risk of psychosis. It has been proposed that the cumulative effect of prolonged exposure to such social stressors may lead to 'social defeat' (Selten & Cantor-Graae, 2005; Wicks et al., 2005). According to this model, social adversity and exclusion lead to a 'subordinate' or 'outsider' status appraised by the individual as stressful. Studies have shown that lower perceived social rank is associated with paranoid ideations (Freeman et al., 2005; Gilbert, Boxall, Cheung, & Irons, 2005) and perception of lower social rank and inferiority has been found in individuals with early psychosis (Allison, Harrop, & Ellett, 2013).

However, the underlying mechanisms by which stressful life events and daily stressors influence the onset of psychosis and paranoia are still unknown. In particular, it is important to study not only the occurrence of stressful events but also how these stressful events are appraised by the individuals, since events that are experienced as humiliating defeats or as entrapping may leave individuals perceiving themselves as powerless and may be more likely to lead to psychopathology (Brown, Harris, & Hepworth, 1995).

Appraisal plays a central role in cognitive models of psychosis, which propose that earlier stressful events may result in a cognitive vulnerability, influencing the interpretation and appraisal of daily stressors, and increasing the likelihood that anomalous experiences develop into a psychotic disorder (Bentall, Fernyhough, Morrison, Lewis, & Corcoran, 2007; Freeman, 2007; Freeman & Garety, 2002; Garety et al., 2001).

1.5.1. Discrimination and Risk of Psychosis

Discrimination can be defined as the prejudicial treatment of an individual or group based on certain characteristics such as ethnicity, immigration status, age and sex (Veling et al., 2007). It has many facets and can be found in opinions, attitudes and behaviours, and may be measured by objective events or by subjective perceptions of events (Meyer, 2003). Discrimination in the real world may be difficult to determine objectively, as it is defined in part by intentions and can be actual or perceived. Thus, in research settings, perceived or subjective experiences of discrimination are measured because of the difficulties in accurately assessing levels of objective or actual discrimination (Berg et al., 2011). There is support that it is perceived discrimination itself and not necessarily actual discrimination that is associated with mental illness (Kessler, Mickelson, & Williams, 1999).

Some studies have shown the importance of social discrimination in increasing the vulnerability to illness. The concept of social defeat appears to be closely related to migration status, particularly amongst ethnic minority groups (Lim et al., 2009). Veling (2007) identified a link between migrant status and psychosis, in particular for people immigrating from developing countries. However, they found that it was not necessarily due to the social factors of adjusting to another culture that created a vulnerability to psychosis; rather it was associated with the level of discrimination experienced in the host country. With respect to psychosis a prospective Dutch population study by Janssen et al. (2003) demonstrated that a chronic experience of discrimination may eventually lead to a paranoid attributional style and consequently increase the likelihood of psychotic-like experiences. They identified age, sex, appearance, sexual orientation and disabilities as significant discriminating factors associated with risk of paranoid delusions (Janssen et al., 2003). Additional studies

have demonstrated significant associations between perceived discrimination and psychosis in ethnic minority and immigrant groups, with the incidence of psychosis being higher when groups perceive more discrimination (Karlsen, Nazroo, McKenzie, Bhui, & Weich, 2005; Veling et al., 2007). Furthermore, incidence rates of psychosis have been shown to be equal among first and second-generation immigrants, indicating that post immigration stressors are equally as important as pre-migration (Morgan & Hutchinson, 2009; Seeman, 2011). Interestingly, bullying has also been found to be positively associated with experiencing sub-threshold psychotic symptoms in the general population (Bebbington et al., 2004; Campbell & Morrison, 2007). In light of the various forms of adversity and experience of discrimination, it has been suggested that a more general problem of social defeat could be an important aspect in individuals with APS (Selten & Cantor-Graae, 2005).

1.5.2. Perceived Ethnic Discrimination

Perceived ethnic discrimination (PED) is considered to be the subjective experience of differential treatment based on appearance, language, religious or socio-cultural characteristics. As it emphasises appraisal, PED is not limited to "objective" discriminatory occurrences but may also include more subtle experiences that outside observers might not identify as discrimination (Clark, Anderson, Clark, & Williams, 1999). PED has been found to be associated with a number of negative health outcomes for ethnic minorities and immigrant groups (Pascoe & Smart Richman, 2009). In recent years, the focus of research has shifted to the understanding of mechanisms of the relationship between PED and psychological functioning. In particular, the concept of social defeat and stress-vulnerability highlights how individual difference variables may influence how people perceive, respond to, and are affected by discrimination. The current interest in prospective

research that examines individuals with APS (McGlashan, Walsh, & Woods, 2010), offers an opportunity to examine the role of perceived ethnic discrimination in the development of psychosis.

1.6. Psycho-Social Risk Factors in the Context of Cognitive Models for Psychosis

1.6.1. Early Adversity and Cognitive Development

Problems in attachment and family environment can be especially confusing and distressing for children, as they are ill equipped to cope with such adversity. These experiences can lead to long-term emotional impact and reduce the individuals' resilience as an adult. Some researchers have sought to understand how these psychological processes become so rigid, leading to internal and often unpleasant experiences, which are divorced from the external reality. Bremner and Narayan (1998) stated that people who experienced adversity in their early developmental years had a lower level of encoding such memory and therefore a more confused and emotionally heightened response to the stressor. Brewin, Dalgleish and Joseph (1996) investigated why early stages of development restrict coping ability for interpersonal environmental adversity, and observed that emotional processing prior to the maturation of language could result in non-conscious processing of sensory experiences, including physiological arousal. This situationally accessible memory (SAM), or physiological arousal memory, would be reactivated on recurrence of the related stimuli to the original experience (Bremner & Narayan, 1998; Brewin et al., 1996). This progressive re-experience would thereby contribute to the psychological development of the individual, and influence interpretations of events in later life.

1.6.2. Adversity, Cognitive Biases and Positive Symptoms of Psychosis

The cognitive approach focuses on positive clinical features such as paranoid thinking, which profoundly impacts upon an individual, and can be determined by their past experiences, general beliefs about oneself and others, and current and past psycho-social stressors. Therefore an individual's appraisals, attributions and schemas are important cognitive areas, which merit further investigation in those at risk of developing psychosis to unravel the complex psychosocial basis of psychotic disorders.

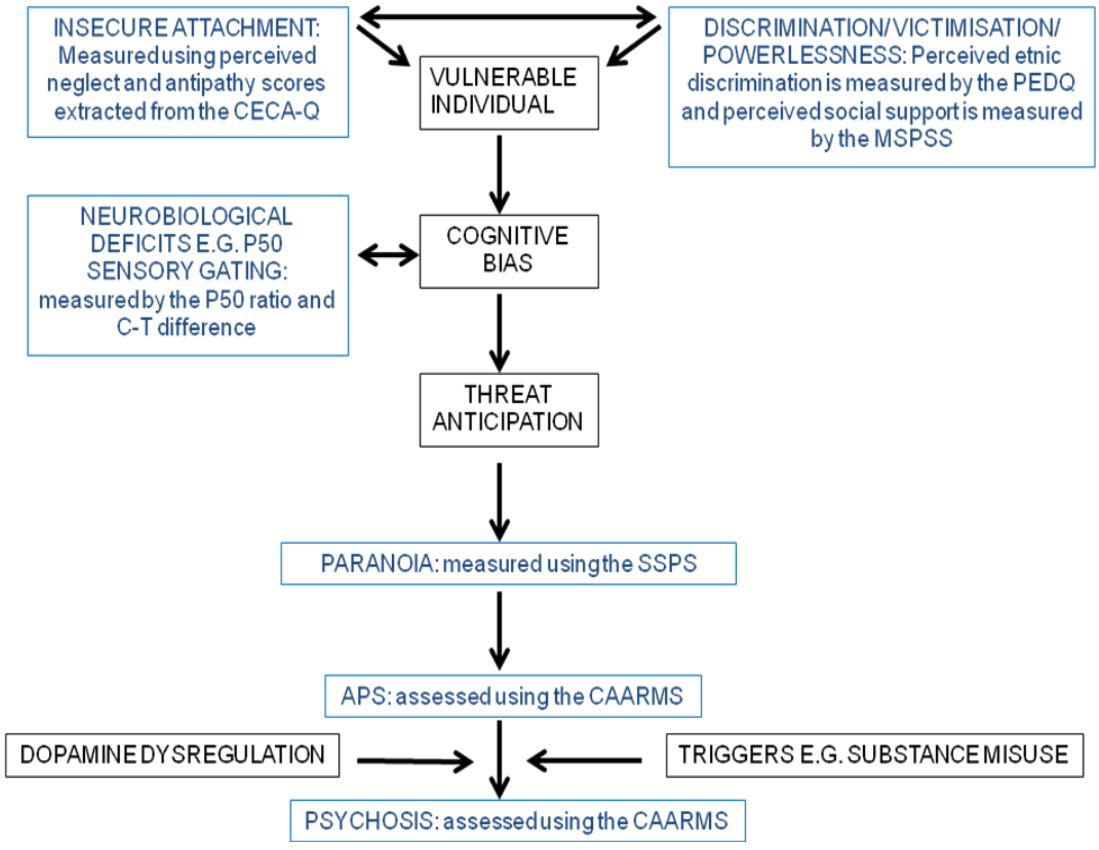
Garety and Freeman (1999) explored appraisal tendencies amongst people with psychosis and found that jumping to conclusions, externalising, and discrepancies in understanding social cues were common biases in thinking. Morrison's (2001), and Freeman and Garety's (2002) cognitive models of psychosis describe how the physiological and somatic experiences, and appraisals of these had an interdependent relationship, leading to perpetuation and occasional increase in selective attention, misattributions, emotional, physiological and behavioural responses due to the continuation of these positive symptoms.

Morrison et al. (2003) formulated an integrated model combining three different cognitive models [Ehlers and Clark's (2000) model of PTSD; Wells and Mathews (1994) self-reference model (S-REF)' and Morrison's (2001) model of psychosis] in order to illustrate the cognitive processes that explain the link between adversity and psychosis. This model illustrates links between intrusive experiences and 'culturally unacceptable interpretations', 'faulty self and social knowledge', 'mood and physiology', 'cognitive and behavioural responses' and 'experience' as the individual exists within their environment. 'Culturally unacceptable interpretations' refer to

unusual interpretations of real or imagined events and tend to distinguish individuals with psychosis from the general population. These interpretations may have developed in order to make sense of unusual experiences or could result from interpretation of bias within the individual. 'Faulty self and social knowledge' refers to maladaptive beliefs that the individuals hold about themselves and others that in turn shapes their perspective and interpretations of real or imagined events. The inclusion of 'mood and physiology' in this model is important, as both these elements can affect the importance an individual places on certain experiences. It summarises how the persistence of adverse experiences could lead an individual to form delusional interpretations whilst accounting for these unpleasant events. This would occur within the context of a predisposed and understandable paranoia secondary to social adversity, and these appraisals could become unusual to the extent of being delusional in intensity and conviction (refer to Figure 1-1).

For example, a trauma in childhood and subsequent experiences of victimisation and discrimination, could lead one to suffer from low self-esteem, and view oneself as vulnerable. An individual may also believe the world around him/her to be unpredictable and threatening, which could lead to paranoia. The individual's past 'experience' and understanding can feed into his/her schemas, contributing to maladaptive beliefs and supporting an attentional bias to notice similar experiences in the present and future. This hyper-vigilance could be an adapted 'self-preservation' strategy to future perceived threats. Frequent experiences of this could lead to a search for meaning where the interpretations can become delusional. This model highlights the importance of interpretations of unusual experiences in relation to established schemas and the on-going internal and environmental experience.

Figure 1-1: A model illustrating the pathway between adversity and paranoia incorporating psychosocial and biological factors. Constructs tested in the current study are highlighted in blue.



1.7. Neurobiological markers for psychosis

As discussed previously, earlier psychosis risk syndrome studies showed conversion rates to psychosis of up to 40% (Yung et al., 2003) with a high number of patients of 60% (McGorry et al., 2009) or more who did not convert to psychosis during the observation period. Thus, adding specific predictors and biomarkers to the clinical psychosis risk syndrome approach that could increase the predictive power of current APS criteria and enhance the ability to predict outcomes is a crucial step for early recognition and intervention efforts (Keshavan, Berger, Zipursky, Wood, & Pantelis, 2005; Ruhrmann et al., 2010; Shah et al., 2012). The term

endophenotypes is used to describe markers that are biological or clinical characteristics associated with a disease that can be easily, objectively and reliably measured as quantitative traits. A variety of potential endophenotypes including neuroimaging, electrophysiological and cognitive markers for schizophrenia have been proposed and investigated, though none have yet been confirmed in large, unselected samples of individuals at risk (Cannon & Keller, 2006; Greenwood et al., 2007; Gur et al., 2007; Nasrallah, Tandon, & Keshavan, 2011; Turetsky et al., 2007). These include disturbances in eye tracking movements (Bittencourt et al., 2013), deviances in neural structures such as grey matter and hippocampal volume reductions (Brent, Thermenos, Keshavan, & Seidman, 2013; Haukvik, Hartberg, & Agartz, 2013; Xiao, Zhang, Lui, Yao, & Gong, 2013), neurocognitive traits such as deficits in episodic memory, working memory, executive function, attention and IQ (Allen, Griss, Folley, Hawkins, & Pearlson, 2009; Kalkstein, Hurford, & Gur, 2011; Nuechterlein et al., 2012), and symptom clusters or dimensions (Dikeos et al., 2006; Ivleva et al., 2010; Potuzak, Ravichandran, Lewandowski, Ongur, & Cohen, 2012; Wickham et al., 2001).

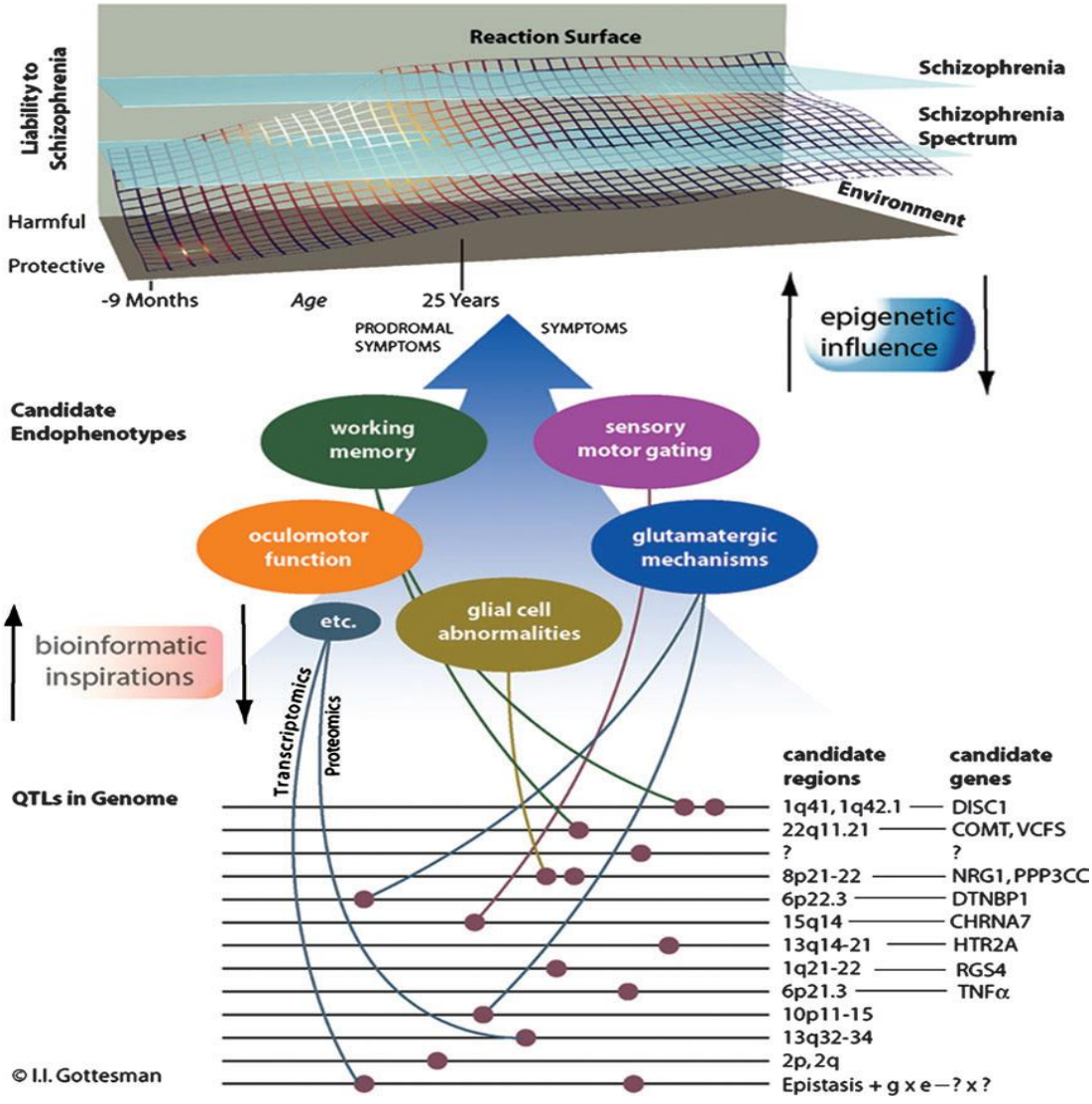
Endophenotypes are heritable traits which lie on the pathway between the genes and the diagnosis in question (Gottesman & Gould, 2003). Endophenotypes vary quantitatively among individuals at risk for the disorder, regardless of whether the illness is expressed phenotypically. While endophenotypes, illness and risk factors that are more closely related to the underlying biology of a disease have been investigated in schizophrenia (Allen et al., 2009), this field of study is more recent in the area of APS research and can help to bridge the gap between genetic and environmental research and the psychiatric diagnosis (Cannon, Gasperoni, van Erp, & Rosso, 2001).

One informative method used in the assessment of biomarkers is the longitudinal design, comparing the level of deviance or impairment on proposed traits before and after the onset of illness, ideally using individuals with APS. Genuinely useful markers should show deviance at both times. A marker that truly reflects a biological trait as opposed to an aspect of psychopathology or state characteristic should be relatively stable and unaffected by symptom exacerbation, severity of illness or medication effects throughout the course of an illness, and indeed the lifetime of a patient.

It is well known that psychotic disorders like schizophrenia have a complex neurodevelopmental basis, with deviations in brain development and function (Murray et al., 2004) that occur well before the emergence of psychotic symptoms. Electroencephalography (EEG) measures ongoing electrical brain activity, and provides a possible basis for biomarkers/endophenotypes of brain function associated with psychosis (Blackwood et al., 2001; Hall, Taylor, Salisbury, & Levy, 2011; Sumich et al., 2006). Some event-related potentials have been shown to be promising markers for psychotic disorders (Bramon et al., 2005; Decoster et al., 2012; Shaikh et al., 2013; Tang et al., 2007; Turetsky et al., 2008) including the P50 event related potential which is investigated and discussed in this thesis. An illustration of the position of endophenotypes on the hypothesised pathway between candidate genes and liability to schizophrenia is outlined in Figure 1-2.

Figure 1-2: From genes, to endophenotypes, to the schizophrenia phenotype

The reaction surface suggests the dynamic developmental interplay among genetic, environmental, and epigenetic factors that produce cumulative liability to developing schizophrenia. A heuristic model of the developmental pathway to schizophrenia from Gottesman et al (2003).



1.7.1. P50 event related potential (ERP) in psychosis

ERPs are small electrical voltage fluctuations in the EEG produced by the brain in response to a stimulus that are time-locked to sensory, motor or cognitive events, reflecting underlying neural network activity and helping to understand the

neurophysiological correlates of such events. ERP waveform consists of a pattern of waves or components, which can be characterised and quantified by their latency, amplitude and scalp distribution. P50 wave is a pre-attentional component of the middle latency auditory evoked potentials recorded about 50 ms after the presentation of an auditory stimulus. P50 sensory gating is typically quantified by computing a ratio of evoked amplitudes to auditory clicks in a paired-click design (de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007; Shaikh et al., 2010b) and an impairment is characterised as a decrease in amplitude when a second stimulus (S2), identical to the first stimulus (S1), is delivered about 500 ms later (Turetsky et al., 2007). This amplitude suppression of the wave evoked by the second stimulus (S2) reflects a sensory gating mechanism aimed at protecting against information overload, (Braff & Geyer, 1990) and a P50 deficit suggests that there is an abnormality that affects very early stages of information processing (Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004; Waldo et al., 2000). Impairment of auditory P50 gating has been observed in a variety of clinical populations, including individuals with traumatic brain injury (Arciniegas et al., 2000), Alzheimer's disease (Jessen et al., 2001), panic disorder (Ghisolfi et al., 2006), and Huntington's disease (Uc, Skinner, Rodnitzky, & Garcia-Rill, 2003).

1.7.1.1. P50 Sensory Gating in Schizophrenia

The most notable findings are in schizophrenia (Olincy et al., 2000b; Patterson et al., 2008), for which P50 suppression has been investigated as a potential endophenotype (Freedman et al., 1996b; Lu et al., 2007; Myles-Worsley, 2002; Sanchez-Morla et al., 2008; Shaikh et al., 2010b). Patients with schizophrenia and about 50% of their unaffected first-degree relatives have impaired sensory gating

(Adler, Hoffer, Griffith, Waldo, & Freedman, 1992; Clementz, Geyer, & Braff, 1998b; Myles-Worsley, Ord, Blailes, Ngiralmau, & Freedman, 2004; Shaikh et al., 2010b; Siegel, Waldo, Mizner, Adler, & Freedman, 1984b; Waldo et al., 1994). There is some controversy regarding whether or not the schizophrenia-related deficit represents a 'gating' phenomenon. Some studies have reported that the amplitude from the second stimulus is the same in patients and controls, while the amplitude and/or latency for the first stimulus is altered in patients, perhaps accounting for the decreased ratio (Jin & Potkin, 1996; Jin et al., 1997). A meta-analysis examining the P50 suppression in patients with schizophrenia and controls showed that severe P50 gating deficits exist in schizophrenia with a pooled effect size of 1.6 (standardised difference between the two group means) (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004).

1.7.1.2. P50 Sensory Gating in APS

Studies have also shown that P50 gating is already impaired in the early stages of schizophrenia. Myles-Worsley et al. (2004) compared a genetically defined high-risk group and a clinically defined sample of at-risk adolescents, and showed that P50 suppression was impaired in both groups. Yet, in the genetically high-risk group, P50 suppression abnormalities were found only in those with clinically-defined prodromal symptoms. Cadenhead et al. (2005) showed that subjects at risk of developing psychosis with a first-degree relative with schizophrenia had statistically significant lower levels of P50 suppression relative to control subjects. Furthermore Brockhaus-Dumke et al. (2008) found that P50 gating deficits are present in high risk individuals who later convert to psychosis, and amongst drug-naïve first-episode patients in comparison to control subjects.

Disrupted P50 gating is not, however, limited to clinical populations. Individual differences in P50 gating have been demonstrated in healthy adults, with some participants' gating scores falling within the range of those observed in individuals with schizophrenia (Patterson et al., 2008). Relatively little is known, however, about the functional consequences of poor sensory gating and especially lacking are data relating P50 gating to measures of cognitive and emotional functioning (Potter, Summerfelt, Gold, & Buchanan, 2006; Sanchez-Morla et al., 2012) and psycho-social influences.

1.7.2. Cognitive Basis of P50 Sensory Gating

Cognitive inhibition is a multidimensional construct (Kramer, Humphrey, Larish, Logan, & Strayer, 1994) that is believed to underlie performance on tasks that require the restriction of attentional access, deletion of no-longer-relevant information from attention and working memory, and restraint over habitual response tendencies (Gorfein & MacLeod, 2007). It has been suggested that sensory overload produces downstream effects on cognition (Venables, 1964) and that a failure of the P50 filtering mechanism may lead to perceptual, attentional, or other cognitive difficulties. For instance, healthy individuals with poorer auditory P50 gating are more likely to report feeling overwhelmed or bombarded with auditory stimuli from the environment (Kisley, Noecker, & Guinther, 2004). Similarly, patients with schizophrenia report being overwhelmed by sensory stimuli from the environment; this may be due to fundamental attentional and inhibitory deficits (McGhie & Chapman, 1961) but can also be related to emotional processing. Sensory overload may affect cognition, for example, when unfiltered sensory stimuli

compete with other stimuli or goals for limited attentional resources. Indeed, if sensory gating is perturbed, the failure to filter sensory information may have fairly broad consequences, possibly including perceptual and cognitive biases leading to misinterpretation (refer to Figure 1-1).

Few published studies have examined the relationship between sensory gating and cognitive processes. The primary cognitive process that has been evaluated is attention. The findings suggest that at least for patients with schizophrenia, attentional processes such as shifting, distraction resolution, and vigilance may share some underlying mechanisms with sensory gating (Cullum et al., 1993; Erwin, Turetsky, Moberg, Gur, & Gur, 1998; Guterman & Josiassen, 1994; Guterman, Josiassen, & Bashore, 1992; Salthouse, 1996). However a recent study found no evidence of an association between P50 ratio and a set of cognitive measures in schizophrenia patients or in healthy controls (Sanchez-Morla et al., 2012). Additional research is necessary that examines theoretically relevant cognitive and emotional processes and psychosocial factors that impact cognition and involving pre-clinical samples such as APS seems critical, in that medication status and/or other clinical features present in the studied samples of individuals with schizophrenia may have influenced the observed relationships between P50 gating and cognition.

A critical issue is the need for accurate and robust techniques for prospectively identifying individuals at highest risk for conversion. Prediction has been complicated by the multifactorial aetiology of psychosis, the interaction of socioenvironmental factors with biological and psychological ones and the breadth of nonspecific psychopathology that precedes psychosis (Keshavan et al., 2008).

Given that diverse risk factors at various developmental stages have relevance for subsequent development of psychosis, models that take into account relationships between factors may offer a powerful approach for optimizing risk ascertainment. Investigating the P50 ERP as a potential biological marker in relation to psycho-social adversity might help to bridge the gap and to understand the complex relationship between biological and psycho-social risk factors in individuals at clinical risk for psychosis and provide greater predictive power for psychosis development than each individual factor alone.

1.8. Summary and Aims

Despite advances in the treatment of psychotic disorders over the past half-century, the illness is frequently associated with a poor outcome (Cornblatt et al., 2007). This is principally related to the late identification and intervention in the course of the illness and patients have experienced a substantial amount of socio-occupational decline that can be difficult to reverse (Boonstra et al., 2012). Based on the understanding of underlying psycho-social mechanisms, including stressors such as social defeat, perceived ethnic discrimination and markers of cognitive dysfunction that influence paranoid thinking, it seems plausible to explore these complex relationships in those at clinical risk of developing psychosis in order to understand not only the aetiological basis but also to be able to use such information for predictive and preventative strategies and evaluating treatments that can prevent transition to psychosis in these high risk groups.

It can be hypothesised that adverse experience affects emotional and cognitive development, thereby leading to symptoms (refer to figure 1-1). Perceived ethnic

discrimination (PED), as previously mentioned, is an important stressor that is associated with heightened risk for psychosis and with the positive symptoms of delusions and overvalued paranoid ideation (Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001; Berg et al., 2011; Janssen et al., 2003; Veling et al., 2007). Early adverse experiences such as insecure attachments have also been associated with paranoid beliefs (Pickering et al., 2008) and are postulated to create an enduring cognitive vulnerability, characterised by negative schematic models of the self and others (e.g. I am vulnerable, others are dangerous) (Fowler, 2000; Garety et al., 2001), thereby increasing sensitivity to threat. Although the experience of different types of adversity in general can be a strong predictor of the development of psychosis, PED as one type of adversity in particular has not attracted a great deal of investigation.

It is likely that early or past experiences influence the development of schemas based around power, subordination and threat, and that the individual will respond to new experiences according to these beliefs. PED might trigger these negative schematic beliefs formed from early attachment and social support experiences; cause emotional distress' make one more vigilant to threat; and give rise to a paranoid attributional style and possibly cognitive deficits and higher rates of paranoid ideation.

Currently there is no research examining the complex relationship between PED and paranoid ideation and its mediating factors, especially in individuals with APS. This thesis seeks to assess these factors in a sample of individuals with APS, compared to matched healthy control participants using a virtual reality paradigm to objectively quantify paranoia. For clarity the thesis has been split into two parts. Data from the virtual reality paradigm is referred to as part one.

This thesis also includes a second sub study (part two) that examines the role P50 ERP abnormalities play in the aetiology of psychosis, and whether it can provide a biomarker for the illness. The concept of multilevel markers has been discussed by Cannon and Keller (2006) and they have argued that various potential markers representing different steps on the pathway between genes and the disorder as seen in Figure 1-2 may well be inter-related and influence one another. Thus, it would be advantageous to measure markers or endophenotypes at several levels, that is across behavioural, emotional, anatomical, neuropsychological and neurochemical levels. Applying this line of investigation might in the future also further the understanding of the aetiology of electrophysiological deviances and shed light on the question whether similarities in ERP abnormalities observed across different diagnostic groups (APS vs first episode psychosis) share similar aetiologies or if they reflect the outcome of distinct pathophysiological mechanisms and psycho-social influences. Therefore research that aims to integrate electrophysiology and psycho-social adversity (e.g. P50 ERP and PED) is the first step towards exploring synergistic effects on the development of psychosis. This is a potentially powerful way to advance our understanding of brain abnormalities and the psycho-social basis of psychosis.

1.9. Hypotheses

Part One

(a) Compared to controls the APS sample will report higher levels of perceived ethnic discrimination, lower levels of social support, and differences in early attachment.

(b) There will be a positive correlation between perceived ethnic discrimination and persecutory paranoid ideation measured via a virtual reality paradigm in the whole sample.

(c) Perceived ethnic discrimination and persecutory paranoid ideation in VR will be positively correlated in the APS group.

(d) The relationship between perceived ethnic discrimination and persecutory paranoid ideation in VR will be mediated by prodromal symptomatology in the APS group

(e) Perceptions of early attachment, levels of social support and positive prodromal symptomatology will mediate the relationship between perceived discrimination and persecutory paranoid ideation in VR.

Part Two

(f) The APS sample will be more impaired on P50 ERP indices in comparison to controls.

(g) Impaired sensory gating measured the P50 ERP will be positively correlated with persecutory paranoia and perceived ethnic discrimination in individuals with APS.

2. METHODOLOGY

2.1. Design

Part One: A cross sectional comparison between APS and controls was suited to explore the hypotheses based on correlations and associations within and between groups. The dependant variable was paranoid persecutory ideation in VR and the primary independent variable was perceived ethnic discrimination. Positive prodromal symptomatology was also used as either an additional independent variable or a mediator variable depending on the hypothesis in question. In addition, perceived maternal neglect and antipathy and perceived social support were included as co-variates to understand the relationship between the dependant and independent variables.

Part Two: A cross sectional design was used to investigate between group differences of the P50 ERP primarily. A longitudinal design for the analysis of P50 ERP in the APS group was also used as follow up data including transition to psychosis was available. Of the APS individuals who completed the follow up (n=36), nine (25%) developed psychosis as defined by the presence of at least 1 positive psychotic symptom at high severity for more than 1 week (Yung et al., 2005). This allowed for analysis comparing the P50 ERP between the APS group and those who made a transition to psychosis over time. Due to the small sample overlapping across ERP (part two) and VR measures (part one) (n=10), a within subject design was used to investigate the associations between sensory gating (P50) and persecutory paranoid ideation in VR in the APS.

2.2. Ethics

The VR study (REC no. 08/H0722/45) and EEG study (REC no. 285/01) were approved by the joint South London and Maudsley NHS Trust/Institute of Psychiatry Research Ethics Committee and Royal Holloway Ethics Committee (2013/025).

It was made clear to participants, both in the information sheet and during discussion, that their participation was entirely voluntary and that they retained the right to withdraw from the study at any time without a reason; that any information provided would be treated in accordance with the Data Protection Act 1998; that information would be stored in a locked filing cabinet at the Institute of Psychiatry and anonymised information would be entered into a password-protected database; and that, for APS clients, participation in the study would in no way affect the clinical care provided by the team.

2.3. Participants

2.3.1. Part One- Virtual Reality

Part one is a sub study that is part of a larger research project designed to investigate psychological, social and biological predictors for psychosis and to better understand the APS. This sub study used archival data from the Outreach and Support in South London (OASIS) service. I have not, however, directly been involved in the data collection for the virtual reality paradigm and relevant questionnaire data. My contributions to this sample and overall project involve

recruitment and screening of healthy controls, EEG data collection, signal processing of raw EEG data, and analysis extracting evoked related potentials for the arm of the larger study exploring biological predictors for psychosis. My specific contributions and involvement are outlined in the relevant sections in relation to part two.

Sixty-five APS participants were recruited via OASIS, a specialised service for young people at risk of psychosis (Fusar-Poli et al., 2012). All participants recruited to the study were over 18 years old and reported not having ever experienced a psychotic episode. The participants were managed clinically at OASIS, the catchment area of which included the boroughs served by South London and Maudsley NHS Trust. APS participants were assessed by this service prior to participation in the research, using the Comprehensive Assessment of the At-Risk Mental State (CAARMS) assessment tool, which is based on the criteria developed by Yung and colleagues (1998) to operationally define a set of clinical features that precede a first psychotic episode (Phillips, Yung, & McGorry, 2000; Yung et al., 2003). The criteria identify young people (14-35 years old) at risk of developing psychosis by assessing psychotic-like symptoms, multiple risk factors and the clinical need for care. Previous studies indicate that around 35 per cent of these individuals deemed to be at risk using the above criteria would develop psychosis within 12 months (Cannon et al., 2008; Fusar-Poli et al., 2012; Yung et al., 2003).

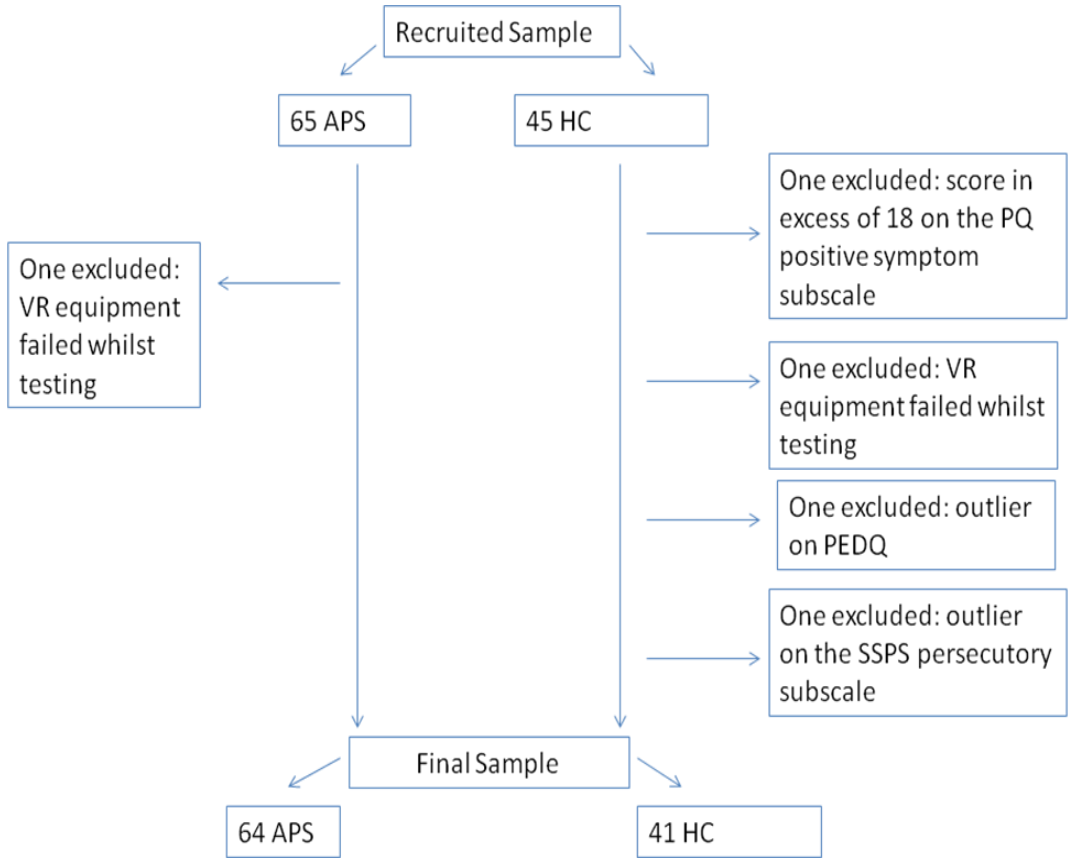
APS participants met one or more of the following criteria, assessed with the CAARMS: (a) attenuated positive psychotic symptoms – experience of symptoms qualitatively similar to those of psychosis but of insufficient severity and frequency to

meet criteria for a diagnosis of psychosis; (b) a brief episode of frank psychosis of less than one week's duration that resolved without antipsychotic medication (Brief Limited Intermittent Psychosis or BLIP); or (c) a recent decline in function (defined as a 30% reduction in scores on the Global Assessment of Function scale; GAF) over the past year, coupled with either schizotypal personality disorder or a first-degree relative with a psychotic disorder. Conferral of an APS status was established by two experienced clinicians, including a Psychiatrist and a Clinical Psychologist, following a diagnostic process that involved pre-screening by telephone contact to check the suitability of the referral; initial screening over two sessions; and a baseline assessment that included detailed assessment of psychosis like symptomatology and neuropsychological testing. Results of the assessments were discussed in the OASIS multidisciplinary clinical team meetings and a decision on inclusion and exclusion criteria was made through consensus.

Local advertisements were used to recruit 45 control participants that self-reported no family or personal history of psychotic disorders. Control participants were from the same geographic region and matched for demographic factors. All participants received a compensation of £20 for their time and travel expenses and provided written informed consent prior to commencement of the study, after having given the opportunity to read the study information sheet, and to ask questions about and discuss the nature of the study with a researcher. The Prodromal Questionnaire (PQ) (Loewy, Bearden, Johnson, Raine, & Cannon, 2005) was completed by all participants and used to screen healthy controls for possible prodromal symptoms.

Boxplots were used to determine departures from normality. In the current study, one control participant was excluded from subsequent analysis due to a score in excess of 18 on the PQ positive symptom subscale. A positive symptom subscale score in excess of 18 indicates that further investigation of potential clinical symptomatology may be required (Loewy et al., 2005). An additional two control participants were excluded due to being outliers (more than three standard deviations from the mean) on the PEDQ and SSPS persecutory subscale separately. The VR equipment failed while testing one control participant and one APS participant so their data was also excluded from the final analysis. This resulted in a total of 64 APS and 41 controls as seen in figure 2-1.

Figure 2-1: Sample acquisition for part one



2.3.2. Part Two- P50 ERP

APS participants were recruited and included in the study using the same clinical assessment methods, outlined in section 2.3.1 for part one. Transition to psychosis was defined according to the criteria in the CAARMS (i.e., presence of at least 1 positive psychotic symptom at high severity for more than one week) (Yung et al., 2005). This sample included 36 APS (sub sample of part one) and 60 matched control participants. Control participants were independent of those included in part one. I recruited healthy controls using the methods outlined for part one and they were assessed by using the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1997). Of the 36 individuals at clinical high risk, none were taking antipsychotics at the time of EEG testing. None of the controls was on any psychotropic medication at the time of EEG testing.

Ten individuals with APS had completed both ERP and VR measures. This overlap only allowed preliminary analysis to examine the correlations between sensory gating and persecutory paranoia using the P50 event related potential (ERP).

2.4. Power analysis

The power calculations presented are not based on the use of PEDQ scores as there has been a relative lack of research/publications specifically using the PEDQ in psychosis samples and/or in relation to paranoia or positive psychotic symptoms. Few studies included in Table 2-1, have addressed similar constructs such as the relationship between perceived discrimination or racism and paranoia/positive

psychotic symptoms and these studies have reported small to medium effect sizes (0.2 – 0.4) (Cohen, 1992). Based on a power calculation using the studies in Table 2-1, a total sample size of 110 (APS & controls) demonstrates >80% power ($p<0.05$) to detect small to medium effect sizes (0.2 – 0.4) (Cohen, 1992) in the context of eliciting correlations between paranoia and perceived discrimination.

Although it is important to understand the relationship between paranoia and perceived ethnic discrimination irrespective of specific clinical group status, the current study would further enable understanding of such relationships in individuals with APS. The current study appears to have statistical power in the range of 61-95% ($p<0.05$) to detect small to medium effect sizes as demonstrated in Table 2-1, using only the APS group (n=65).

Table 2-1: Power analysis

Study	**Variables Correlated**	**Reference Sample Size**	**Statistic**	**Effect size**	**Power (n=110) to detect this effect**
Combs et al (2006)	Perceived Racism Scale & Paranoia Scale	128	Correlation	0.4	99%
Berg et al (2011)	Perceived Discrimination & PANSS Positive.	90	Correlation	0.26	87%
Simpson (2003); Thesis	Perceived Discrimination Scale & Paranoia Sub-Scales from the Personality Assessment Inventory	241	Correlation	0.24	80%

2.5. Measures

2.5.1. Virtual Reality Environment

The Virtual Reality (VR) equipment used in this study to assess paranoid ideation was identical to that used in previous research (Fornells-Ambrojo et al., 2008; Freeman, 2008; Valmaggia et al., 2007).

Environment:

The VR scenario was modelled on a London Underground tube train ride (developed by the Department of Computer Science at University College London). Clinical observation suggests that the most immediate trigger for a paranoid thought is the misinterpretation of an everyday experience such as a person's facial expression. For this reason the chosen neutral social environment was an underground train ride.

Prior to beginning the VR session, verbal instructions were provided by the researcher. Participants were asked to - “Try and form an impression of what the people in the tube think about you and what you think about them”.

Technical details for VR experience:

The environment was displayed in colour via a lightweight headset; the display used was a Virtual Research VR 1280 (Virtual Research Systems, Aptos, California), with a resolution of 1280x1024 pixels, 60° diagonal field of view and a refresh rate of 60 Hz. Participants would virtually enter the London Underground Central line at St.

Paul's, and asked to remain on the train during the first stop, Chancery Lane. Following this, participants would then disembark at the second stop, Holborn Station, with a total journey time of approximately four minutes. Background noises were played using a Creative sound card, mimicking noises associated with a London train ride (e.g., background rumble of the moving train, a 'Mind the doors' announcement with closing doors, and fragments of passenger conversation). Participants were free to move around the virtual carriage, walking or turning, as they wished.

2.5.2. Measures of Paranoid Ideation & Prodromal Symptoms

2.5.2.1. State Social Paranoia Scale (Freeman et al., 2007)

The State Social Paranoia Scale (SSPS) is a 20-item self-report assessment measure of persecutory ideation used to assess thoughts about the virtual reality avatars. Each item is scored on a 5-point scale (Do not agree – Totally agree) and higher scores indicate greater levels of persecutory thinking. The scale has 3 sub-scales: virtual reality–persecution (10 items) (e.g. 'Someone had it in for me', 'Someone stared at me in order to upset me', 'Someone was trying to isolate me', 'Someone was trying to make me distressed'); virtual reality–neutral (5 items) (e.g. 'No-one had any particular feelings about me') and virtual reality–positive (5 items) (e.g. 'I felt very safe in their company'). The items for this measure of recent paranoid thinking in a social situation were derived from a clear definition by Freeman and Garety (2002), such that all measure items contained both elements of threat and intention (i.e., clear persecutory thinking was assessed). In the scale, 5 items concerning neutral views of the people in the social situation, and 5 items

concerning positive views of the people in the social situation are dispersed randomly. These positive and neutral items are used to form 2 subscales to establish the divergent validity of the SSPS, but are not considered of psychometric interest in their own right. It is helpful in understanding the estimates of divergent validity to remember that it is possible for participants to view some computer characters positively but other characters in the same environment negatively. SSPS has excellent internal reliability (Cronbach's alpha =0.91), adequate test-retest reliability ($r = 0.73$, $p \leq 0.001$), clear convergent validity ($r = 0.41$, $p < 0.001$) as assessed by both independent interviewer ratings and self-report measures, and showed divergent validity with measures of positive ($r=0.27$, $p< 0.001$) and neutral thinking ($r=0.44$, $p <0.001$) (Freeman et al., 2007). The scale was found to have excellent reliability (Cronbach's alpha =0.96) in the APS sample (Freeman et al., 2007) used in the current study. The VR-persecution subscale alone has good convergent validity ($r=0.55$; $p=0.002$) and reliability (Cronbach's alpha =0.66) (Freeman et al., 2005).

2.5.2.2. Prodromal questionnaire (Loewy et al., 2005)

The Prodromal Questionnaire (PQ) is a 92-item self-report screening measure developed for people at high clinical risk for psychosis. The instrument includes adapted items from the Schizotypal Personality Questionnaire (Raine, 1991) and probe questions from a structured clinical interview for the ascertainment of people at high risk of developing psychosis (Miller et al., 1999). The PQ comprises four symptom subscales: 1) Positive symptoms (e.g. unusual thinking, perceptual abnormalities and cognitive disorganisation) (45 items), 2) Negative symptoms (e.g. flat affect and social isolation) (19 items), 3) Disorganized symptoms (e.g. odd

behaviour) (13 items) and 4) General symptoms (e.g. depression and role functioning) (15 items). Participants indicated whether or not they experienced each item within the last month by circling either ‘true’ or ‘false’. The number of true responses was summed to give a score for attenuated symptoms for each of the four symptom subscales. Loewy et al (2005) consider that a cut off point of the positive subscale of 14 points (71% sensitivity and 81% specificity) indicates that the subject is at clinical high risk for psychosis. The positive symptom subscale was used for the purpose of all subsequent statistical analysis. The PQ shows good preliminary validity in detecting individuals with an interview-diagnosed prodromal or psychotic syndrome (Loewy et al., 2005).

2.5.2.3. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1997)

SCID-I is a semi-structured interview for making the major DSM-IV Axis I diagnoses such as schizophrenia or other psychotic disorders. It can be administered by a clinician or trained researcher and includes an introductory overview followed by nine modules, seven of which represent the major axis I diagnostic classes. Due to its modular construction, it can be adapted for use in studies in which particular diagnoses are not of interest. Using a decision tree approach, the SCID guides the administrator in testing diagnostic hypotheses as the interview is conducted. The output of the SCID is a record of the presence or absence of each of the disorders being considered, for current episode (past month) and for lifetime occurrence (Spitzer, Williams, Gibbon, & First, 1992). SCID-I was used to establish the absence of psychiatric diagnoses in the healthy control group used in part two of the study.

The SCID-I has demonstrated high inter-rater reliability (Kappa= 0.94) (Skre, Onstad, Torgersen, & Kringlen, 1991) and moderate test-retest reliability (Kappa= 0.65) (Williams et al., 1992) for a diagnosis of schizophrenia. The validity of a diagnostic assessment technique is generally measured by determining the agreement between the diagnoses made by the assessment technique and some hypothetical "gold standard." Unfortunately, a gold standard for psychiatric diagnoses remains elusive. Perhaps the most accepted standard used in psychiatric diagnostic studies is known as a "best estimate diagnosis." Spitzer (Aboraya, France, Young, Curci, & Lepage, 2005; Spitzer, 2001) has proposed an operationalisation of this best estimate diagnosis which he termed the "LEAD" (Longitudinal, Expert, All Data) standard. This standard involves conducting a longitudinal assessment (L) (i.e., relying on data collected over time), done by expert diagnosticians (E), using all data (AD) that are available about the subjects, such as family informants, review of medical records, and observations of clinical staff. Although conceptually the LEAD standard is appealing, the difficulty in implementing it accounts for its limited use. Several studies (Fennig, Craig, Lavelle, Kovasznay, & Bromet, 1994; Kranzler, Kadden, Babor, Tennen, & Rounsaville, 1996; Ramirez Basco et al., 2000) used approximations of the LEAD procedure and demonstrated superior validity of the SCID over standard clinical interviews at intake episode.

2.5.3. Perceived Ethnic Discrimination Questionnaire - Community version (PEDQ-CV) (Brondolo et al., 2005)

The PEDQ-CV, a modification of the PEDQ, was developed by Contrada et al. (2001) to assess perceived exposure to ethnic discrimination in college students from any ethnic/racial background. The PEDQ-CV is capable of assessing experiences of racial/ethnic discrimination in a manner appropriate for multiple

ethnic groups (Contrada et al., 2001; Brondolo et al., 2005), and allows the development of an integrated body of empirical and theoretical work concerning the prevalence, determinants, and effects of racial/ethnic discrimination without denying the importance of factors unique to the history and culture of particular groups. As PEDQ-CV can be used to assess ethnic discrimination in any group it permits the evaluation of both within-group and between-group differences in perceived exposure to ethnic discrimination (Kwok et al., 2011).

Specifically, the complete PEDQ-CV is a 70-item questionnaire assessing lifetime experiences of ethnic discrimination. The first 34 items comprise the Lifetime Exposure Discrimination scale. These items begin with the statement "Because of my ethnicity . . ." and are followed by an item describing exposure to some form of mistreatment or difficulty (e.g., "a clerk or waiter ignored me"). This 34 item subscale (Lifetime Exposure Discrimination scale) was used for the purpose of statistical analysis. There are four additional scales that were not used for statistical analysis, including Discrimination in the Media, Discrimination Against Family Members, Discrimination in Different Settings, and Past Week Discrimination. Discrimination Against Family Members scale assesses participants' awareness of friends' and family members' exposure to discrimination, since this type of indirect exposure may also have health consequences (Krieger, 1999). For all scales except Past Week Discrimination, participants were asked to indicate how often they had ever "had these experiences during their lifetime," and each item was rated on 5-point Likert scale ranging from 1 (never happened) to 5 (happened very often). The Past Week Discrimination scale contains 10 items inquiring about everyday experiences of stigmatization, threat, and exclusion or rejection, similar to those included in the Lifetime Exposure scale. Items were rated on a 4-point scale of 0 (never in the past

week), 1 (once), 2 (twice), or 3 (3 or more times in the past week). Two additional items are included to provide an estimate of the relative likelihood of inter-group versus intra-group ethnic discrimination. Inter-group racism or ethnic discrimination occurs when the ethnicity/race of the perceived perpetrator differs from that of the victim. Intra-group racism occurs when the perceived perpetrator is of the same ethnicity as the victim, but the event is still perceived to be motivated by ethnic or racial bias. The first item asked participants to indicate which of the following groups gave them the most difficulty: White, Black, Asian, Other, Please specify. The second item asked whether the participant experienced more discrimination from men or from women.

The PEDQ has displayed good reliability (Cronbach's alpha > 0.87) (Brondolo et al., 2005; Kwok et al., 2011). There is also evidence of construct validity, with those who reported higher levels of exposure to discrimination also indicating that they felt more threatened ($r = .43$, $p < .0001$) and harmed ($r = .46$, $p < .0001$) by these experiences (Brondolo et al., 2005). PEDQ in the sample from part one of this thesis demonstrates good reliability (Cronbach's alpha = 0.97)

2.5.4. Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet, Dahlem, Zimet, & Farley, 1988)

MSPSS is a self-report measure of the perceived availability of support. It contains 12 items assessing 3 sources of support: family, friends, and significant other, or global perceived support. Items are rated on a 7-point Likert-scale ranging from 1 (very strongly disagree) to 7 (very strongly agree). The Significant Others Scale measures the perceived availability of, as well as satisfaction with, the support

provided by three named significant others, typically partners, parent figures, siblings, etc. (Power, Champion, & Aris, 1988). Internal consistencies of the subscales and total scale are excellent (Cronbach's alphas= .85 to .91). The scale has demonstrated strong test-retest reliability over a 2- to 3-month interval (r= .72 to .85) and validity has been established through the negative association of scores on the MSPSS with scores on measures of depression.

2.5.5. Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Bifulco, Bernazzani, Moran, & Jacobs, 2005)

Exposure to early adverse or traumatic experiences focused on the period prior to age 17 was assessed using the CECA.Q, which was administered as a semi-structured interview by a Clinical Psychologist or by an assistant psychologist trained in using the scale. The CECA.Q records basic demographic material on current relationships, employment status, childhood information on family arrangements and parental loss in order to identify the relevant parent figures raising the child. Physical and sexual abuse is introduced with screening questions, while perceived antipathy and neglect are measured by scales repeated for mother and father figure. The CECA.Q as a self-report measure for adverse childhood experience shows good internal scale consistency for perceived antipathy (Cronbach's alpha = 0.81) and neglect (Cronbach's alpha = 0.80) and test-retest reliability of maternal antipathy ($r = 0.77$, $p = < 0.001$), paternal antipathy($r = 0.73$, $p = < 0.001$), maternal neglect ($r = 0.71$, $p = < 0.001$) and paternal neglect ($r = 0.79$, $p = < 0.001$) (Bifulco et al., 2005; Smith, Lam, Bifulco, & Checkley, 2002).

Participants were asked about 16 indicators of psychosocial stress or adversity that could have occurred before the age of 17. For the purpose of this study only perceived maternal neglect and antipathy scores were used in the analysis:

- disrupted living arrangements
- being taken into local authority care
- death of mother figure
- death of father figure
- separation from mother figure
- separation from father figure
- perceived neglect from mother figure
- perceived neglect from father figure
- perceived antipathy from mother figure
- perceived antipathy from father figure
- lack of supportive figures
- severe physical abuse from mother figure
- severe physical abuse from father figure
- severe sexual abuse
- severe bullying during primary school
- severe bullying during secondary school

For each item, participants were coded for ‘exposure’ (1) or ‘no exposure’ (0). In many cases these categories actually distinguish between ‘severe exposure’ and ‘no or non-severe exposure’. In order to determine whether or not exposure to severe adversity had occurred, the conservative thresholds described by the authors of the CECA.Q (Bifulco et al., 2005) were applied (see below). Each questionnaire contained 16 items: eight perceived neglect items and eight perceived antipathy

items. The participant indicated the extent to which each antipathy and neglect item occurred within his or her relationships with father and mother figures by circling a number on a five point scale (1= ‘no, not at all’ , 5= ‘yes, definitely’). Exposure to severe maternal neglect was indicated by a score of 25 or more while exposure to severe paternal neglect was indicated by a score of 26 or more on the neglect items. Exposure to severe maternal antipathy was defined as a score of 28 or more and exposure to severe paternal antipathy was defined as a score of 30 or more on the antipathy items. These scores are the severity cut-offs recommended by Bifulco et al (2005) and scores less than these cut-offs were coded as no exposure.

Perceived exposure to neglect and antipathy was assessed by asking the participant to complete a 16 item questionnaire about the relationship they had with each parent figure up until the age of 17. When participants had lived with more than one mother or father figure, they were asked to complete the questionnaire regarding the parent figure with whom they had lived the longest or found it most difficult to live. Perceived neglect was assessed in terms of the parent figure’s disinterest in material care: feeding and clothing, health, schoolwork, and friendships etc. An example neglect question is “She was concerned about my whereabouts.” Antipathy was assessed as hostility, coldness, or rejection shown to the child by parent figures, including ‘scapegoating’ behaviour, and an example antipathy question is “He made me feel unwanted.”

2.5.6. P50 Event Related Potential (ERP)

ERPs are small electrical voltage fluctuations in the EEG (electroencephalogram) produced by the brain in response to a stimulus that are time-locked to sensory, motor or cognitive events, reflecting underlying neural network activity and helping to understand the neurophysiological correlates of such events. ERP waveform consists of a pattern of waves or components, which can be characterised and quantified by their latency, amplitude and scalp distribution. The high temporal resolution of ERPs, lends itself to study very early stages of sensory information processing and given that extremely basic cognitive deficits are thought to be characteristic of psychosis (Hermens et al., 2010; Keefe & Harvey, 2012; Keshavan, Montrose, Miewald, & Jindal, 2011), there is a substantial case for the use of ERP markers as potential markers or endophenotypes for psychosis. In contrast to blood flow neuroimaging techniques such as functional magnetic resonance imaging (fMRI), the EEG/ERP provides a direct and real-time index of neuronal activity at a millisecond scale of resolution that is non-invasive and inexpensive to implement (Picton et al., 2000; Regan, 1989). Due to its high temporal resolution, the EEG/ERP is ideally suited to examine the rapidly changing patterns of brain activities involved in cognitive dysfunction in psychosis.

Event-related potentials elicited by sensory stimuli are customarily characterised in terms of a series of positive or negative peaks or components that occur at particular times following the stimuli. These ERP components can be seen as being on a continuum between exogenous and endogenous potentials. Exogenous ERP components will be those that are elicited by external stimuli, their characteristics being dependent on the features of these stimuli, and endogenous potentials will be

cognitive components which index information processing in the brain (Picton et al., 2000). ERPs are conventionally described in terms of their peak amplitude in microvolts and latency in milliseconds.

2.5.6.1. P50 component

The P50 paradigm examines amplitude to two consecutive auditory stimuli separated by several hundred milliseconds (usually a clicking noise) (Freedman, Adler, Waldo, Pachtman, & Franks, 1983; Siegel, Waldo, Mizner, Adler, & freedman, 1984a; Siegel et al., 1984b). The normal response is for subjects to have a reduced P50 response to the second stimulus, suggesting this repeated stimulus is actively suppressed, perhaps because it is less relevant and this phenomenon is referred to as "sensory gating". In other words, the first stimulus produces an excitatory response (i.e., a large P50 wave) and activates inhibitory pathways, so that the response to the testing stimulus (2^{nd} stimulus) is normally suppressed. The degree of each suppression, conventionally measured as the ratio of the test to the conditioning p50 amplitude multiplied by 100 as percentage, provides a measure of sensory inhibitory mechanism of the brain which reflects individual's ability to screen out trivial or repeated stimuli in order to focus on important aspects of the environment (Freedman et al., 1996b). Lower value or percentage is believed to indicate increased sensory inhibition.

2.5.6.2. Heritability and reliability of P50

P50 suppression ratio components have demonstrated a high level of reliability (ICC= 0.66) and heritability (68%) (Hall et al., 2006). A substantial portion of the

variance in P50 suppression ratio is of genetic origin and is stable over time, thus making P50 a promising endophenotype.

2.5.6.3. Montage and electrode placement

I carried out EEG recordings at The Eric Byers Magnetic Resonance Suite of Mapother House, King's College Hospital. Continuous electroencephalogram (EEG) data were recorded using the SCAN software package (SCAN versions 4.0 through 4.3, Compumedics Neuroscan, Texas, USA). Data were collected from the scalp using caps with 64 silver/silver-chloride electrodes (CompumedicsNeuroscan, Texas, USA) referenced to the mastoids and positioned according to the 10/20 International System (Jasper, 1958) as shown in figure 2-2.

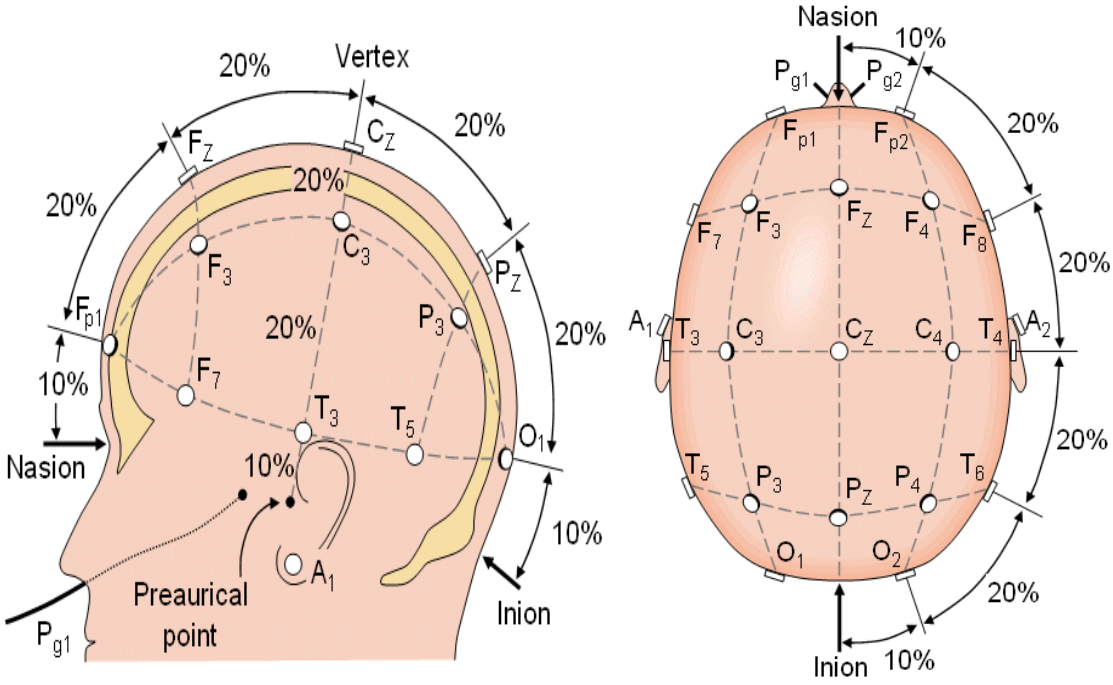


Figure 2-2 : The 10/20 International System for electrode placement

FPZ (mid-forehead) served as ground and electrode impedances were kept below 5 kΩ at all sites with the use of conductive gel (ECI ElectrogelTM, Electro-Cap International Inc. Ohio, USA). A small amount of gel was applied to the scalp through holes in each electrode using 10 ml syringes (BD 10 ml Syringe with Luer-LokTM tip, Becton Dickson & Co., NJ, USA) fitted with blunt needles (BD 16G¾ Blunt Square Grind PrescisionGlide® Needle, Becton Dickson & Co., NJ, USA). To prepare skin on the face and mastoids for the placement of electrodes, abrasive gel was gently applied (NuPrep Abrasive Skin Prepping Gel, D.O Weaver and Co., Colorado, USA), and cleansed with an alcohol swab (70% Isopropyl Alcohol Alcotip Swab, Universal Hospital Supplies Ltd., UK).

Electromyographic (EMG) activity of eye movements and blinking was recorded from electro-oculogram (EOG) electrodes placed at four locations (the outer canthus of each eye, and above and below the right eye over the orbicularis oculi) as shown in figure 2-3. The SCAN software automatically computed a single bipolar vertical electro-oculogram (VEOG) by subtracting the upper and lower eye channels.

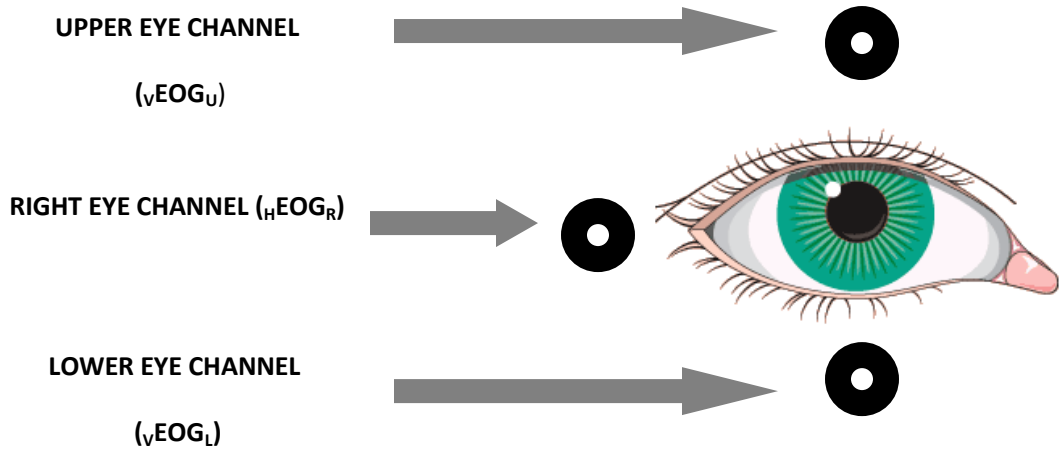


Figure 2-3: Placement of electro-oculogram (EOG) electrodes at right eye

2.5.6.4. Stimuli – general information

Auditory stimuli were generated and presented using the STIM system (Compumedics Neuroscan, Texas, USA) and delivered though intra-aural earphones (ER3-14A Eartips for ER-3 and ER-5, Etymotic Research Inc. Illinois, USA).

2.5.7. P50 stimulation paradigm

P50 suppression was recorded with a conditioning–testing paradigm (figure 2-4). Three blocks of 30 conditioning (C) – testing (T) click pairs were presented. The C and T clicks were of 1-millisecond duration and separated by 500 ms, with 10 s between consecutive conditioning stimuli. Acquisition time was 100–400 ms per trial (Shaikh et al., 2010b). Participants were asked to disregard the sounds presented to them and instructed to try to avoid blinks and eye movements during presentation of

the clicks and to rest their gaze on a fixed target on the table in front of them. Continuous EEG data was recorded.

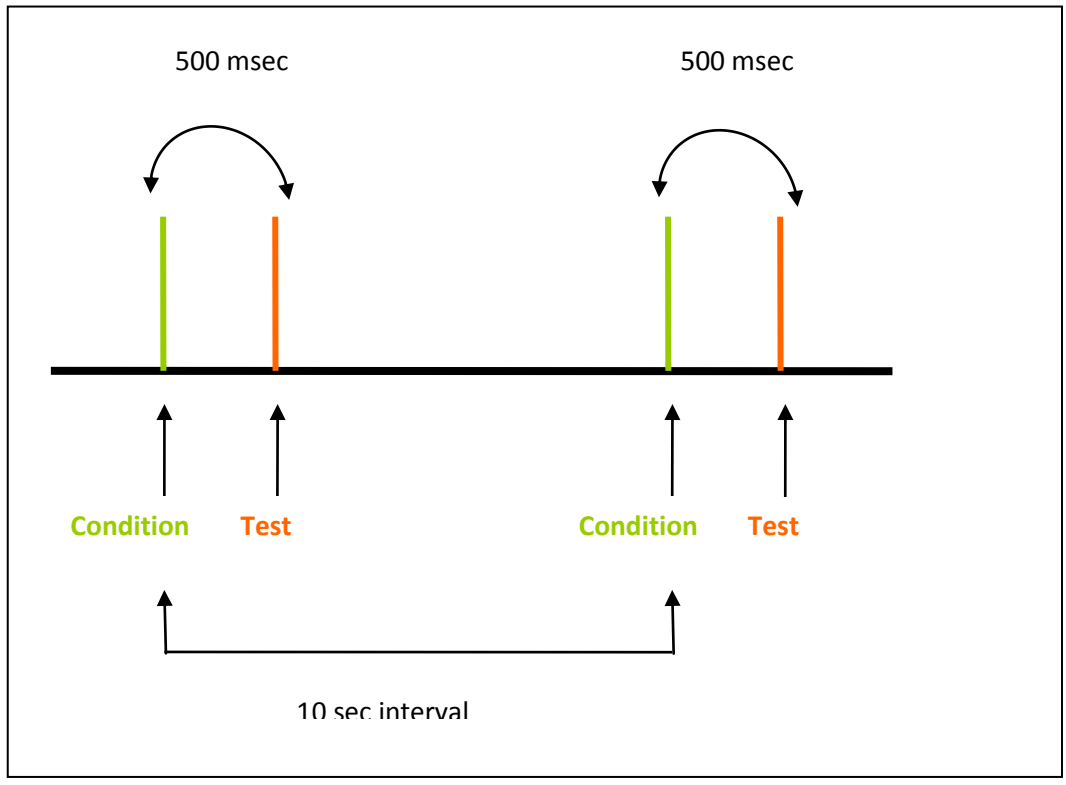


Figure 2-4: Diagram of the P50 paradigm

2.5.8. P50 data processing

Signal processing was performed using Neuroscan (4.3) software. A 1-Hz high-pass filter (24 dB/octaves) was applied to all channels. Epochs were then base line corrected using the pre-stimulus interval. An automatic ocular artefact rejection procedure identified and rejected any sweeps with activity exceeding ± 35 μV in the vertex (Cz) or the ocular channel 0–75 ms after stimulus (to capture blinks and other slow wave activity).

Accepted sweeps were averaged for each of the blocks of 30 trials for C and T separately. Ideally, each individual would have one average waveform for C and T from each of the blocks. However, if the number of accepted sweeps per block was too small (<50% of trials) due to excessive eye movement or other artefacts, trials from consecutive blocks were combined by averaging. Average waveforms were then digitally filtered with a zero phase shift 10Hz high pass filter (24dB/oct) and smoothed using a 7-point moving average applied twice.

2.5.8.1. P50 peak selection

P50 ratio was evaluated at CZ. The averaged waveforms for the C and T responses in each block were presented simultaneously on a computer monitor for visual inspection. For the C response, the most prominent peak 40-75msec post-stimulus was selected as the P50 peak (Nagamoto, Adler, Waldo, & Freedman, 1989). The preceding negative trough with a latency no less than 30msec post-stimulus was then used to calculate P50 amplitude. In the absence of a trough at CZ, at least one other channel (FZ or PZ) was used to identify the start of the P50 response.

For the T response, the positive peak with latency closest to that of the C P50 peak was selected as the P50 T response. The T P50 wave amplitude was determined in the same way as for the conditioning response.

2.5.8.2. Block selection for the grand average

Blocks without identifiable P50 response, with a C amplitude of <0.4μV, with electro-oculographic activity in the 40-75msec post-stimulus window that exceeded the P50

wave or blocks showing a large negative-positive P30 complex (>1.5 times bigger than the P50 wave) were identified by the rater and excluded from the grand average.

Individual blocks with identifiable P50 responses were included in the grand average. Grand averages for the C and T responses were compiled separately and the P50 peak for the C and T responses were determined in the same way as described above for individual block averages. P50 suppression was quantified in two ways following previous research; 1) The P50 ratio was calculated as the ratio of T amplitude to C amplitude, expressed as percentage (T/C * 100), with lower values indicating increased auditory sensory gating and 2) the difference between the click 1 amplitude and the click 2 amplitude (difference score resulting from click 1 minus click 2) (Clementz, Geyer, & Braff, 1997, 1998a; Smith, Boutros, & Schwarzkopf, 1994).

Participants were excluded from P50 analysis if no P50 response could be identified in their recordings, due to excessive noise from eye movement or presence of a large startle response.

3. RESULTS

3.1. Characteristics of sample

3.1.1. Exploratory data analysis

As previously outlined in the methodology chapter, boxplots were used to determine departures from normality and participants were excluded if they were considered outliers as can be seen in figure 2-1. Sixty-four APS and 41 HC participants provided information on experiences of persecutory paranoid ideation measured by the SSPS, and prodromal symptomatology measured by the PQ; two APS participants and one HC did not complete the PEDQ. The distribution of PQ and persecutory paranoia scores were approximately normal in the APS group and positively skewed in the HC group (refer to Table 3-1 for skewness and kurtosis statistics), indicating that these are a reasonable measure of current psychosis-like experiences and paranoid ideation (Figure 3-1 & 3-2). The distribution of PEDQ scores were positively skewed in the APS and HC group (Figure 3-3).

Table 3-1: Skewness and Kurtosis scores for variables of interest

		APS	HC
Skewness Z scores	PEDQ	4.23	3.28
	PQ	1.06	2.96
	SSPS	3.12	3.79
Kurtosis Z scores	PEDQ	1.28	0.76
	PQ	-1.04	0.93
	SSPS	-0.16	1.07

Figure 3-1 : Distribution of Prodromal Questionnaire scores for psychotic symptoms for APS and healthy control participants.

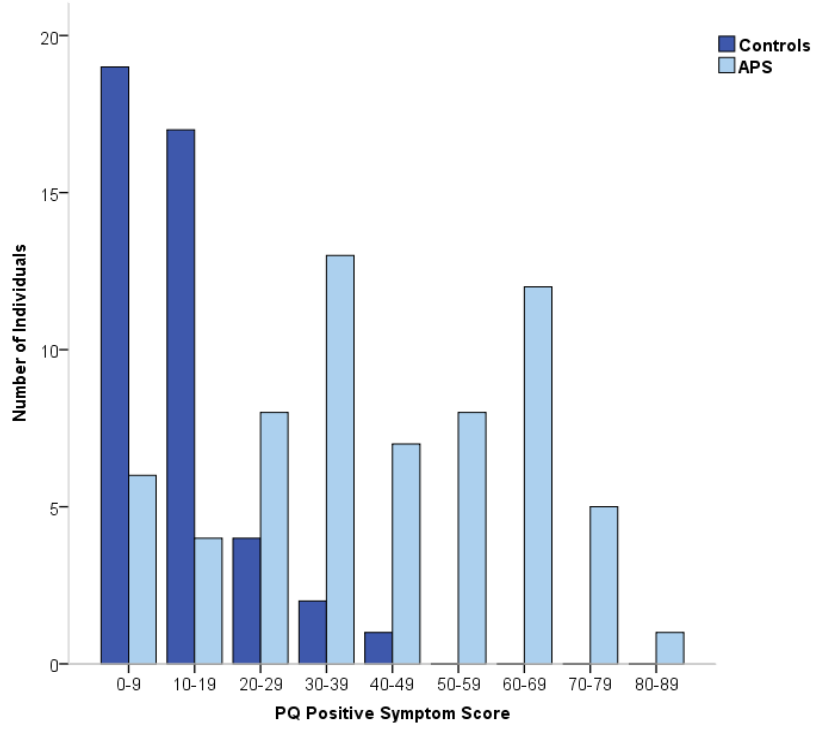


Figure 3-2 : Distribution of Persecutory Paranoid Ideation in the VR environment for APS and healthy control participants.

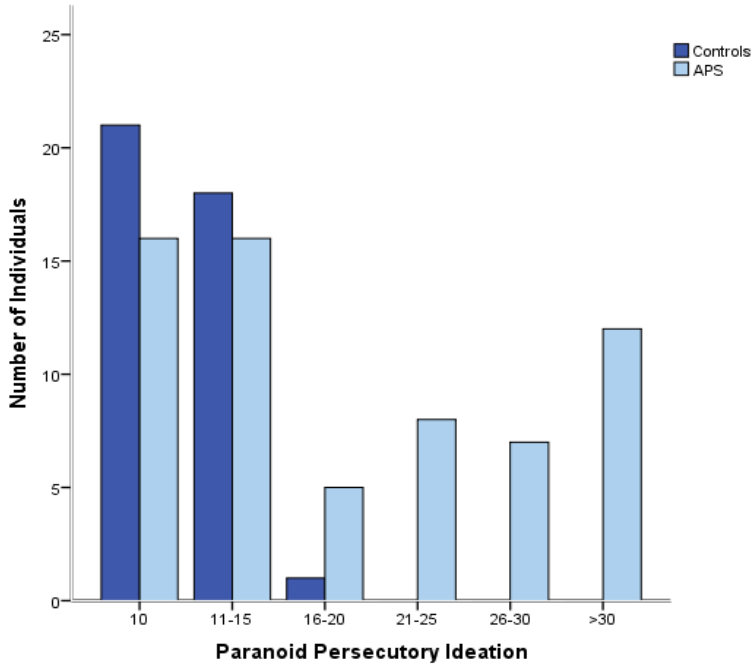
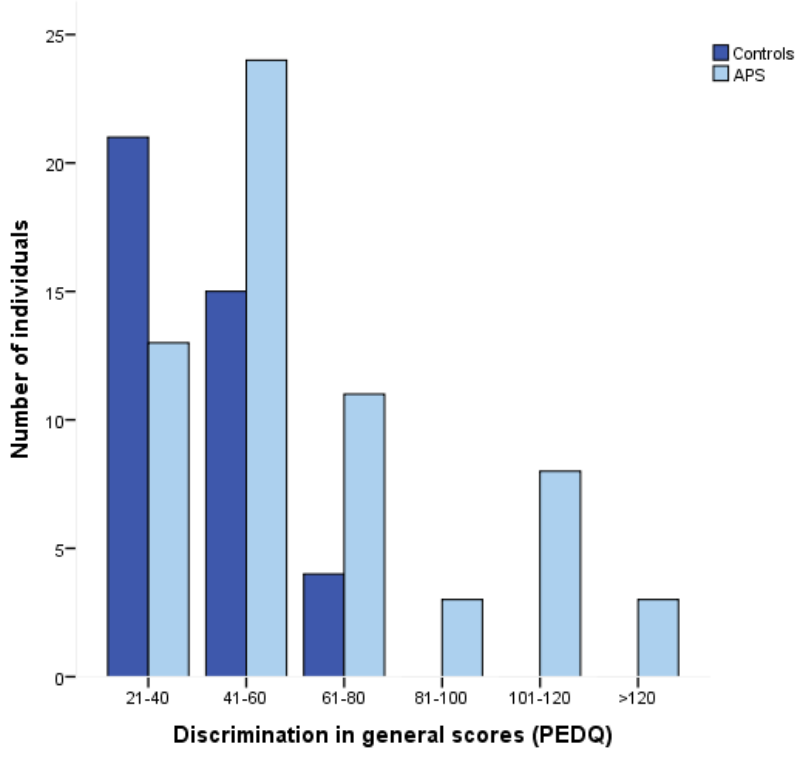


Figure 3-3 : Distribution of Perceived Ethnic Discrimination scores for APS and healthy control participants.



3.1.2. Socio-demographic characteristics of sample

Alpha of P<0.05 was considered statistically significant for all subsequent analysis. There were 64 APS individuals and 41 healthy controls (HC) participants in part one. There were no gender (χ^2=2.40, p=0.12), age ($F_{(103)}$=0.41, p>0.05), migration status ($\chi^2_{(2)}$=5.9, p=0.05) or ethnic ($\chi^2_{(3)}$=1.37, p=0.71) differences between the two groups. The APS and HC were also similar in ethnicity ($\chi^2_{(3)}$=1.37, p=0.71). However, the APS individuals had fewer years in education in comparison to the HC ($t_{(101)}$=3.97, p<0.01). 'Years of education' was not controlled for in subsequent analysis as there was no published evidence to suggest a relationship between 'years of education' and the primary measures (PEDQ, SSPS) under investigation. Table 3-2 shows the demographic characteristics of the sample.

3.1.3. Clinical characteristics of sample

Independent t-tests were used to compare scores on the measures of interest outlined below for APS and HC participants (See Table 3-2). Separate variance estimates were used when homogeneity of variance assumptions were not met. There was a marked difference in affective scores between the APS and HC participants, with the HC scoring substantially and significantly lower on depression ($t_{(80)}$=-10.95, p<0.001), anxiety ($t_{(72)}$=-9.13, p<0.001) and stress ($t_{(91)}$=- 8.80, p<0.001) levels. Persecutory paranoid ideation in VR, as measured by the SSPS Persecution score, was also observed to be significantly lower in the HC group than APS ($t_{(68)}$=-6.48, p<0.001). Positive prodromal symptomatology ($t_{(85)}$=-8.52, p<0.001) was also significantly lower in the HC group than APS.

Table 3-2: Sample demographics and mean scores for variables of interest

		APS	Controls	Statistic
N		64	41	
Female		26	23	$X^2_{(1)}$=2.40, p=0.12
Age, Mean (SD)		22.55 (+/-4.01)	24.15 (+/-4.11)	$F_{(103)}$=0.41, p>0.05
Years in education		13.25 (+/-2.26)	14.76 (+/-1.59)	$t_{(101)}$=3.97, **p<0.01**
Ethnicity	Black	19	9	$X^2_{(3)}$=1.37, p=0.71
	White British	23	16	
	White Other	11	6	
	Other	11	10	
Migration status	Non-migrant	41	20	$X^2_{(2)}$=5.9, p=0.05
	1st generation immigrant	14	7	
	2nd generation immigrant	9	14	
Affective states	DASS Depression	21.10 (+/- 12.13)	3.07 (+/- 3.92)	$t_{(80)}$=-10.95, **p<0.001**
	DASS Anxiety	14.38 (+/- 10.32)	2.00 (+/- 2.45)	$t_{(72)}$=-9.13, **p<0.001**
	DASS Stress	20.57 (+/- 12.06)	5.41 (+/- 5.19)	$t_{(91)}$=-8.80, **p<0.001**
PQ		17.97 (+/- 11.45)	4.63 (+/- 4.06)	$t_{(85)}$=-8.52, **p<0.001**
PEDQ		63.77 (+/- 29.89)	44.53 (+/- 10.15)	$t_{(81)}$=-4.67, **p<0.001**
Paranoid Ideation in VR (SSPS)		20.33 (+/- 11.01)	11.23 (+/- 1.76)	$t_{(68)}$=-6.48, **p<0.001**

3.2 Main Findings

All statistical analyses were performed using the Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, USA; www.spss.com).

3.2.1. Hypothesis (a): The APS sample will report higher levels of perceived ethnic discrimination, and lower levels of social support and quality of early attachment than controls.

Differences between groups were analysed using t-tests and Chi square test as appropriate. As reported in table 3-1, perceived ethnic discrimination as measured by the PEDQ was observed to be significantly lower in the HC group than APS ($t_{(81)}$=-4.67, p<0.001). Perceived availability of support as measured by the MSPSS was also observed to be higher in the HC group than APS ($F_{(96)}$=1.14, p <0.001). Perceived maternal antipathy ($F_{(99)}$=3.67, p=0.01) and neglect ($F_{(99)}$=1.68, p =0.008) were observed to be significantly higher in the APS than HC. There were no group differences for perceived paternal antipathy ($F_{(95)}$=0.65, p =0.17) and neglect ($F_{(94)}$=1.46, p =0.07).

3.2.2. Hypothesis (b): There will be a positive correlation between perceived ethnic discrimination and persecutory paranoid ideation measured via a virtual reality paradigm in the whole sample.

Bi-variate Pearson's correlations and partial correlations were carried out to explore the relationship between paranoid ideation in VR and perceived ethnic discrimination. Baseline scores from PQ were used to control for confounding effects of baseline paranoia on PEDQ.

There was a significant positive correlation between PEDQ and paranoia in VR in the entire sample ($r_{(100)}$= 0.27, p=0.006), that is higher levels of perceived ethnic discrimination were associated with greater paranoid persecutory ideation in VR (Figure 3-4). Partial correlations were carried out in the total sample between PEDQ and paranoid Ideation in VR, controlling for positive prodromal symptomatology. These results suggest that PEDQ is not correlated with persecutory paranoia in VR when controlling for positive prodromal symptomatology ($r_{(99)}$= 0.006, p=0.95) (Refer to figure 3-5).

Figure 3-4: Correlation between perceived ethnic discrimination and persecutory paranoia

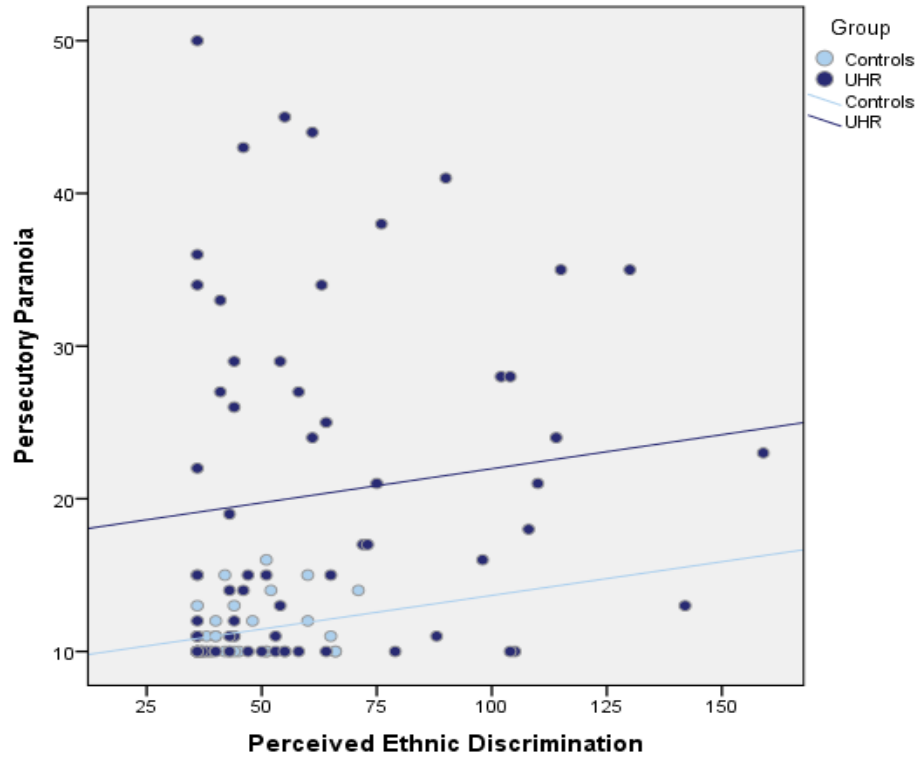
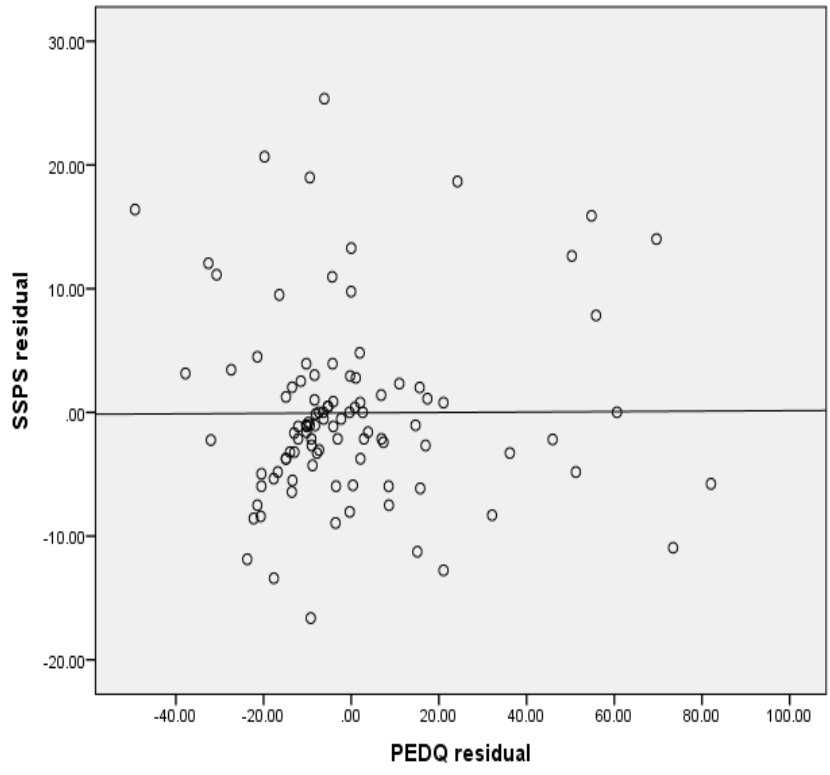


Figure 3-5: Scatter plot showing a partial correlation between PEDQ and paranoid Ideation in VR after controlling for prodromal symptomatology



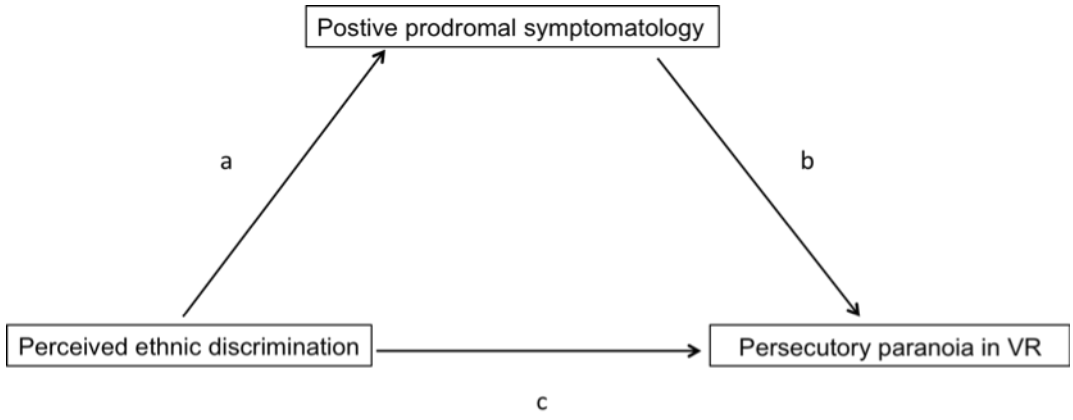
3.2.3. Hypothesis (c): Perceived ethnic discrimination and persecutory paranoid ideation will be positively correlated in the APS group.

Bi-variate Pearson's correlations and partial correlations were carried out to explore the relationship between paranoid ideation in VR and perceived ethnic discrimination in the APS. Baseline scores from PQ were used in the partial correlation to control for confounding effects of baseline paranoia on PEDQ. PEDQ and paranoid Ideation in VR were not correlated in the APS ($r_{(62)}$= 0.119, p=0.36), even when controlling for positive prodromal symptomatology ($r_{(59)}$= -0.02, p=0.86).

3.2.4. Hypothesis (d): The relationship between perceived ethnic discrimination and paranoia will be mediated by prodromal symptomatology in the APS group.

An SPSS script developed by Preacher and Hayes (2008) was used to estimate direct and indirect effects of perceived ethnic discrimination on persecutory paranoia with prodromal symptomatology as a mediating variable. This included Baron and Kenny's (1986) mediation model (see figure 3.6) and bootstrapping analysis (Preacher & Hayes, 2004).

Figure 3-6: Baron and Kenny (1986) Mediation analysis model



According to Baron and Kenny (Baron & Kenny, 1986) support for an indirect or mediation effect is dependent upon three criteria outlined by: (1) a significant effect of an independent variable (i.e. perceived ethnic discrimination) on the proposed mediator (i.e. prodromal symptomatology); (2) a significant effect of the mediator (i.e. prodromal symptomatology) on the dependent variable (i.e. persecutory paranoia); (3) the strength of the relation between the predictor variable (i.e. perceived ethnic discrimination) and the outcome variable (i.e. persecutory paranoia) should be significantly reduced when the mediator is added to the model (see Figure 3.6). The mediator is considered a "complete" mediator if the association between the independent variable and the outcome variable becomes non-significant upon the introduction of the mediator to the model. The mediator is considered a "partial mediator" if the association between the independent variable and the outcome variable remains significant, but becomes significantly smaller upon the introduction of the mediator variable to the model (Frazier, Tix, & Barron, 2004).

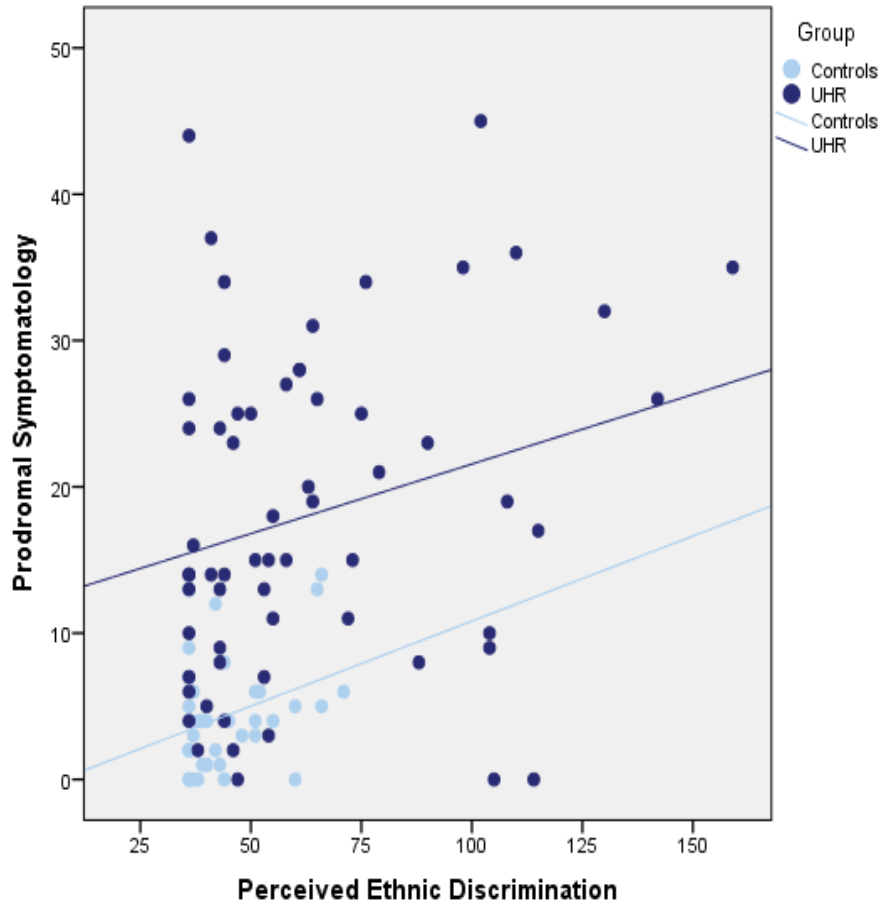
However, Preacher and Hayes method for assessing an indirect effect or mediation does not require an initial relationship to exist between the independent and

outcome variables. This method to detect mediation is favoured (Preacher & Hayes, 2004, 2008; Shrout & Bolger, 2002) as it has been shown to provide the least Type I and Type II errors and is thought to have greater power to detect indirect effects than alternative 'causal steps' or 'normal theory' approaches to mediation such as that of Baron & Kenny. Additionally, this method does not assume normality of data (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

Significance of mediation was investigated using 5000 bias corrected and accelerated bootstrapped confidence intervals, using a macro developed for SPSS (Preacher & Hayes, 2004). Confidence intervals at the 95% significance levels were used to determine indirect relationships between perceived ethnic discrimination and persecutory paranoia, with prodromal symptomatology included as a potential mediator. Significant indirect effects are present when confidence intervals do not include zero (Preacher & Hayes, 2004, 2008). The indirect effect is subsequently significant at $p<.05$.

As illustrated in Figure 3-7, there was a positive linear correlation between PEDQ and positive PQ scores in the whole sample ($r_{(102)}= 0.41$, $p <0.001$), demonstrating that positive prodromal symptomatology was greater in those with higher perceived ethnic discrimination.

Figure 3-7: Correlation between perceived ethnic discrimination and positive prodromal symptomatology



An SPSS script (Preacher & Hayes, 2004, 2008) was used to estimate direct and indirect effects of perceived ethnic discrimination on persecutory paranoia with prodromal symptomatology as a mediating variable. Persecutory paranoid ideation, which was scored as a continuous variable, was transformed into dichotomous categorical data, based on a cut-off criteria that includes an affirmative response on at least four items demonstrating persecutory paranoia (score greater than 16= persecutory paranoia). One HC and thirty-two individuals with APS scored greater than 16 on the SSPS persecution scale.

According to the Baron and Kenny (1986) approach the results suggest that the association between perceived ethnic discrimination and persecutory paranoia is fully mediated by positive prodromal symptomatology in the APS. The a path (p=0.049) (IV on mediator), b path (p=0.0004) (mediator on DV) and c path (p=0.03) are significant (IV on DV). However, the c path is no longer significant (p=0.12) when controlling for the mediator (c' path), suggesting complete mediation (see table 3.3).

As a final step, a robust bootstrapping analysis (Preacher & Hayes, 2004) was carried out to test the indirect effect of perceived ethnic discrimination on persecutory paranoia via positive prodromal symptomatology. However, as the bootstrapping 95% Confidence Interval contained a zero (-0.0032 to 0.0318), this suggests the indirect effect is not significant. Nonetheless, the confidence intervals are very close to zero therefore suggestive of a mediation effect. Bootstrapping mediation analyses, although not significant, provide some support for the hypothesis that there is an indirect relationship between perceived ethnic discrimination and persecutory paranoia via positive prodromal symptomatology.

Table 3-3: Mediation analysis for hypothesis d in the APS group.

IV to Mediators (a path)				
	Coeff	Se	t	p
PQ	0.1	0.05	2.01	0.049
Direct Effects of Mediators on DV (b path)				
	Coeff	Se	Z	p
PQ	0.12	0.04	3.53	.0004
Total Effect of IV on DV (c path)				
	Coeff	Se	Z	p
PEDQ	0.02	0.01	2.18	0.03
Direct Effect of IV on DV (c' path)				
	Coeff	Se	Z	p
PEDQ	0.02	0.01	1.54	0.12
Indirect Effects of IV on DV through Proposed Mediators (ab paths)				
	Bias	SE	Bias Corrected Confidence Intervals	
PQ	0.002	0.01	-0.003 to 0.03	

3.2.5. Hypothesis (e): Perceptions of early attachment, levels of social support and positive prodromal symptomatology will mediate the relationship between perceived discrimination and persecutory paranoid ideation.

Mediation analysis was also used to estimate direct and indirect effects of perceived ethnic discrimination on persecutory paranoia with perceptions of early attachment, levels of social support and positive prodromal symptomatology as multiple mediating variables.

There was a significant negative correlation between perceived availability of support and perceived ethnic discrimination, that is higher levels of discrimination were observed with lower levels of support ($r_{(99)}$ =-.31, p= 0.002) in the whole sample. A significant positive correlation was observed between perceived ethnic discrimination and perceived maternal antipathy ($r_{(99)}$ =0.28, p=0.005) and neglect ($r_{(99)}$ = 0.34, p <0.001) respectively. Higher levels of perceived ethnic discrimination were associated with higher levels of perceived maternal antipathy and neglect in the entire sample. No significant correlations were observed between perceived ethnic discrimination, perceived availability of support and perceived maternal antipathy in the APS group. Perceived ethnic discrimination and perceived maternal neglect were significantly correlated in the APS group ($r_{(60)}$=0.32, p= 0.01) only. Figure 3-8 illustrates a positive linear relationship between perceived ethnic discrimination and perceived maternal neglect in the APS group.

Figure 3-8: Relationship between PEDQ and perceived childhood maternal neglect

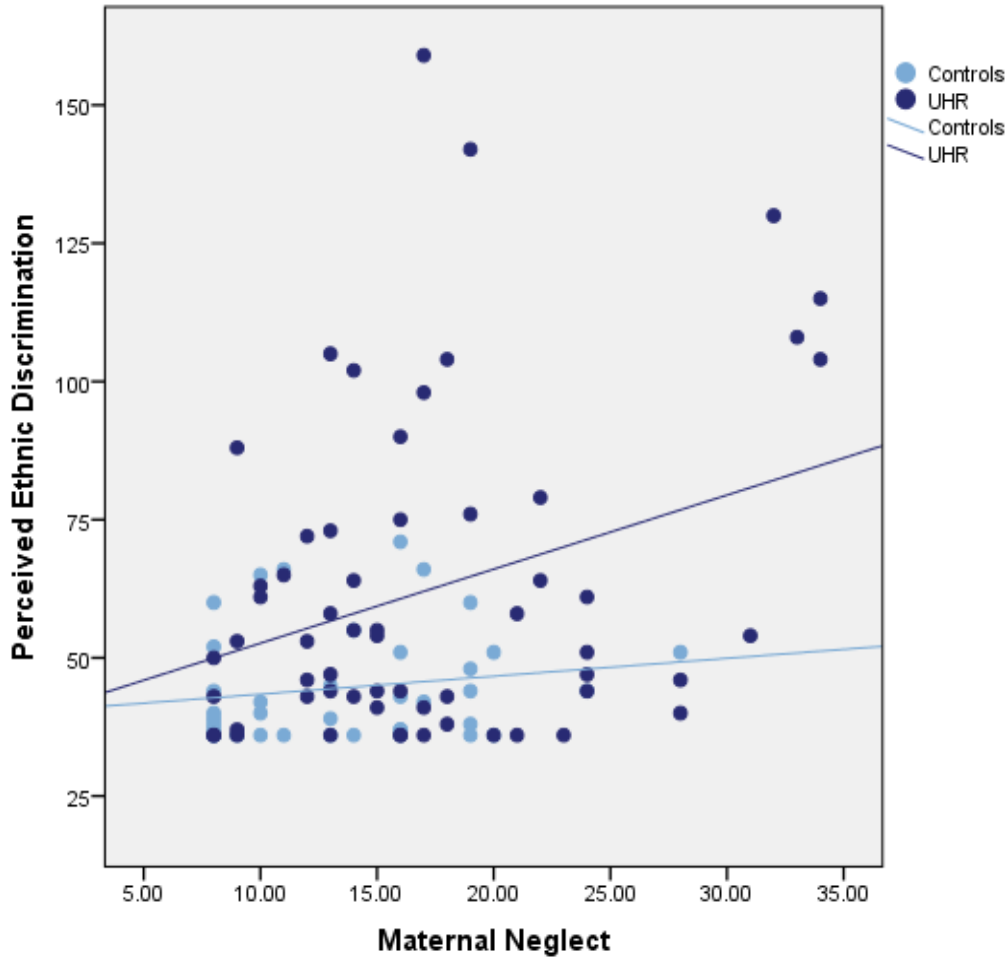


Table 3-4: Mediation analysis for hypothesis e in the entire sample.

IV to Mediators (a path)				
	Coeff	se	T	P
PQ	0.18	0.04	4.38	<0.001
Social support	-0.23	0.07	-3.16	0.002
Maternal antipathy	0.09	0.03	3.07	0.003
Maternal neglect	0.09	0.02	4.02	0.0001
Direct Effects of Mediators on DV (b path)				
	Coeff	se	Z	P
PQ	0.17	0.04	4.07	.001
Social support	0.02	0.02	0.83	.4090
Maternal antipathy	0.04	0.05	0.72	.4713
Maternal neglect	0.06	0.07	0.92	.3567
Total Effect of IV on DV (c path)				
	Coeff	se	Z	P
PEDQ	.0321	.0102	3.1453	.0017
Direct Effect of IV on DV (c' path)				
	Coeff	se	Z	P
PEDQ	.0074	.0147	.5022	.6155
Indirect Effects of IV on DV through Proposed Mediators (ab paths)				
	Bias	SE	Bias Corrected Confidence Intervals	
PQ	.0062	.0158	.0070 to .0555	
Social support	-.0013	.0066	-.0170 to .0071	
Maternal antipathy	.0001	.0084	-.0131 to .0213	
Maternal neglect	.0020	.0100	-.0095 to .0273	

Bootstrapping mediation analysis as used for hypothesis d was applied to estimate direct and indirect effects of perceived ethnic discrimination on persecutory paranoia with prodromal symptomatology, perceived availability of support and perceived maternal neglect as mediating variables. The results suggest that the association between perceived ethnic discrimination and persecutory paranoia is fully mediated by positive prodromal symptomatology in the APS (95% CI .0070 to .0555) above and beyond the other mediators. Nonetheless, the confidence intervals for perceived social support, perceived maternal antipathy and neglect are very close to zero and therefore suggestive of possible mediation effects. However, due to a small sample size there might be insufficient power to detect these indirect effects.

3.2.6. Hypothesis (f): The APS sample will be more impaired on P50 ERP indices in comparison to controls.

An independent analysis examining sensory gating using the P50 event related potential (ERP) in individuals at APS for psychosis was carried out. Linear regression was used to assess P50 deficits by comparing healthy controls to the APS sample followed by a second analysis comparing converters to psychosis versus non-converters. The P50 index (T/C ratio, C–T amplitude difference) was the dependent variable and group, sex and age were the independent variables. Backwards elimination was used to derive the most parsimonious model.

There were 36 APS individuals and 60 healthy controls (HC) participants in the study. There were no gender (χ^2=1.65, p=0.20) or age ($t_)$=0.2, p=0.86) differences

between the two groups. Table 3.5 shows the demographic characteristics of the sample.

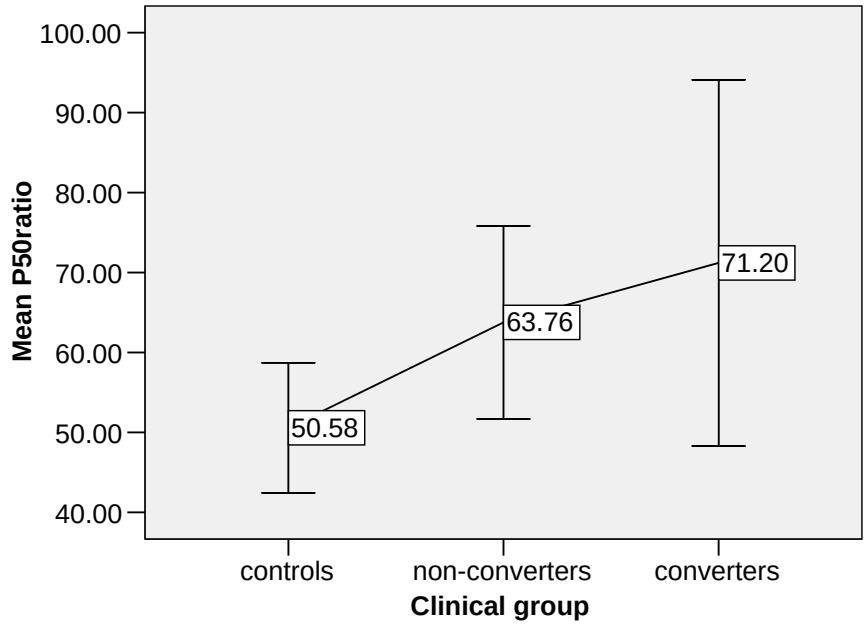
Table 3-5: P50 sample demographics

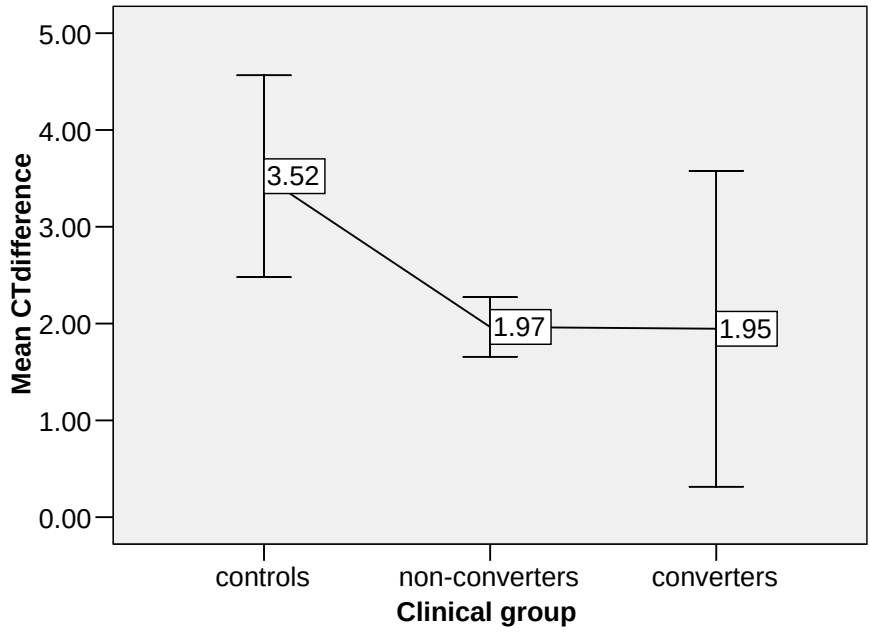
		APS (n=36)	**HC (n=60)**	**Statistics**
AGE (years)	*Mean (SD)*	24.7 (5.0)	24.9 (4.8)	t=0.2, p=0.86
SEX	*% Females*	33%	47%	$\chi 2$=1.65, p=0.20

Mean P50 ratios and C-T differences are shown in figure 3.6. The mean P50 ratio is lower, with higher C-T difference in the controls, when compared to the APS group. The most parsimonious model for P50 ratio was one which included only clinical group as a predictor variable. This model was able to explain up to 5% of the variability in the P50 ratio (R=0.23; R Square= 0.05; F=5.30; p= 0.02). In this model, the variable "group" had a significant contribution to the model (Beta=0.231; p=0.02). The removal or inclusion of the rest of the predictor variables (sex and age) in the model did not affect the contribution of group or its level of statistical significance (Beta=0.228; p=0.02 when all the variables where included). The most parsimonious model for P50 C-T difference was one which included group and sex as predictor variables. This model was able to explain up to 9% of the variability in the C-T difference (R=0.11; R Square= 0.09; F=5.43; p= 0.006). In this model, the variable "group" (Beta=-0.200; p=0.05) and sex had a significant contribution to the model (Beta=0.242; p=0.019).

Of the APS who completed the follow up (n=36), nine (25%) developed psychosis. To elucidate further whether P50 ratio or C-T difference could be used as predictors of risk of developing psychosis we compared APS subjects who made a transition to psychosis to those who did not within the follow up period. There were no statistically significant differences between the non-converters and converters, in the linear regression model for the P50 ratio or its C-T difference. This is probably due to the small number of converters leading to limited power. However, Figure 3.9 illustrates a linear relationship between P50 ratio and conversion to psychosis ($F=5.53$, $p=0.021$). Cases that made a conversion to psychosis display higher P50 ratios and the non-converters are intermediate between healthy controls and the conversion group. C-T difference also shows a linear trend ($F=4.09$, $p=0.046$). Mean C-T difference is highest in the control group and the non-converters and converters perform similarly.

Figure 3-9: Relationship between P50 indexes and conversion to psychosis





3.2.7. Hypothesis (g): Impaired sensory gating measured the P50 ERP will be positively correlated with persecutory paranoia and perceived ethnic discrimination in the APS.

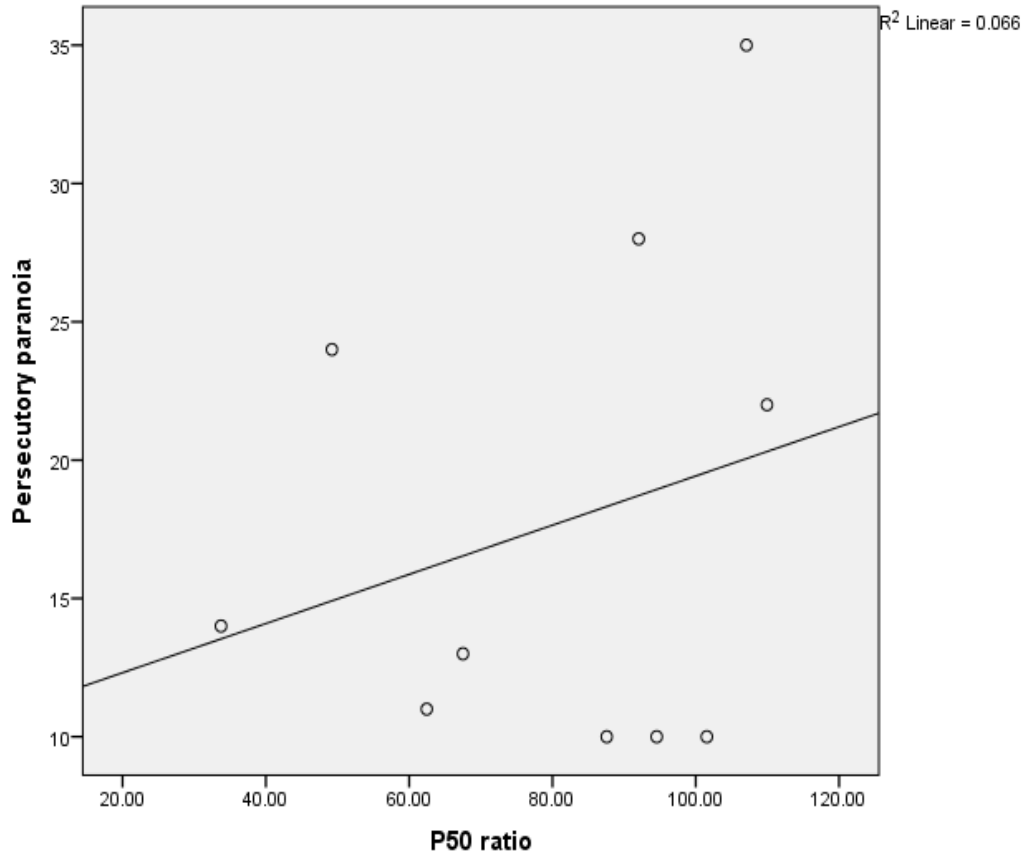
A separate preliminary analysis examining the correlations between sensory gating, persecutory paranoia and perceived ethnic discrimination using the P50 event related potential (ERP) was carried out. This analysis was preliminary as the sample overlapping across ERP and VR measures was very small (n=8-10).

Table 3-6 shows that there were no significant correlations between P50 indexes, persecutory paranoia and perceived ethnic discrimination in the APS sub-group. However, the scatter plot in figure 3-10 suggests a possible weak linear relationship between persecutory paranoid ideation and impaired sensory gating measured by an increased P50 ratio.

Table 3-6: Correlations between P50 ERP and persecutory paranoia and PEDQ

		Persecutory paranoia	PEDQ
P50 ratio	Pearson Correlation	.26	.02
	Sig. (2-tailed)	.47	.96
	N	10	10
CT difference	Pearson Correlation	-.19	-.03
	Sig. (2-tailed)	.66	.95
	N	8	8

Figure 3-10: Scatter plot showing the relationship between P50 and persecutory paranoia.



4. DISCUSSION

The aim of this thesis was to investigate the association between paranoid persecutory ideation and PED, levels of social support and quality of attachment in individuals with APS, using a novel virtual reality paradigm, which simulated a real world scenario. A secondary aim was to investigate the status of a neurophysiological biomarker (P50) for psychosis in APS individuals and to examine its association with PED, and paranoid persecutory ideation. The thesis demonstrates that perceived exposure to adverse experiences observed in individuals with APS, along with the presence of sensory gating deficits, are consistent with current biopsychosocial models of psychosis, in which early psychosocial stress, later psychosocial adversity and neurocognitive dysfunction play a key role in the development of this complex and enduring disorder. However, the temporal relationship of these factors and their yet complex interactions, relating to the exact aetiology of psychosis remains unknown. Nonetheless, an understanding of at-risk mental states, preceding the onset of psychosis, which acknowledges that psychosocial factors are causal, should have a long term impact on mental health services, emphasising on life experiences and subjective meaning of symptoms, and addressing the reduction of psycho-social stressors in order to prevent transitions to the illness stage.

This chapter includes a summary of the main findings and a discussion of findings in relation to previous research followed by reflections on the limitations of the work, clinical and theoretical implications of the findings and future directions.

4.1. Summary of main findings from Part One: VR Paradigm and Psychosocial Adversity

4.1.1. Review of hypotheses and main findings

(a) Compared to controls the APS sample will report higher levels of perceived ethnic discrimination, lower levels of social support, and differences in early attachment.

This hypothesis was supported.

(b) There will be a positive correlation between perceived ethnic discrimination and persecutory paranoid ideation measured via a virtual reality paradigm in the whole sample.

This hypothesis was supported.

(c) Perceived ethnic discrimination and persecutory paranoid ideation in VR will be positively correlated in the APS group.

This hypothesis was rejected.

(d) The relationship between perceived ethnic discrimination and persecutory paranoid ideation in VR will be mediated by prodromal symptomatology in the APS group.

This hypothesis was partially supported.

(e) Perceptions of early attachment, levels of social support and positive prodromal symptomatology will mediate the relationship between perceived discrimination and persecutory paranoid ideation in VR.

This hypothesis was rejected.

4.1.2. Group differences between HC and APS on variables of interest

The results showed heightened levels of PED and lower levels of perceived social support in participants with APS in comparison to HC. Higher rates of perceived maternal neglect and antipathy were also observed in the APS group in comparison to HC participants.

4.1.3. Relationships between variables of interest

Higher levels of PED were associated with higher levels of perceived maternal antipathy and neglect in the entire sample, and PED and perceived maternal neglect were also positively correlated in the APS group. In addition, it was observed that higher levels of PED were associated with increased paranoid persecutory ideation in VR in the whole sample. However, this relationship was no longer significant when controlling for prodromal symptomatology either in the total sample or specifically in the APS group.

4.1.4. Mediating factors between PED and persecutory paranoia

Baseline prodromal symptomatology was not a significant mediator between PED and paranoid persecutory ideation in VR. Nonetheless, positive prodromal

symptomatology was found to mediate the relationship between PED and persecutory paranoid ideation in VR in the presence of other non-significant mediators (perceptions of early attachment and levels of social support). However, these non-significant results were marginal, therefore an indirect relationship between PED and persecutory paranoia via perceptions of early attachment and levels of social support remains a possibility but the current sample appeared not to have sufficient statistical power to detect an effect, as discussed below in the limitations section.

4.1.5. Discussion of findings in relation to previous research

The higher rates of exposure to perceived neglect and antipathy from the mother figure and PED in the APS group are broadly consistent with the studies reporting increased prevalence rates of such experiences of early adversity in people with psychosis (Morgan & Fisher, 2007; Rubino et al., 2009; Saleem et al., 2014) and associations between adversity and psychotic symptoms or disorder in general population samples (Bebbington et al., 2004; Janssen et al., 2004; Spauwen et al., 2006; Whitfield et al., 2005; Wicks et al., 2005). These findings provide evidence to suggest that perceived adversity in early life and young adulthood might increase vulnerability to psychosis. Thus, these are important factors that can contribute to the psychosocial aetiology of psychosis.

Lower levels of perceived social support in the APS group, as observed in this study, are consistent with previous findings, linking social isolation and poor quality relationships with significant others with psychosis risk and outcome (Brown, Birley, & Wing, 1972; Cohen & Sokolovsky, 1978; Leff, Kuipers k, Berkowitz, Eberlein-

Fries, & Sturgeon, 1982; Nettelbladt, Svensson, Serin, & Ojehagen, 1995; Sawant & Jethwani, 2010). This idea would also apply to higher levels of perceived antipathy and neglect from the mother figure in the APS group, as it indicates a poor relationship between the mother figure and offspring. This would likely cause the offspring distress through a perceived lack of affection and support from a significant figure at a key stage in his/her life. However, whether the experiences of perceived antipathy and neglect from the mother figure are of importance regarding psychosis risk, beyond the obvious distress associated with them, needs to be investigated further in a larger sample before any conclusions can be drawn.

While the increased exposure to perceived adverse experiences in the APS group is consistent with previous studies and what would be expected on the basis of current stress-vulnerability models of psychosis, the lack of any association between PED and persecutory paranoid ideation when controlling for baseline prodromal symptomatology was surprising, given the significant group differences in perceived early adversity, levels of social support and PED. Rather, the absence of an association was possibly due to the fact that the vast majority of help seeking APS participants were selected on the basis of having attenuated psychotic symptoms, which, in a relatively small sample, would limit the detection of such an association. Furthermore, it is possible that PED might be more prevalent in ethnic minority groups and studies have shown that incidence of schizophrenia and other psychotic disorders are higher in these populations (Fearon et al., 2006). Berg et al (2011) found that among immigrants from Africa with psychotic disorders, visible minority status was associated with perceived discrimination and with more severe positive and depression/anxiety symptoms, and that these perceptions functioned as a mediator of illness severity for immigrants. These results suggest that context-

specific stressful environmental factors influence specific symptom patterns and severity. In the UK, the risk for developing psychosis in African-Caribbean's is much higher than for South Asians (Fearon et al., 2006) who are likely to experience a higher degree of discrimination (Cantor-Graae & Selten, 2005; Karlsen et al., 2005). Ethnic minority groups are known to differ in terms of their stigmatised status in society. The current study includes a sample from South London which has a high percentage of African-Caribbean's ("Southwark JSNA Executive Summary, 2011") and thus their non-minority status within the specific region might have contributed to their overall perception of discrimination. Other geographical regions might be more likely to have higher rates of perceived discrimination amongst ethnic minorities. In addition, perceived discrimination remains an important determinant of psychotic disorders not only at individual level, but also at group level. Perceptions and impact of discrimination appear to be influenced by group characteristics such as ethnic support, collective self-esteem (Crocker & Major, 1989; Morgan, McKenzie, & Fearon, 2008; Noh & Kaspar, 2003) and perhaps also sensitivity for discrimination which were not directly addressed in the current study. Nonetheless, these results suggest that it is possible that adverse experiences such as perceived maternal neglect/antipathy and PED may have directly contributed to the risk of developing the APS state, but once this was established, other factors, for example, recent stressful life events, may have played a greater role in the expression of progressive symptoms, which would be consistent with the stress-sensitisation model (Myin-Germeys & van Os, 2007; van Winkel et al., 2008). However, future work needs to examine the associations between recent stressful experiences and attenuated psychotic symptoms.

As previously stated, there is now much evidence to show that adverse experiences contribute towards the vulnerability to developing psychosis (Bebbington et al., 2004; Lataster et al., 2012; Varese et al., 2012) and that early adversity may impact on later expression of psychosis by increasing stress sensitivity to later stressful life events (Lardinois, Lataster, Mengelers, Van Os, & Myin-Germeys, 2010; Lataster et al., 2012) and the experience of social defeat (Selten & Cantor-Graae, 2005). Several theories, as previously mentioned in the introduction chapter, could be used to understand the association between perceived adverse experiences and paranoia. The finding that perceived maternal neglect is associated with PED is of importance in terms of bringing a developmental understanding of the influence of early adversity in the development of individuals' patterns of adaptation and coping. These associations are important, as attachment theory provides a framework to understand processes of affect regulation that contribute towards stress sensitivity and coping, and to the vulnerability of developing psychosis. Life events involving threat such as PED, bullying, or victimisation activate the attachment system, and this is reflected in patterns of affect regulation that can lead to paranoid attributions.

The Threat-Anticipation Model (Freeman, 2007) acknowledges that there are multiple causes of paranoid thinking, but identifies the following as particularly important: affective processes, especially anxiety, worry, and interpersonal sensitivity; anomalous experiences such as hallucinations and perceptual abnormalities; reasoning biases, particularly jumping to conclusions and belief inflexibility; and social factors such as adverse events and environments. Based on the Threat-Anticipation model an individual at a time of stress interprets his/her environment in a threatening way because of an anxious affective state and previous adverse experiences such as perceived maternal neglect and antipathy,

which predispose to negative schematic beliefs and social defeat and activate an individual's threat system, resulting in increased perceptions of ethnic discrimination or other adverse experiences.

Similarly, psychosocial adverse experiences early in life are thought to contribute to the development of a cognitive vulnerability for psychosis. According to the cognitive model of positive symptoms of psychosis proposed by Garety et al. (2001), early adverse or traumatic experiences lead to the development of negative or maladaptive core beliefs about the self, other people, and the world in general. Such beliefs are thought to facilitate the development of cognitive biases, such as an externalising attributional style, which in turn lead to the development and maintenance of psychotic appraisals of anomalous experiences later in life (Bentall et al., 2007; Garety et al., 2001). Indeed, negative schematic beliefs have been found to be related to trauma and psychotic symptoms in individuals with and without psychosis (Gracie et al., 2007; Kilcommons & Morrison, 2005). A recent study has reported that higher levels of perceived discrimination are associated with increased negative schemas in the APS group (Saleem et al., 2014). The elevated rates of exposure to early adversity and perceived ethnic discrimination in the present APS sample are consistent with this model. It has also been suggested that the experience of abuse in early life might result in hostile attributions of the intentions of other people and increased awareness of potentially threatening behaviour in others, which could render individuals more prone to suspiciousness and paranoia (Bentall et al., 2001). Other research has confirmed the presence of negative schematic beliefs, particularly regarding rejection and disconnection, in the APS group and such beliefs appear to be related to attenuated psychotic symptoms (Morrison et al., 2006).

Given that this thesis demonstrates a higher rate of PED, perceived childhood maternal neglect and antipathy in individuals with APS, further work is required to investigate the possible psychological and social processes associated with such experiences and how these relate to the development of psychosis vulnerability. In particular, the question of how perceived discrimination might relate to the development of negative schematic beliefs and the cognitive biases associated with the tendency to appraise anomalous experiences using a paranoid attributional style is of great interest.

4.2. Summary of main findings from Part Two: P50 ERP

4.2.1. Review of hypotheses and main findings

(f) The APS sample will be more impaired on P50 ERP indices in comparison to controls.

This hypothesis was supported.

(g) Impaired sensory gating measured by the P50 ERP will be positively correlated with persecutory paranoia and perceived ethnic discrimination in individuals with APS.

This hypothesis was rejected.

This study demonstrated deficits in P50 suppression indexed by the P50 ratio and C-T difference in the APS group, indicating an association between this well established neurophysiological marker and early clinical symptomatology. The hypothesis that P50 in antipsychotic-free APS individuals would differ from that in HC was confirmed, with its ratio significantly increased and CT difference smaller in the APS group. P50 deficits were not found to be greater in the subgroup of APS participants who subsequently developed psychosis than in those who did not. However, there was a linear relationship, although not significant, between group and P50 ratio with the participants who later became psychotic showing greatest P50 deficits. Nine individuals (25%) at the time of analysis in this relatively small sample developed psychosis, which is broadly consistent with published transition rates (Fusar-Poli et al., 2013). However, the analysis comparing only 9 individuals who transitioned to psychosis to those who did not lacked statistical power, therefore, the results should be taken as preliminary. On a similar note, there was no apparent relationship between P50 and persecutory paranoia or perceived ethnic discrimination in a very small APS sample (n=10). To date, this is the first study to examine the associations between P50 and persecutory paranoia or perceived ethnic discrimination in an APS sample.

The P50 results in this thesis are in line with previous reports of diminished P50 suppression in the clinical high-risk sample, first episode psychosis (Brockhaus-Dumke et al., 2008; Myles-Worsley et al., 2004), schizophrenia and psychotic bipolar disorder (Freedman et al., 1996a; Olincy & Martin, 2005; Olincy et al., 2000a; Schulze et al., 2007; Shaikh et al., 2010a), and support the suggestion that P50 gating deficits are not specific to schizophrenia or bipolar disorder, but might be associated with psychosis in general, and also reflect studies showing support for

P50 sensory gating deficits as a stable biomarker for psychosis. These findings are also consistent with previous reports showing that P50 deficits are present early in the disease even in individuals at clinical high risk who did not develop a full blown psychotic episode within the follow-up period of 2 years, though these deficits are most prominent in chronic stages (Brockhaus-Dumke et al., 2008). As found in the current study, APS participants with and without conversion to psychosis did not significantly differ on P50 impairment (Brockhaus-Dumke et al., 2008), thus future studies would need to clarify the role of illness progression and its impact on sensory gating disturbances.

Our findings support the hypothesis that the P50 ratio and C-T amplitude difference, which reflect disturbances in sensory registration and gating, are already present in people with APS and are potential risk indicators of psychosis liability (Brockhaus-Dumke et al., 2008; Hsieh et al., 2012). As such, the current study suggests that the P50 deficit in schizophrenia is related to the development of the disease and could be of help in the prediction of outcomes amongst APS populations. However, longitudinal assessments of P50 sensory gating would be needed to establish to what extent early impairment in P50 sensory gating increases risk for subsequent transition to psychosis and cross sectional designs comparing HC, APS, first episode and schizophrenia groups can help to understand whether P50 deficits fluctuate with clinical symptomatology and treatment in a way that could be useful in clinical practice.

Future research in larger samples is essential to explore synergistic effects of biological and psychosocial predictors on the development of psychosis. The preliminary analysis exploring the relationship between P50, PED and persecutory paranoia did not reveal

any relations between these factors. To date, no study has examined the associations among such factors in APS samples, although some do suggest that if present, the overlap between neurobiological, neurocognitive, psychosocial and clinical dysfunction may not be substantial in APS samples (Byrne et al., 2003; Eack et al., 2008), compared to the more pervasive relations seen in chronic populations (Antonova, Sharma, Morris, & Kumari, 2004). The modest sample size employed in this research may have precluded the detection of significant, albeit small relations between these factors and restricted range of ERPs and measures of perceived adversity in this APS sample may have further impeded the detection of significant relations. It is also possible that neurophysiological markers of cognition, psychosocial adversity, and psychosis proneness represent largely independent risk factors many years prior to the onset of psychotic illness. As early neurodevelopmental insults come to bear on brain development, neurocognitive functions decline and schizophrenia and related psychotic disorders progress, and psychopathology emerges (Keshavan & Hogarty, 1999). At such a time, associations between these factors may become much stronger as they orchestrate the disease progression toward overt illness manifestations. Subsequent investigations will need to examine the longitudinal convergence of these factors over time to more clearly understand their possible interconnectedness and synergistic effects as psychosis develops.

4.3. Limitations and Reflections

4.3.1. APS Terminology

There had been considerable debate on the proposal to include a new diagnostic category based on the clinical high-risk group of attenuated psychotic symptoms in the DSM-5 (APA, 2013). This current version does not include a specific coded diagnostic category for this clinical high-risk group but nevertheless highlights the presence of this important clinical phase, preceding the onset of psychotic symptoms. The addition of a new clinical category should be considered carefully as this would have clinical, ethical and economic considerations, with substantial impact on people potentially diagnosed with this specific syndrome, their families, mental health professionals, and the wider community. Although the APS terminology has been used in DSM-5, it has not been uncommon for clinical services around the world to focus their intervention on the clinical high risk phase (Broome et al., 2005; McGorry et al., 2009; von Reventlow et al., 2014) over the last several years. Clinicians and researchers in favour of a diagnostic category argue that the definition of high risk as a new diagnostic category could encourage clinicians to identify and manage such patients; and effective interventions could alleviate distress, delay or prevent the onset of psychosis, and reduce the subsequent duration of untreated psychosis for those who make a transition (McGorry et al., 2009). Therefore, the purpose of clinical management of this prodromal state is not only to prevent the subsequent onset of overt illness, but also to potentially change the long term trajectory and to improve the patient's presenting distress, which are often of more concern to them than the long-term risks (Fusar-Poli et al., 2009). Adding specific predictors and biomarkers that could increase the predictive power of current APS criteria and enhance the ability to predict outcomes is a crucial step to inform both high-risk and population-based strategies, and could become a key component of early detection, intervention and prevention programs (Keshavan et al., 2005).

However, there are several arguments against the inclusion of the high-risk category. The main concerns relate to the potential high number of false-positive diagnoses of individuals who are not actually at risk of making a transition and the consequences of intervention and labelling of people, and the 'over-medicalisation' of normal experiences (Broome & Fusar-Poli, 2012; Cornblatt, Lencz, & Kane, 2001; Haroun, Dunn, Haroun, & Cadenhead, 2006). Additionally, people meeting the criteria might be incorrectly thought of as being in the range of schizophrenia spectrum disorders. In a survey, most clinicians and general practitioners incorrectly regarded attenuated psychosis syndrome as a mental disorder related to psychosis and schizophrenia (Jacobs, Kline, & Schiffman, 2011). Possible unintended negative consequences of such a diagnosis include stigma, discrimination, and unnecessary treatment (Drake & Lewis, 2010). Furthermore, some clinically high-risk individuals are given antipsychotics that can impact on the brain (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011), even though these drugs are not recommended in treatment guidelines for the prodromal phase ("International clinical practice guidelines for early psychosis," 2005).

Concerns remain that the term APS, as firmly introduced in the DSM-5, could result in individuals with attenuated clinical features being labelled as having an illness, and could lead them to seek treatment unnecessarily, or for others to seek treatment on their behalf. Since this group is heterogeneous in presentation, clinical needs, and outcome, further research is needed to enable detection of those individuals most at risk of psychosis in the APS phase. Research incorporating biomarkers and psychosocial factors can potentially increase predictive power and contribute to the objective characterisation of the APS.

4.3.2. APS Transition Rates

As for clinical outcomes after an average of two years follow up, the rate of transition in the sample, as observed in part two, was lower than in some early studies of the APS (Addington et al., 2007; Broome et al., 2005a; Klosterkotter et al., 2001; Miller et al., 2002; Schultze-Lutter et al., 2010; Yung et al., 2007; Yung et al., 2003a; Yung et al., 2004), but there is considerable variation across centres, reflecting different populations and ascertainment methods. A rate of 25% is consistent with that reported in recent work from European centres (Kaymaz et al., 2012; Morrison et al., 2002; Ruhrmann et al., 2010; Simon et al., 2010; Ziermans, Schothorst, Sprong, & van Engeland, 2010). The average duration of the prodromal phase is of 5 to 6 years (Hafner et al., 1998; Schultze-Lutter et al., 2010) and this takes account of the early and late prodrome definitions. This study uses a 'late' definition of prodrome (Broome et al., 2005; Fusar-Poli et al., 2012), however, it remains a possibility that our observation period of two years may still be insufficient to determine the true final outcome of some non-converters.

The APS construct is a more heterogeneous concept than either schizophrenia or first episode psychosis and it is likely to include a mixture of true prodromal schizophrenia, affective psychosis and other psychotic disorders, individuals who are in the psychotic spectrum but have a favourable outcome, and a majority of individuals who will never develop the illness. Therefore future studies should be large and long enough to follow sufficiently large numbers of patients who can be characterised into subgroups of psychotic disorders and outcome trajectories. It is likely that the reduction in the heterogeneity of the prediction endpoint will yield a

greater possibility to identify specific predictors and biomarkers with clinically sufficient predictive power (Yung, Phillips, Yuen, & McGorry, 2004). In this regard, the recent development toward large, multi-centric studies is clearly beneficial to detect potential deficits and characterise the differences in cognitive function and developmental trajectory of psychosis leading to the development and testing of markers that are predictive of conversion and readily measureable during APS.

As a result of heterogeneity in APS, it is expected that a lesser percentage of APS individuals would for example, have P50 deficits leading to modest effect sizes. Furthermore, based only on two years of observation, one cannot rule out that further APS participants may develop psychosis. Consequently, as in almost all current early detection studies, conclusions about the predictive validity are limited to the respective investigated period. Nevertheless, like other early anomalies predisposing to psychosis, any potential neurophysiological deficits are likely to be subtle and will require large samples for convincing replication and longitudinal designs to establish whether P50 can definately contribute to the prediction of conversion to psychosis. Whether the P50 deficit represents a state or a trait could not be addressed in this study since this would require re-testing P50 at two different time points at least, before and after any symptoms emerge.

4.3.3. Design

The cross-sectional nature of this data, primarily Part one, inevitably limits the inferences that can be drawn regarding causation. There is the possibility that some recent life events, for example a racially motivated attack, may have been a

consequence of attenuated psychotic symptoms, such as persecutory paranoia. This, however, is less likely to be the case for more distal life events and for childhood exposures. Therefore, studies that can more robustly delineate the temporal sequence of exposure and outcome are required. Cross-sectional data such as that presented here nonetheless, provide important pointers to the factors and mechanisms that may underlie the development of psychopathology.

One potential methodological advantage of investigating individuals with APS is that participants can be studied prospectively, and measures of interest obtained at the baseline assessment can then be related to the later onset of psychosis in the same individuals. However, in the absence of clinical follow up of the present APS sample, it was not possible to draw any conclusions regarding causation for the measures found to be associated with the APS participants. The follow up of participants is ongoing, thus future studies could potentially employ a longitudinal design to investigate further the relationship between psychosocial adversity, biomarkers, paranoia and the onset of psychosis and ascertain trajectories in the APS and to investigate longitudinal changes over the transition to psychosis.

4.3.4. Socio-demographic Differences between Groups

While the groups were well matched on key demographic variables of age, gender, ethnicity and migration status, there were significant differences in years of education between APS and HC's. There might also have been differences in other variables such as social class and employment status that were not measured in this study. It is possible that these factors might be related to the psychosocial adversity measures investigated in this study and thus account for some of the observed group differences. However, dropping out of education can be considered

a possible consequence of the development of the APS, making it difficult to match APS and HC participants. In addition, matching educational achievement between groups might reduce the size of any genuine differences on perceived adversity between the groups due to an over-representation of HC participants exposed to the potentially negative consequences of low educational achievement. Recruitment of more HC participants from similar backgrounds (e.g., social class) to the APS participants, could improve the comparability of the two groups by allowing the assumption that APS and HC participants would be equally likely to have been exposed to any adverse experiences potentially associated with similar socio-economic status. Thus, effort should be made in future studies to ensure better matching of participants in this regard.

4.3.5. Sampling and Generalisability

A potential limitation of the present study relates to the type of sampling used to recruit participants. Both APS and HC participants were convenience samples, thus, the generalisability of the findings to the whole APS group is limited. However, the socio-demographic and clinical characteristics of the APS sample are similar to that of the OASIS client group as a whole, which suggests that the sample might be reasonably representative of the help-seeking APS group overall within the limited geographic region.

Another factor affecting the generalisability of the findings is that help-seeking young people at high risk of developing psychosis from the OASIS service may not be representative of all people in the general population who are at risk. The ethical

concerns around the treatment of ‘false positives’, has led early intervention services to see individuals that are help-seeking. It is possible that the characteristic of being help-seeking is in some way associated with the measures assessed in this study, and so the reliance on a sample of help-seeking APS participants in attempting to investigate the relationship between perceived adversity and paranoia as measured by VR could mask any genuine associations that might exist in non-help seeking participants chosen at random from an epidemiological pool.

4.3.6. Co-morbid Problems

Possible confounding effect of co-morbid mental health problems of APS participants was not thoroughly investigated. Psychosocial adverse experiences have been found to be common in a range of mental health problems (Weich, Patterson, Shaw, & Stewart-Brown, 2009), including depression (Bifulco, Brown, & Adler, 1991; Harris, 2001; Saveanu & Nemeroff, 2012), and PTSD (Morrison et al., 2003), and perceived discrimination has been linked to depression and anxiety (Kessler et al., 1999; Miranda, Polanco-Roman, Tsypes, & Valderrama, 2013). High rates of co-morbid psychiatric symptoms and diagnoses are often found in people with psychosis (Bendall, Allott et al., 2008), and this is also true in people at high risk of developing the disorder (Haroun et al., 2006; Yung et al., 2004). This calls into question the specificity of any associations between perceived adverse experiences, persecutory paranoia and psychosis. It is likely that exposure to perceived discrimination and psychosocial adversity increases vulnerability to psychiatric disorders in general. As no record of co-morbid symptoms was available for the present sample, with the exception of current symptoms of depression and anxiety, it was not possible to address this issue comprehensively in the current study.

However, in the larger OASIS dataset (n=509), 73% of APS participants had a comorbid axis I diagnosis in addition to the "at-risk" signs and symptoms. About 40% of APS participants had a comorbid diagnosis of depressive disorder while anxiety disorders were less frequent (8%) (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014). These symptoms may reflect core emotional dysregulation processes and delusional mood in prodromal psychosis. Anxiety and depressive symptoms are likely to impact the ongoing psychopathology, the global functioning, and the overall longitudinal outcome of these patients (Fusar-Poli et al., 2014).

Furthermore studies suggest a relationship between social anxiety and psychosis in general (Birchwood et al., 2007; Voges & Addington, 2005). Several explanations for the high rate of social anxiety in people with a psychotic disorder, and the high rate of psychosis in people with social anxiety, have been proposed. The first explanation is that symptom clusters overlap (Birchwood et al., 2007; Gilbert et al., 2005). The second is that social anxiety is a psychological reaction to psychosis. Birchwood and colleagues found that social anxiety emerges after the onset of psychosis. Possibly, they have more stigmatising thoughts about their illness (Birchwood et al., 2007). A third explanation is that social anxiety is a co-morbid or a prodromal symptom of schizophrenia (Cassano, Pini, Saettoni, Rucci, & Dell'Osso, 1998; Pallanti, Quercioli, & Hollander, 2004). There is also some evidence that social or situation anxiety is a predictor of future psychosis in a genetic at-risk group (Owens, Miller, Lawrie, & Johnstone, 2005; Tien & Eaton, 1992). However, the nature and phenomenology of social anxiety in psychosis is unclear, given its overlap with social anhedonia, depression and persecutory symptoms. Two longitudinal studies (Rietdijk et al., 2009; Schutters et al., 2012) investigated the linear progression of social anxiety and paranoia in the general population. The findings are suggestive of paranoid ideation predicting later onset of social anxiety. An additional limitation of this study is that it did not examine the association of

social anxiety and paranoid ideation in individuals at risk of developing psychosis. A prospective study could reveal some temporal aspects of the association and/or mediating effects on the development of persecutory paranoia in the APS. Future studies incorporating a comprehensive assessment of symptom profile, as well as the development of any supra-threshold mental health problems aside from psychosis, will allow investigations into the specificity of the association between perceived psychosocial adversity, paranoia, and psychosis.

4.3.7. Substance Misuse

Another relevant factor that was not assessed is substance misuse. Substance misuse, especially cannabis, has been shown to be associated with the development of psychosis (Addington, Case et al., 2013; Casadio, Fernandes, Murray, & Di Forti, 2011; Di Forti & Murray, 2005; Di Forti et al., 2014; Donoghue et al., 2014), and several studies have also shown it to be more common in people who have experienced psychosocial adversity (Dube et al., 2003; Mersky, Topitzes, & Reynolds, 2013). It is possible that individuals who have been exposed to early adverse experiences are more likely to begin using illicit substances later on, which in turn could increase their risk of developing psychosis (Harley et al., 2009). A recent study has shown that in individuals with APS, lifetime cannabis use was common but not related to outcome. Amongst cannabis users, frequent use, early-onset use and continued use after clinical presentation were associated with transition to psychosis (Valmaggia et al., 2014). It is also possible that effects of substance use on neurophysiology might underlie the differences found between APS and HC participants on the P50 ERP measures (Gallinat, Rentzsch, & Roser, 2012). Thus, future studies should investigate the role of current and lifetime substance use as a potential mediator and/or confounder.

4.3.8. Other Environmental and Psychosocial Factors

There is a breadth of environmental and psychosocial stressors that influence the development of psychosis which could not be included in this thesis. Many experiences that could also have been relevant to investigating psychosocial adversity and paranoid ideation had not been recorded, for example, serious accidents, illnesses, natural disasters, interpersonal relationships, unemployment. Additional factors that have been implicated in psychosis, such as obstetric complications, prenatal stress and growing up in an urban environment (Ellett, Freeman, & Garety, 2008; Howes & Kapur, 2009) could help to understand the relationship between very early psychosocial stressors and psychosis. Furthermore, perceived discrimination on the basis of other factors such as age, sex, appearance, sexual orientation, or handicap has been shown to similarly increase delusional ideation (Janssen et al., 2003), therefore perceived discrimination in general might increase vulnerability to positive symptoms such as paranoid ideation.

4.3.9. Statistical Power

The present sample is relatively small, and it is likely that several factors investigated in this study that might genuinely be associated with the APS status were not detected due to limited power. This issue is of particular importance with regard to determining which factors are associated with the subsequent onset of psychosis, especially given the declining rates of transition to psychosis that have been reported in APS samples in recent years (McGorry, Killackey, & Yung, 2008). Future research in larger samples of young people with APS is required to clarify the findings presented in this thesis. However, recruitment of APS individuals is difficult

and one solution is to do multicentre studies which are increasingly becoming common for these samples. The required sample size to detect the mediated effect for hypothesis d (The relationship between perceived ethnic discrimination and persecutory paranoid ideation in VR will be mediated by prodromal symptomatology in the APS group) with 80% power, based on the Fritz and MacKinnon's (2007) estimate is at least 462 for small effect sizes (0.14). Hence, the current results for hypothesis d, which demonstrate effect sizes of 0.1, would ideally require a significantly larger sample size.

4.4. Clinical and Research Implications

4.4.1. Psychosocial Adversity a Risk Factor for APS

It takes considerable time to translate aetiological findings into clinical, social and economic arenas, and a lack of robust and consistent findings present more questions, which need further exploration. The differing methods employed across studies investigating psychosocial adversity in psychosis makes comparison of the rates of different types of adverse experiences problematic. However, an understanding of psychosis, which acknowledges that psychosocial factors are causal, should have a long term impact on services and the wellbeing of patients with a greater emphasis placed on life experiences and individualised meaning of symptoms. In the long term, an understanding of the role of adversity in psychosis is likely to lead to the development of a discipline and/or service that focuses on ameliorating social adversities that lead to mental ill-health and is likely to lead to long-term economic benefits.

The detection of individuals with APS and provision of clinical services for such individuals has facilitated considerable research in recent years into the factors associated with the onset of psychosis and the effectiveness of novel interventions in this group (McGorry et al., 2008; McGorry et al., 2009; Ruhrmann et al., 2010). At present, however, early intervention teams are unable to identify those APS individuals who are going to develop psychosis on purely clinical grounds.

The results of the present study indicate that the P50 ERP could potentially be a neurophysiological marker, and that perceived ethnic discrimination might be an important psychosocial risk factor for the development of the APS state and psychosis, thus exploring the synergistic effects of these markers could potentially improve predictive power. This is significant because adversity has also been associated with poorer outcomes in terms of persistence of symptoms and social functioning in people with psychosis (Lysaker, Buck, & LaRocco, 2007; Lysaker, Outcalt, & Ringer, 2010; Varese et al., 2012). Even in those who may not develop psychosis, there is still an increased risk of other mental health problems associated with perceived discrimination and early childhood adversity, such as depression and anxiety (Kessler et al., 1999; Miranda et al., 2013; Saveanu & Nemeroff, 2012). Thus, it is important that these factors are identified in those at high risk for psychosis and that appropriate support relating specifically to the experience of adverse events is provided (Read et al., 2003; Read et al., 2005).

4.4.2. Psychosocial Interventions

Evidence implicating adverse experiences in early psychosis indicates an opportunity to provide psychosocial interventions directed towards improving the ability to cope with stressful experiences, and the use of stress reduction and relaxation strategies, which may then lead to a reduction in the severity of symptoms, or at least in distress related to the abnormal experiences (Phillips, Francey, Edwards, & McMurray, 2009). Given that perceived ethnic discrimination is associated with the APS, this finding highlights the potential utility of exploring how an individual's perception of adverse experience might relate to how he or she responds to current challenges and stressors. This could be beneficial in helping the individual to develop an understanding of his or her mental health difficulties which lends itself well to psychological therapy approaches such as Cognitive Behavioural Therapy (CBT). Therapeutic processes including decatastrophising symptoms and fear of exacerbation, normalization of experiences, generation and evaluation of alternative, more reality based interpretations, as well as testing them in behavioural experiments could be potentially helpful CBT interventions in the APS group (Bechdolf et al., 2006; Bechdolf et al., 2005; Morrison & Barratt, 2009). In addition, such interventions could also include stress management, problem solving, coping, and psychoeducational components. In comparison to antipsychotic medication, psychosocial interventions offer the advantage of being more acceptable and less stigmatising, not exposing potentially false-positive APS individuals to side-effects, as well as providing effective treatment even to false-positives (McGorry et al., 2009).

4.4.3. Importance of Biopsychosocial Models

Accurate prediction of psychosis development in the APS has been complicated by the multifactorial aetiopathology of these illnesses and the breadth of nonspecific psychopathological features that precedes full blown clinical symptoms (Keshavan et al., 2008), and thus multivariate biopsychosocial predictive models might better reflect the complex aetiology. Few studies thus far have evaluated the predictive power of integrative models incorporating a range of early and late risk factors from neurobiological, socio-environmental, cognitive and clinical domains (Eack et al., 2008; Shah et al., 2012). The results of this thesis suggest that diverse risk factors at various developmental stages including perceived maternal neglect, PED, cognitive dysfunction marked by the P50 ERP have relevance for subsequent development of psychosis. Thus, models that take into account relationships between factors may offer a powerful approach for optimizing risk criteria for APS.

4.5. Future Directions

4.5.1. Multivariate Predictive Models

Accurate prediction of psychosis development during the premorbid and prodromal periods has long been sought by researchers studying psychosis (Meares, 1959; Sullivan, 1994), however this remains insufficient to reliably predict which individuals with APS will transit to psychosis (Nelson & Yung, 2010). If achieved, prediction could suggest early detection and targeted intervention strategies, and might lead to

substantial decreases in morbidity and burden of illness, and improvements in quality of life (Keshavan et al., 2005; McGorry et al., 2002; Wyatt, 1991).

Thus far, APS prediction studies, attempting to incorporate a biopsychosocial approach have investigated the role of social, cognitive, clinical and neurobiologic markers, alongside family history. Eack et al. (2008) found that total brain volume, baseline neurocognitive deficits, and baseline psychosis proneness prospectively predicted emerging psychopathology development (rather than psychosis specifically) in a familial high-risk population, with little overlap among these domains. In a larger North American population of individuals with APS, Cannon et al. (2008) calculated that familial risk with recent functional impairment, unusual thought content or suspicion/paranoia, social impairment and substance abuse were all predictive of later psychosis, with increased predictive power achieved via combinations of these variables. This analysis was replicated in an independent Australian cohort, with similar but non-identical results (Thompson, Nelson, & Yung, 2011), and in a European study combining APS and cognitive “basic symptom” criteria, Ruhrmann et al. (2010) report high positive predictive value for a six-variable model and introduce a prognostic index for assigning individual risk. Currently, the Avon Longitudinal Study of Parents and Children (ALSPAC) are combining neuroimaging and cognitive data with longitudinal clinical data to explore predictive models in the APS group.

Psychobiological models utilized in these studies have generally had higher specificity (0.92) than sensitivity (0.50) (Eack et al., 2008), illustrating the need for further refinement to enable use as clinical screening tools. In this light, recent

decades have seen increasing attention directed to the interaction of socio-environmental, biological and psychological factors in psychosis (Morgan et al., 2008; Shah et al., 2012; Tandon, Keshavan, & Nasrallah, 2008). Despite small effect sizes and low specificity, the widespread exposure to socio-environmental risk factors suggests their substantial population-attributable risk (Kirkbride et al., 2010; Kirkbride et al., 2013; McGrath et al., 2004). An initial multivariate familial high risk prediction study developed a model of interactive genetic and environmental factors (Carter, Schulsinger, Parnas, Cannon, & Mednick, 2002); subsequent investigations have been sparse, with mixed results, and primarily in APS populations exploring premorbid psychosocial functioning (Dragt et al., 2011; Mason et al., 2004).

Shah and colleagues (2012) examined the relevant contribution of such socio-environmental, cognitive and clinical factors to subsequent development of psychosis in adolescent at-risk relatives, using structural equation modelling. Their findings suggest that baseline clinical psychosis proneness is directly predictive of subsequent transition to psychosis, while baseline neurocognitive impairment and early exposure to known familial and socio-environmental risk factors are indirectly predictive of subsequent conversion through the mediating clinical measure. Thus, certain socio-environmental factors can contribute to individual-level risk prediction, especially in those individuals who carry genetic risk. This study demonstrated relatively high specificity (0.99) but low sensitivity (0.17), again limiting its utility as an initial screening test. Nonetheless, such models with relatively high specificity might be particularly effective in highlighting those for whom preventative intervention would beneficial (Shah et al., 2012). These results provide support to integrative modelling of multivariate data from a broad array of domains (cognitive, social, imaging, electrophysiologial, genetics). Research that aims to integrate

neurophysiological markers of cognitive function and psycho-social adversity (e.g. P50 ERP and PED) can advance our understanding of brain abnormalities and the psycho-social basis of psychosis and represents a powerful approach to prospective prediction of psychosis development.

Future research could draw upon additional risk and protective factors or differentially theorised relationships among variables. It is also conceivable that the constellation of factors (or the relationships among factors) relevant to accurate psychosis prediction will change based on the combination of early exposures and individual/ecological risks borne and experienced by particular individuals and populations at various developmental stages (Shah et al., 2012). Models could therefore be adjusted to account for the potentially staggered, latent, synergistic and/or cascading effects of risk and protective factors acting at critical time-points.

4.6. Conclusion

This thesis shows that perceived parental neglect and antipathy in childhood, perceived ethnic discrimination and perceived social support are key factors in young adults with APS. Also the experience of PED is related to attenuated psychotic symptoms such as persecutory paranoia. Furthermore, individuals with APS displayed sensory gating impairments indexed by the P50 ERP. The results of this thesis demonstrate that the findings of perceived exposure to adverse experiences and sensory gating deficits observed in individuals with APS are present before the first episode and are consistent with current biopsychosocial models in which early psychosocial stress, later psychosocial adversity and

neurocognitive functioning play a key role in the development of psychosis. However, many questions remain to be answered about the exact nature of this role. Further research in larger samples of individuals at increased risk for psychosis, investigating a wider range of psychosocial and biological factors repeatedly over the high risk period, will allow exploration of the temporal relationship of these factors and how the interplay between them relates to the development of psychosis.

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APPENDIX 1: Ethics Approval RHUL

Ref: 2013/025 Ethics Form Approved

Psychology-Webmaster@rhul.ac.uk

Mon 08/04/2013 13:53

To:nwjt073@rhul.ac.uk <nwjt073@rhul.ac.uk>; Ellett, Lyn <Lyn.Ellett@rhul.ac.uk>;

Cc:PSY-EthicsAdmin@rhul.ac.uk <PSY-EthicsAdmin@rhul.ac.uk>; Leman, Patrick <Patrick.Leman@rhul.ac.uk>;

Application Details:

Applicant Name:	**Madiha Shaikh**
Application title:	**Paranoia and perceived ethnic discrimination in the at-risk mental state for psychosis**

APPENDIX 2: NHS Ethics Approval

08/H0722/45

NHS
National Research Ethics Service

Camden & Islington Community Local Research Ethics Committee
Room 3/14
Third Floor, West Wing
St Pancras Hospital
4 St Pancras Way
London
NW1 0PE

Telephone: 020 7530 3799
Facsimile: 020 7530 3931

14 July 2008

Dr Lucia R. Valmaggia
Peggy Pollak Research Fellow/Clinical Lecturer
Institute of Psychiatry, KCL
Dept of Psychological Medicine, PO 67
De Crespigny Park
London
SE5 8AF

Dear Dr Valmaggia

Full title of study: **The impact of early adverse experiences on the vulnerability for psychosis**

REC reference number: **08/H0722/45**

Thank you for your letter of 04 July 2008, responding to the Committee's request for further information on the above research and submitting revised documentation, subject to the conditions specified below.

The further information was considered at the meeting of the Sub-Committee of the REC held on 09 July 2008. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		28 April 2008
Investigator CV	C.I.s CV - Lucia Valmaggia	30 April 2008
Protocol	Version 1	30 April 2008
Summary/Synopsis	Version 1	30 April 2008
Interview Schedules/Topic Guides	Post VR interview guide - Version 1	30 April 2008
Questionnaire: Perceived Stress Scale	Version 1	30 April 2008
Questionnaire: Brief Life Events Questionnaire	Version 1	30 April 2008
Questionnaire: Family Relationships in Childhood - CECA-Q	Version 1	30 April 2008
Questionnaire: Retrospective Bullying Questionnaire	Version 1	30 April 2008
Questionnaire: OASIS SF Scale	Version 1	30 April 2008
Questionnaire: Achievement - Expectation Scale	Version 1	30 April 2008
Questionnaire: Defeat Scale (SDS)	Version 1	30 April 2008
Questionnaire: Entrapment Scale (SES)	Version 1	30 April 2008
Questionnaire: Social Comparison Scale	Version 1	30 April 2008
Questionnaire: Perceived Ethnic Discrimination Questionnaire - Community Version	Version 1	30 April 2008
Questionnaire: Post VR VAS Scales	Version 1	30 April 2008
Questionnaire: SSPS	Version 1	30 April 2008
Questionnaire: IPSM		30 April 2008
Questionnaire: DASS	Version 1	30 April 2008
Questionnaire: Multidimensional Scale of Perceived Social Support	Version 1	30 April 2008
Participant Information Sheet: For participants	Version 2	04 July 2008
Participant Information Sheet: For control participants	Version 2	04 July 2008
Participant Consent Form: For participants	Version 2	04 July 2008
Participant Consent Form: For control participants	Version 2	04 July 2008
Response to Request for Further Information		04 July 2008
Virtual reality study of paranoid thinking in the general population	D. Freeman et al.	01 January 2008
'Studying and treating schizophenia using virtual reality; A new paradigm'	D. Freeman	28 March 2008
'Virtual reality and paranoid ideations in people with an 'at-risk mental state' for psychosis'	Valmaggia et al.	01 January 2007

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/H0722/45	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Ms Stephanie Ellis
Chair

Email: katherine.ouseley@camdenpct.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Sponsor and Research Governance contact:*

Mrs Gill Lambert
Research Governance/ Clinical Trials Facilitator
Institute of Psychiatry/ SLAM, Room P005, R&D Office
De Crespigny Park, Denmark Hill
London, SE5 8AF

Camden & Islington Community Local Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 09 July 2008

Committee Members:

Name	*Profession*
Ms Stephanie Ellis (CHAIR)	Former Civil Servant
Professor David Caplin	Senior Research Investigator, Professor of Physics

APPENDIX 3: Information Sheet for Controls- Part 1

Participant Information Control

The impact of early adverse experiences on the vulnerability for psychosis

You are being invited to take part in a study being conducted at the Institute of Psychiatry, King's College London by Dr Lucia Valmaggia

Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

WHAT IS THE PURPOSE OF THE STUDY?
People who are experiencing symptoms that suggest they could be at risk of developing a mental illness may also be experiencing changes in hormone levels in their blood (cortisol) in their daily life. This study will measure cortisol in your saliva before and after a virtual tube train journey and also assess several aspects of your psychological state at or around the time of the virtual tube train journey. Salivary samples are obtained by chewing on a pad and inserting it into a sealed container. The samples may be mailed back to the researchers, or other means of recovery may be arranged.

WHY HAVE I BEEN INVITED TO TAKE PART?
You have been invited to take part as part of the control sample. This means that we are measuring the levels of the cortisol hormone in the normal populations and you have been asked to participate in this study as a control subject.

DO I HAVE TO TAKE PART?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time, without giving a reason. Your decision will not affect the standard of care you receive from any medical services at any time.

WHAT WILL HAPPEN TO ME IF I TAKE PART?
Everyone who decides to take part in the study will be interviewed by one of the researchers for about thirty minutes. During the interviews, the researcher will ask you about how you have been feeling and recent experiences you have had. Instruction in the use of the virtual reality equipment will then be given to ensure you feel comfortable with the equipment. Subsequently you will be asked to take a virtual 'tube train' journey for a few minutes. You will then be asked about your experience of the virtual environment and to complete some questionnaires. The samples will be taken at 9 times during a 2 hour period, before, and after the virtual reality tube ride

If you are willing, some of your responses will be tape-recorded. These tapes will be destroyed at the end of the study. We would also like to contact you by phone one week after your involvement in the study to ask you some further questions about your virtual experience.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?
When people use virtual reality systems, some people sometimes experience some degree of nausea. If at any time you wish to stop taking part in the study due to this or any other reason, please just say so and we will stop.

There has been some research that suggests that people using head-mounted displays might experience some disturbances in vision afterwards. No long term studies are known to us, but the studies which have been carried out do testing after about 30 minutes, and find the effect is still sometimes there. It is advised that participants do not drive a car, motorcycle, or use any piece of complicated machinery in the four hours immediately following being in virtual reality.

There have been various reported side effects of using virtual reality equipment, such as 'flashbacks'. There is a possibility that an epileptic episode may be generated by the Virtual Reality equipment. This, for example, has been reported for computer video games. If you have a history of epilepsy we would not want you to take part in the study.

If you would like to take part in the study, please read and sign the consent slip below. Please do not hesitate to contact Dr Lucia Valmaggia (details below) should you require any further information.

Care should be taken not to swallow the pads that will be chewed to gather the saliva.

WHAT IF SOMETHING GOES WRONG?
You have the right at law to claim compensation for injury where you can prove negligence. The researchers will not compensate you where such injury results from any procedure carried out which is not in accordance with the protocol for the study.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?
If you consent to take part in the research any of your medical records may be looked at by people from the research group to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital/GP surgery. By signing the consent form you are giving permission for this to be done.

The information collected during the study will be stored in a computer but your name will not be linked to it in any way.

If during the course of this study we obtain information that indicates that you may be at risk of harming yourself or harming others we will discuss this with you and we will let your GP know about it.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study are unlikely to be published before 2011. Copies of the published results will be available to you on request. The researcher will also explain the results to you in person.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

The study has been funded by the Psychiatry Research Trust and by the NARSAD, The World's

Leading Charity Dedicated to Mental Health Research.

WHO HAS REVIEWED THE STUDY?

An ethics committee has reviewed the study for compliance with medical and ethical standards and for scientific value.

CONTACT FOR FURTHER INFORMATION

Whenever you want to get more information on this study, please contact: Dr Lucia Valmaggia

Address: PO67, Institute of Psychiatry
De Crespigny Park, Denmark Hill
London, SE5 8AF

Tel: 0207 848 0958
E-mail: lucia.valmaggia@iop.kcl.ac.uk

Thank you for considering taking part in this study. You will be given a copy of the information sheet and a signed consent form to keep.

APPENDIX 4: Information Sheet for OASIS Clients- Part 1

Participant Information

The impact of early adverse experiences on the vulnerability for psychosis

You are being invited to take part in a study being conducted at the Institute of Psychiatry, King's College London by Dr Lucia Valmaggia

Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

WHAT IS THE PURPOSE OF THE STUDY?
People who are experiencing symptoms that suggest they could be at risk of developing a mental illness may also be experiencing changes in hormone levels in their blood (cortisol) in their daily life. This study will measure cortisol in your saliva before and after a virtual tube train journey and also assess several aspects of your psychological state at or around the time of the virtual tube train journey. Salivary samples are obtained by chewing on a pad and inserting it into a sealed container. The samples may be mailed back to the researchers, or other means of recovery may be arranged.

WHY HAVE I BEEN INVITED TO TAKE PART?
You have been invited to take part because you are experiencing symptoms that suggest you may be at risk of developing a mental health problem.

DO I HAVE TO TAKE PART?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time, without giving a reason. Your decision will not affect the standard of care you receive from any medical services at any time.

WHAT WILL HAPPEN TO ME IF I TAKE PART?
Everyone who decides to take part in the study will be interviewed by one of the researchers for about thirty minutes. During the interviews, the researcher will ask you about how you have been feeling and recent experiences you have had. Instruction in the use of the virtual reality equipment will then be given to ensure you feel comfortable with the equipment. Subsequently you will be asked to take a virtual 'tube train' journey for a few minutes. You will then be asked about your experience of the virtual environment and to complete some questionnaires. The samples will be taken at 9 times during a 2 hour period, before, and after the virtual reality tube ride

If you are willing, some of your responses will be tape-recorded. These tapes will be destroyed at the end of the study. We would also like to contact you by phone one week after your involvement in the study to ask you some further questions about your virtual experience.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?
When people use virtual reality systems, some people sometimes experience some degree of nausea. If at any time you wish to stop taking part in the study due to this or any other reason, please just say so and we will stop.

There has been some research that suggests that people using head-mounted displays might experience some disturbances in vision afterwards. No long term studies

are known to us, but the studies which have been carried out do testing after about 30 minutes, and find the effect is still sometimes there. It is advised that participants do not drive a car, motorcycle, or use any piece of complicated machinery in the four hours immediately following being in virtual reality.

There have been various reported side effects of using virtual reality equipment, such as 'flashbacks'. There is a possibility that an epileptic episode may be generated by the Virtual Reality equipment. This, for example, has been reported for computer video games. If you have a history of epilepsy we would not want you to take part in the study.

If you would like to take part in the study, please read and sign the consent slip below. Please do not hesitate to contact Dr Lucia Valmaggia (details below) should you require any further information.

Care should be taken not to swallow the pads that will be chewed to gather the saliva.

WHAT IF SOMETHING GOES WRONG?
Your have the right at law to claim compensation for injury where you can prove negligence. The researchers will not compensate you where such injury results from any procedure carried out which is not in accordance with the protocol for the study.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?
If you consent to take part in the research any of your medical records may be looked at by people from the research group to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital/GP surgery. By signing the consent form you are giving permission for this to be done.

The information collected during the study will be stored in a computer but your name will not be linked to it in any way.

If during the course of this study we obtain information that indicates that you may be at risk of harming yourself or harming others we will discuss this with you and we will let your care-coordinator in OASIS know about it.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?
The results of the study are unlikely to be published before 2011. Copies of the published results will be available to you on request. The researcher will also explain the results to you in person.

WHO IS ORGANISING AND FUNDING THE RESEARCH?
The study has been funded by the Psychiatry Research Trust and by the NARSAD, The World's
Leading Charity Dedicated to Mental Health Research.

WHO HAS REVIEWED THE STUDY?
An ethics committee has reviewed the study for compliance with medical and ethical standards and for scientific value.

CONTACT FOR FURTHER INFORMATION
Whenever you want to get more information on this study, please contact: Dr Lucia Valmaggia

Address: PO67, Institute of Psychiatry
De Crespigny Park, Denmark Hill
London, SE5 8AF

Tel: 0207 848 0958
E-mail: lucia.valmaggia@iop.kcl.ac.uk

Thank you for considering taking part in this study. You will be given a copy of the information sheet and a signed consent form to keep.

APPENDIX 5: Consent Form – Part one

Consent Form

The impact of early adverse experiences on the vulnerability for psychosis

Participant Number: Participant Initials: Name of Investigator:

Please initial box

I confirm that I have read and understand the information sheet dated 04/07/2008 for the above study and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that the information that I provide will be processed and analysed as is required by this research study and according to the Data Protection Act	☐
I agree to take part in the above study.	☐
I consent to having the results of this study correlated with the results of any other research studies I might participate in.	☐

Name of Participant	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

APPENDIX 6: Questionnaires used in the study

PQ

Prodromal Questionnaire

By Rachel Loewy, Adrian Raine and Tyrone Cannon.

ID: _____

Age: _____

Date: _____

May 2002

This questionnaire asks a number of questions about your thoughts, feelings, and experiences. Please read each item carefully and indicate whether you agree or disagree with it by circling true or false in the right-hand margin next to that item. Please try to answer each question.

1.	I am easily distracted by noises or other people talking.	True	False
2.	The passage of time feels unnaturally faster or slower than usual.	True	False
3.	I often have difficulty organizing my thoughts or finding the right words.	True	False
4.	When I look at a person, or look at myself in a mirror, I have seen the face change right before my eyes.	True	False
5.	I sometimes get strange feelings on or just beneath my skin, like bugs crawling.	True	False
6.	I do not get along well with people at school or at work.	True	False
7.	Familiar surroundings sometimes seem strange, confusing, threatening or unreal.	True	False
8.	I often seem to live through events exactly as they happened before (déjà vu).	True	False
9.	I sometimes smell or taste things that other people can't smell or taste.	True	False
10.	I have difficulty concentrating, listening or reading.	True	False
11.	I have had troubles at school or work recently.	True	False
12.	Sometimes I think that people can read my mind.	True	False
13.	I have heard things other people can't hear like voices of people whispering or talking.	True	False
14.	I can't express my feelings as well as I used to.	True	False
15.	I have interests that other people find odd.	True	False
16.	I have lost a sense of who I am.	True	False
17.	I am less interested than I used to be in keeping clean or dressing well.	True	False
18.	I often hear unusual sounds like banging, clicking, hissing, clapping or ringing in my ears.	True	False
19.	I often mistake shadows for people or noises for voices.	True	False
20.	Things that I see appear different from the way they usually do (brighter, duller, larger, smaller, or changed in some other way).	True	False
21.	I tend to be very quiet and keep in the background on social occasions.	True	False
22.	People sometimes stare at me because of my odd appearance.	True	False
23.	I wander off the topic or ramble on too much when I am speaking.	True	False
24.	I believe in telepathy, psychic forces, or fortune-telling.	True	False
25.	I often feel that others have it in for me.	True	False

26.	My sense of smell sometimes becomes unusually strong.	True	False
27.	Sometimes I have felt that I'm not in control of my own ideas or thoughts.	True	False
28.	I have been feeling unhappy or depressed lately.	True	False
29.	Everyday things affect me more than they used to.	True	False
30.	I believe that I am especially important or have abilities that are out of the ordinary.	True	False
31.	Other people think that I am a little strange.	True	False
32.	Sometimes my thoughts seem to be broadcast out loud so that other people know what I am thinking.	True	False
33.	I often feel that I have nothing to say or very little to say.	True	False
34.	I am unusually sensitive to noise.	True	False
35.	I am superstitious.	True	False
36.	I have heard my own thoughts as if they were outside of my head.	True	False
37.	I have trouble focusing on one thought at a time.	True	False
38.	I often feel that other people are watching me or talking about me.	True	False
39.	I get very nervous when I have to make polite conversation.	True	False
40.	People comment on my unusual mannerisms and habits.	True	False
41.	I am less interested in school or work lately.	True	False
42.	I find it hard to be emotionally close to other people.	True	False
43.	I tend to avoid social activities with other people.	True	False
44.	I feel very guilty.	True	False
45.	I am an odd, unusual person.	True	False
46.	I sometimes feel that things I see on television or read in the newspaper have a special meaning for me.	True	False
47.	My moods are highly changeable and unstable.	True	False
48.	I have been unable to enjoy things that I used to enjoy .	True	False
49.	My thinking feels confused, muddled, or disturbed in some way.	True	False
50.	Sometimes I feel suddenly distracted by distant sounds that I am not normally aware of.	True	False
51.	Recently, I have begun talking to myself.	True	False
52.	I have had the sense that some person or force is around me, even though I could not see anyone.	True	False
53.	I am in danger of failing out of school, or have been fired from my job.	True	False

54.	I have some eccentric (odd) habits.	True	False
55.	At times I worry that something may be wrong with my mind.	True	False
56.	I have felt that I don't exist, the world does not exist, or that I am dead.	True	False
57.	I have been confused at times whether something I experienced was real or imaginary.	True	False
58.	People find me aloof and distant.	True	False
59.	I tend to keep my feelings to myself.	True	False
60.	I have experienced unusual bodily sensations (tingling, pulling, pressure, aches, burning, cold, numbness, shooting pains, vibrations or electricity).	True	False
61.	I hold beliefs that other people would find unusual or bizarre.	True	False
62.	People say that my ideas are strange or illogical.	True	False
63.	I feel worthless.	True	False
64.	I feel that parts of my body have changed in some way, or that parts of my body are working differently than before.	True	False
65.	My thoughts are sometimes so strong that I can almost hear them.	True	False
66.	I am not very good at returning social courtesies and gestures.	True	False
67.	I sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around me.	True	False
68.	I often pick up hidden threats or put-downs directed at me in what people say or do.	True	False
69.	I sometimes use words in unusual ways.	True	False
70.	I am often angry, easily irritated or offended.	True	False
71.	I have felt like I am looking at myself as in a movie, or that I am a spectator in my own life.	True	False
72.	I am less able to do usual activities or tasks.	True	False
73.	I have not been sleeping well lately.	True	False
74.	At times I have felt that some person or force interferes with my thinking or puts thoughts into my head.	True	False
75.	I have had experiences with the supernatural, astrology, seeing the future or UFOs.	True	False
76.	Some people drop hints about me or say things with a double meaning.	True	False
77.	I am often concerned that my closest friends, classmates, or co-workers are not really loyal or trustworthy.	True	False
78.	I have little interest in getting to know other people.	True	False

79.	I have seen unusual things like flashes, flames, blinding light, or geometric figures.	True	False
80.	I get extremely anxious when meeting people for the first time.	True	False
81.	I have felt like I am at a distance from myself, as if I am outside my own body or that a part of my body did not belong to me.	True	False
82.	I find that when something sad happens, I am no longer able to feel sadness, or when something joyful happens, I can no longer feel happy.	True	False
83.	I cry often.	True	False
84.	I have seen things that other people apparently can't see.	True	False
85.	I feel unable to carry out everyday tasks because of fatigue or lack of motivation.	True	False
86.	Everyday things are more stressful than before, like school or work, social situations, deadlines or changes in a schedule.	True	False
87.	I often avoid going to places where there will be many people because I will get anxious.	True	False
88.	I have felt more nervous or anxious lately, and find it hard to relax.	True	False
89.	I feel uninterested in the things I used to enjoy.	True	False
90.	People often find it hard to understand what I am saying.	True	False
91.	I have trouble remembering things.	True	False
92.	People say that I seem “spacey” or “out of it”.	True	False

Social State Paranoia Scale

We are interested in your views of the other people who were on the tube. Please circle **how much you agree or disagree** with the following statements based upon your thoughts when you were on the tube.

	Do not agree	Agree a little	Moderately agree	Agree very much	Totally agree
1. Someone was hostile towards me	**1**	**2**	**3**	**4**	**5**
2. No-one had any particular feelings about me	**1**	**2**	**3**	**4**	**5**
3. Someone had bad intentions towards me	**1**	**2**	**3**	**4**	**5**
4. Someone was friendly towards me	**1**	**2**	**3**	**4**	**5**
5. Someone was trying to make me distressed	**1**	**2**	**3**	**4**	**5**
6. I felt very safe in their company	**1**	**2**	**3**	**4**	**5**
7. Someone stared at me in order to upset me	**1**	**2**	**3**	**4**	**5**
8. Everyone was trustworthy	**1**	**2**	**3**	**4**	**5**
9. Someone wanted me to feel threatened	**1**	**2**	**3**	**4**	**5**
10. I wasn't really noticed by anybody	**1**	**2**	**3**	**4**	**5**
11. Someone had kind intentions toward me	**1**	**2**	**3**	**4**	**5**
12. Someone would have harmed me in some way if they could	**1**	**2**	**3**	**4**	**5**
13. Someone had it in for me	**1**	**2**	**3**	**4**	**5**
14. Everyone was neutral towards me	**1**	**2**	**3**	**4**	**5**
15. Someone was trying to intimidate me	**1**	**2**	**3**	**4**	**5**
16. Everyone was pleasant	**1**	**2**	**3**	**4**	**5**
17. Someone was trying to isolate me	**1**	**2**	**3**	**4**	**5**
18. No-one had any intentions towards me	**1**	**2**	**3**	**4**	**5**
19. Everyone seemed unconcerned by my presence	**1**	**2**	**3**	**4**	**5**
20. Someone was trying to irritate me	**1**	**2**	**3**	**4**	**5**

Perceived Ethnic Discrimination Questionnaire

Think about your ethnicity/race. What group do you belong to?

YOUR ETHNICITY/RACE: _____

How often have any of the things listed below happened to you, **because of your ethnicity**?

BECAUSE OF YOUR ETHNICITY/RACE …

A.	**How often…**	**Never**		**Sometimes**		**Very Often**
1.	Has someone said something disrespectful, either to your face or behind your back?	1	2	3	4	5
2.	Have you been kept out of a public place or group?	1	2	3	4	5
3.	Have you been treated unfairly by teachers, principals, or other staff at school?	1	2	3	4	5
4.	Have others thought you couldn't do things or handle a job?	1	2	3	4	5
5.	Have others **threatened** to hurt you (ex: said they would hit you)?	1	2	3	4	5
6.	Have others **actually** hurt you or tried to hurt you (ex: kicked or hit you)?	1	2	3	4	5
7.	Have others avoided talking to you or answering you?	1	2	3	4	5
8.	Have you felt that you were kept out of certain places?	1	2	3	4	5
9.	Have policemen or security officers been unfair to you?	1	2	3	4	5
10.	Have others hinted that you are stupid?	1	2	3	4	5
11.	Have others **threatened** to damage your property?	1	2	3	4	5
12.	Have others **actually** damaged your property?	1	2	3	4	5
13.	Have people called you bad names related to your ethnicity?	1	2	3	4	5

BECAUSE OF YOUR ETHNICITY/RACE …

A.	**How often…**	**Never**		**Sometimes**		**Very Often**
14.	Have others made you feel like an outsider who doesn't fit in because of your dress, speech, or other characteristics related to your ethnicity?	1	2	3	4	5
15.	Were you left out when others were planning a party or get-together?	1	2	3	4	5

16.	Have you been treated unfairly by co-workers or classmates?	1	2	3	4	5
17.	Have others hinted that you are dishonest or can't be trusted?	1	2	3	4	5
18.	Has someone made rude gestures?	1	2	3	4	5
19.	Have others avoided touching or sitting next to you (ex: in class or on a bus)?	1	2	3	4	5
20.	Have you been left out of social gatherings or get-togethers (ex: going to lunch or to a bar)?	1	2	3	4	5
21.	Have people like waiters, bank tellers, or secretaries been unfair or treated you badly?	1	2	3	4	5
22.	Has a clerk or waiter ignored you or made you wait longer than others to be served?	1	2	3	4	5
23.	Have people been nice to you to your face, but said bad things about you behind your back?	1	2	3	4	5
24.	Have people who speak a different language made you feel like an outsider?	1	2	3	4	5
25.	Have people on the street been unwilling to help you or give you directions?	1	2	3	4	5
26.	Has a taxi driver passed you by or refused you service?	1	2	3	4	5
27.	Have others hinted that you must be violent or dangerous?	1	2	3	4	5
28.	Have others physically harmed members of your family?	1	2	3	4	5

BECAUSE OF YOUR ETHNICITY/RACE …

A.	**How often…**	**Never**	**Sometimes**			**Very Often**
29.	Have others ignored you or not paid attention to you?	1	2	3	4	5
30.	Has your boss or supervisor been unfair to you?	1	2	3	4	5
31.	Have others hinted that you must not be clean?	1	2	3	4	5
32.	Have people not trusted you?	1	2	3	4	5
33.	Have people not taken you seriously or not wanted to give you responsibility?	1	2	3	4	5
34.	Has it been hinted that you must be lazy?	1	2	3	4	5
35.	Have you been the target of obvious, direct, "in-your-face" discrimination?	1	2	3	4	5
36.	Have you been the target of subtle, indirect, not-so-obvious, "deniable" discrimination?	1	2	3	4	5

B.	**How often…**	**Never**	**Sometimes**			**Very Often**
1.	Have you seen newspapers or magazines that make your ethnic group look bad?	1	2	3	4	5
2.	Have you heard disrespectful comments about your ethnic group on talk radio or in song lyrics?	1	2	3	4	5

3.	Have you seen people of your ethnic group made to look bad on TV or in the movies?	1	2	3	4	5
4.	Have you heard outsiders say bad things about other members of your ethnic group?	1	2	3	4	5
5.	Have you heard disrespectful comments about your ethnic group said to your face or behind your back?	1	2	3	4	5

C. If you have experienced episodes of discrimination:

which group has given you the most difficulty?

White Black Asian Other, please specify _____

D. Have you had more difficulty from men or women? **Men** **Women** **Neither**

E. How often have any of the things listed below happened to a *close friend* or *relative* who has the *same ethnicity/race* as you do?

		Never	**Sometimes**			**Very Often**
1.	Has a policeman or security officer been unfair?	1	2	3	4	5
2.	Have other people called someone close to you bad names related to ethnicity?	1	2	3	4	5
3.	Have friends or relatives from your ethnic group been **threatened** with physical harm?	1	2	3	4	5
4.	Have friends or relatives from your ethnic group been **actually** harmed or beat up because of their ethnicity?	1	2	3	4	5
5.	Has a friend or relative lost a job or been denied a job because of his or her ethnicity?	1	2	3	4	5
6.	Have friends or relatives had their property damaged or threatened because of their ethnicity?	1	2	3	4	5

F. How often have you been discriminated against in the following places…

		Never	**Sometimes**			**Very Often**
1.	In the criminal justice system (ex: police, judge, etc.)?	1	2	3	4	5
2.	When looking for housing?	1	2	3	4	5
3.	In medical services?	1	2	3	4	5
4.	In school?	1	2	3	4	5
5.	At work?	1	2	3	4	5
6.	At a religious institution: (e.g. church, synagogue, mosque…?)	1	2	3	4	5
7.	In public places: (e.g. a restaurant, store, bank, government offices, supermarket, airport?)	1	2	3	4	5
8.	On the street, in a park?	1	2	3	4	5
9.	At private functions: (e.g. someone's home, a party, wedding?)	1	2	3	4	5
10.	Somewhere else (please specify) _____?	1	2	3	4	5

THINK ABOUT THIS PAST WEEK:

THINK ABOUT ALL THE THINGS YOU DO DURING THE WEEK –

(e.g. *SPEND TIME WITH FAMILY OR FRIENDS, AT WORK OR DOING CHORES*….)

THINK ABOUT ALL THE PLACES YOU ARE DURING THE WEEK –

(e.g. *ON THE BUS, ON THE STREET, ON THE TRAIN, AT WORK, AT HOME, IN A STORE*…)

DURING THIS PAST WEEK, HOW OFTEN DID ANY OF THESE OCCUR BECAUSE OF YOUR ETHNICITY/RACE…

		Never (0)	Once (1)	Twice (2)	Three or more times (3+)
1.	Did someone ignore you?	0	1	2	3
2.	Did someone avoid talking to you?	0	1	2	3
3.	Were you left out of an activity or event?	0	1	2	3
4.	Did someone say something mean or nasty to you?	0	1	2	3
5.	Did someone look at you in a mean or nasty way?	0	1	2	3
6.	Did someone say or do something threatening?	0	1	2	3
7.	Did someone treat you unfairly?	0	1	2	3
8.	Did someone act as if you couldn't be trusted?	0	1	2	3
9.	Did someone act as if you were lazy?	0	1	2	3
10.	Did someone act like you couldn't be taken seriously or handle responsibility?	0	1	2	3

If you would like to tell us more about your experiences of discrimination, please write your story here:

Multidimensional Scale of Perceived Social Support

Zimet, Dahlem, Zimet & Farley, 1988

Instructions: We are interested in how you feel about the following statements

Read each statement carefully. Indicate how you feel about each statement

Circle the “1” if you Very Strongly Disagree
Circle the “2” if you Strongly Disagree
Circle the “3” if you Mildly Disagree
Circle the “4” if you are Neutral
Circle the “5” if you Mildly Agree
Circle the “6” if you Strongly Agree
Circle the “7” if you Very Strongly Agree

1. There is a special person who is around when I am in need.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

2. There is a special person with whom I can share my joys and sorrows.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

3. My family really tries to help me.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

4. I get the emotional help and support I need from my family.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

5. I have a special person who is a real source of comfort to me.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

6. My friends really try to help me.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

7. I can count on my friends when things go wrong.

Very Strongly Very Strongly

Disagree	1	2	3	4	5	6	7	Agree

8. I can talk about my problems with my family.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

9. I have friends with whom I can share my joys and sorrows.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

10. There is a special person in my life who cares about my feelings.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

11. My family is willing to help me make decisions.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

12. I can talk about my problems with my friends.

Very Strongly								Very Strongly
Disagree	1	2	3	4	5	6	7	Agree

The items tended to divide into factor groups relating to the source of the social support, namely family (Fam), friends (Fri) or significant other (SO).

1. SO
2. SO
3. Fam
4. Fam
5. SO
6. Fri
7. Fri
8. Fam
9. Fri
10. SO
11. Fam
12. Fri

Significant other score :

Family score :

Friends score :

Sum score :

Childhood Experience of Care and Abuse Questionnaire

FAMILY RELATIONSHIPS IN CHILDHOOD – CECA-Q

1. WHO BROUGHT YOU UP BEFORE AGE 17

Please write below the *Parent Figures* who brought you up in childhood. List each family arrangement with different parent figures which lasted *one year or longer*.

Consider natural parent, step-parent (including parent's live-in partner), aunt, friend of the family, adoptive parent, foster parent etc.

Fill in the first family arrangement below. For example, if this was with your natural parents, write in 'Mother' and 'Father' and age '0'; or if this was with just your mother write in 'Mother', leave the father column blank and age '0'

Family arrangement	**Mother figure**	**Father figure**	**Your age at start**
FIRST family	1a	1b	1c

If this was your *only* family up to the age of 17, then SKIP to the starred question below.

If you have lived in *more than just one* family arrangement, such as with mother and stepfather, then list them below, together with the age you were when the arrangement began.

Family arrangement	**Mother figure**	**Father figure**	**Your age at start**
SECOND family	1d	1e	1f
THIRD family	1g	1h	1i

**** Were you ever in a children's home or institution before age 17? YES NO**

(please circle the appropriate answer)

If 'YES' fill in the boxes below. If 'NO' skip to question 2 overleaf

TYPE OF INSTITUTION **e.g. local authority care, hospital, boarding school**	**age when you started**	**age when you left**
1.	1j	1k
2.	1l	1m

2. PARENTAL LOSS

Please circle the appropriate answers, and write in the age you were when it happened.

	MOTHER	**FATHER**
2a. Did either parent die before you were aged 17?	YES NO	YES NO
If YES, what age were you?	2b	2c

	MOTHER	**FATHER**
2d. Have you ever been separated from your parent *for one year or more* before the age of 17?	YES NO	YES NO

If YES, then fill in the boxes below; if NO then SKIP to question 3 overleaf.

	MOTHER	**FATHER**
At what age were you first separated?	2e	2f
How long was this separation, in years?	2g	2h
Please circle the reason for the separation:		
Parent's illness (2i)	YES NO	YES NO
Parent's work (2j)	YES NO	YES NO
Parents' divorce or separation (2k)	YES NO	YES NO
Abandoned by parent or never knew parent (2l)	YES NO	YES NO
Other reason (2m)	YES NO	YES NO

2n Please describe your experience…….

3. Please circle the appropriate numbers to describe your **Mother Figure, as you remember her in your first 17 years**. If you had more than one, choose the one you were with *the longest*, or the one you found *most difficult* to live with.

3a. Which mother figure are you describing below?

1. Natural mother
2. Step-mother/father's live-in partner
3. Other relative e.g aunty, grandmother
4. Other non-relative e.g. foster mother, godmother
5. Other (describe)……

	Yes, definitely		Unsure		No, not at all

3b She was very difficult to please	1	2	3	4	5
3c She was concerned about my worries	1	2	3	4	5
3d She was interested in how I did at school	1	2	3	4	5
3e She made me feel unwanted	1	2	3	4	5
3f She tried to make me feel better when I was upset	1	2	3	4	5
3g She was very critical of me	1	2	3	4	5
3h She would leave me unsupervised before I was 10 years old	1	2	3	4	5
3i She would usually have time to talk to me	1	2	3	4	5
3j She would hit me	1	2	3	4	5
3k At times she made me feel I was a nuisance	1	2	3	4	5
3l She often picked on me unfairly	1	2	3	4	5
3m She was there if I needed her	1	2	3	4	5
3n She was interested in who my friends were	1	2	3	4	5
3o She was concerned about my whereabouts	1	2	3	4	5
3p She cared for me when I was ill	1	2	3	4	5
3q She neglected my basic needs (e.g. food and clothes)	1	2	3	4	5
3r She did not like me as much as my brothers and sisters (*leave blank if no siblings*)	1	2	3	4	5

Do you want to add anything about your mother?……..

……..

4. Please circle the appropriate numbers to describe **your Father Figure, as you remember him in your first 17 years**. If you had more than one, choose the one you were with *the longest*, or the one you found *most difficult* to live with.

4a. Which father figure are you describing below?

1. Natural father
2. Step-father/mother's live-in partner
3. Other relative e.g uncle, grandfather
4. Other non-relative e.g. foster father, adoptive father
5. Other (describe)……

	Yes, definitely		Unsure		No, not at all
4b He was very difficult to please	1	2	3	4	5
4c He was concerned about my worries	1	2	3	4	5
4d He was interested in how I did at school	1	2	3	4	5

4e He made me feel unwanted	1	2	3	4	5
4f He tried to make me feel better when I was upset	1	2	3	4	5
4g He was very critical of me	1	2	3	4	5
4h He would leave me unsupervised before I was 10 years old	1	2	3	4	5
4i He would usually have time to talk to me	1	2	3	4	5
4j He would hit me	1	2	3	4	5
4k At times he made me feel I was a nuisance	1	2	3	4	5
4l He often picked on me unfairly	1	2	3	4	5
4m He was there if I needed him	1	2	3	4	5
4n He was interested in who my friends were	1	2	3	4	5
4o He was concerned about my whereabouts	1	2	3	4	5
4p He cared for me when I was ill	1	2	3	4	5
4q He neglected my basic needs (e.g. food and clothes)	1	2	3	4	5
4r He did not like me as much as my brothers and sisters (*leave blank if no siblings*)	1	2	3	4	5

Do you want to add anything about your father?……..

……

5. CLOSE RELATIONSHIPS IN CHILDHOOD

(please circle as appropriate – if you circle NO to any question, SKIP the rest of that section and go on to the next one)

5a When you were a child or teenager, were there any ADULTS you could go to with your problems or to discuss your feelings?

YES NO

5b If YES: Who was that? (circle more than one if relevant)

1. mother / mother figure
2. father / father figure
3. other relative
4. family friend
5. teacher, vicar etc
6. other (describe) …….

5d Do you want to note anything about the relationship(s)? ……

5e Were there other CHILDREN/TEENAGERS your age that you could discuss your problems and feelings with?

YES NO

5/f If YES: Who was that? (circle more than one if relevant)

1. sister
2. brother
3. other relative
4. close friend
5. other less close friend(s)
6. other person (describe)……..

5h Do you want to note anything about the relationship(s)?……

5i Who would you describe as the TWO CLOSEST people to you as a child/teenager? (circle up to two)

1. mother / mother figure
2. father / father figure
3. sister or brother
4. other relative
5. family friend (adult)
6. friend your age
7. other (describe) …….

5j/c Do you want to note anything about the relationship(s)?……

6. PHYSICAL PUNISHMENT BEFORE AGE 17 BY PARENT FIGURE OR OTHER HOUSEHOLD MEMBER - INTERVIEW

6a When you were a child or teenager were you ever hit repeatedly with an implement (such as a belt or stick) or punched, kicked or burnt by someone in the household?

YES NO

If YES, then fill in the boxes below; if NO then SKIP to question 7 overleaf.

	MOTHER FIGURE	**FATHER FIGURE**
How old were you when it began, in years?	6b	6c
Did the hitting happen on more than one occasion?	6d YES NO	YES NO
How often did the hitting happen?		

How old were you when the hitting stopped? How long did it go on for?		
How were you hit?	6e 1. belt or stick 2. punched/kicked 3. hit with hand 4. other	6f 1. belt or stick 2. punched/kicked 3. hit with hand 4. other
Were you ever injured e.g. bruises, black eyes, broken limbs?	6g YES NO	YES NO
Was this person so angry they seemed out of control?	6h YES NO	YES NO

Can you describe these experiences ……..

Did you experience this from anyone else in the household? YES NO

If YES: describe your experiences…….

7. UNWANTED SEXUAL EXPERIENCES BEFORE AGE 17
(please circle as appropriate)

7a. When you were a child or teenager did you ever have any unwanted sexual experiences? **YES NO UNSURE**

7b. Did anyone force you or persuade you to have sexual intercourse against your wishes before age 17? **YES NO UNSURE**

7c. Can you remember any upsetting sexual experiences YES NO UNSURE
before age 17 with a related adult or someone in authority e.g. a teacher?

If NO to all these, then SKIP to question 8 overleaf

If YES or UNSURE to any of them, then please complete the following questions:

	FIRST EXPERIENCE	**SECOND EXPERIENCE**

What age were you when it began (in years)?	7d	7e
Was the other person someone you knew?	7f YES NO	YES NO
How old was the other person?		
Was the other person a relative?	7g YES NO	YES NO
Did the other person live in your household?	7h YES NO	YES NO
Did this person do it to you on more than one occasion?	7i YES NO	YES NO
How often did it happen? How old were you when it stopped/how long did it go on for?		
Did it involve touching private parts of your body?	7j YES NO	YES NO
Did it involve touching private parts of the other person's body?	7k YES NO	YES NO
Did it involve sexual intercourse?	7l YES NO	YES NO

7l/c Can you describe these experiences?……

8. YOUR CURRENT RELATIONSHIPS AND WORK

(Please circle or write in your answer – if you circle NO to any question, SKIP the rest of that section and go on to the next one)

8a. Do you have a partner? YES NO

If YES:

8b. Are your currently living with your partner?

0. No
1. Yes, cohabiting
2. Yes, married

8c. Does your partner work?

0. No

1. Student only
2. Part-time employment
3. Full-time employment

8d. What is your partner's job? ……..

8e. Do you have children? YES NO EXPECTING FIRST BABY

If YES:

8f. How many children do you have? ……

8g. How many are currently living with you? ……

8h. How old is your eldest child?……

8i. How old is your youngest child?…….

8j. Do any of your partner's children live with you YES NO
(i.e. your step-children)

8k Are you currently employed?

0. No
1. Student only
2. Part-time employment
3. Full-time employment

8l. If YES, what is your job? …….

8m. Your gender: MALE FEMALE

8n. Your current age ……

Thank you for your help with this questionnaire. We realise that it is difficult to give a true picture of your childhood experience in a questionnaire, so if you have any comments you would like to add, please write them below. Your responses will be treated in the strictest confidence.