Duration of untreated prodromal symptoms in individuals at clinical high risk for psychosis; analysis of onset of prodromal symptoms, and the effect of duration on outcomes in clinical high-risk populations.

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Abstract

Introduction: It is believed that people affected by schizophrenia, who have a long gap between the onset of psychotic symptoms, and the start of treatment have worse outcomes, both in the short and long-term. This is called the duration of untreated psychosis hypothesis

An area where there is limited current research is the effect of the duration of prodromal symptoms in people at clinical high risk for psychosis (CHR-P). These prodromal symptoms are reported in a majority of those who transition to psychosis, suggesting that they may be significant for later outcomes. This study focuses on the timing of the relative onset of attenuated psychotic symptoms (APS) and basic symptoms (BS); on the reported duration of BS and APS, from participants at CHR-P; and the effects of these on functional outcomes, and on cognition. There is a specific hypothesis that APS are a consequence of BS, implying that BS should commence before APS.

Methods: Participants were recruited as part of the Youth mental health, risk and Resilience (YouR) study. This is a community-based study, carried out among people aged 16 to 35 in Glasgow and Edinburgh, analyzing emerging psychotic symptoms. Data from 134 CHR-P participants were analyzed for the duration of APS and BS and these were related to global assessment of functioning (GAF), role functioning and social functioning. Two measures of cognition were collected during baseline assessments. An analysis was conducted to compare duration of APS and BS symptoms, and to assess the effect of duration on GAF scores, role functioning, social functioning and cognition measures.

Results: There was no significant relationship between BS onset and APS, and in a significant percentage of the sample (n = 24, 37.5%) the reported APS onset was prior to BS onset. Only CHR-P individuals with long BS showed some evidence for the hypothesized relationship of BS preceding APS (n = 13, p = 0.04). Duration of APS and BS showed no significant effects on cognition, except for small effects on motor speed and verbal fluency. Duration of prodromal symptoms also did not show any significant effects on any of the measures of functioning.

Discussion: The current study did not support the hypothesis that BS precedes the emergence of APS in individuals who are CHR-P. This could have significant implications for current conceptions of APS and BS in the prodromal period. A number of factors have been previously reported to effect recall of duration of prodromal symptoms, including years of education and age at onset of symptoms. No evidence was found of between group differences. These findings produce two key questions; how accurate is the hypothesis that APS are a secondary

consequence of BS, and are there between group differences previously not considered which may affect the difference in reported symptoms. Areas for future research on this topic are discussed.

The implications of the negative findings for functioning and cognition are compared to current research into duration of untreated psychosis. The differences in the finding are theorized to be linked to two key hypotheses in psychosis; the critical period of psychosis and the neurodevelopmental theory of psychosis. Both these theories have time dependent components, but current research using duration of prodromal symptoms is limited. Potential implications of this study as preliminary evidence for them are discussed.

Finally, this study reported significantly longer duration of prodromal symptoms in a non-help seeking sample, compared to previous findings conducted on clinical samples. The implications of these findings and suggestion for future research are discussed.

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Abbreviations

APS	Attenuated psychosis syndrome
ARMS	At-risk mental state
BACS	Brief Assessment of Cognition in Schizophrenia
BOLD	Blood oxygenation level dependent
BS	Basic symptoms
BLIPS	Brief limited intermittent psychotic symptoms
CAARMS	Comprehensive Assessment of At-Risk Mental States
CBT	Cognitive behavioural therapy
CHR-P	Clinical high risk for psychosis
CNS	Central nervous system
CNV	Copy number variation
COGDIS	Cognitive disturbances
COPER	Cognitive-perceptive basic symptoms
DAergic	dopaminergic
DNA	deoxyribonucleic acid
DS	Disorganised speech
DSM	Diagnostic and Statistical Manual of Mental Disorders
DUI	Duration of untreated illness
DUP	Duration of untreated psychosis
DUPrS	Duration of untreated prodromal symptoms
ERIraos	Early Recognition Inventory
FEP	First episode psychosis
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GAF	Global assessment of functioning
GF: Role	Global functioning role scale
GF: Social	Global functioning social scale
IRR	Inter-rater reliability
IRRs	Incidence rate ratios
MRI	Magnetic resonance imaging
NBI	Non-bizarre ideas
OR	Odds ratio

PA	Perceptual abnormalities
PACE	Personal Assessment and Crisis Evaluation study
PCA	Perceptual-cognitive anomalies
PFC	Prefrontal cortex
PQ	Prodromal questionnaire
RAP	Recognition and Prevention program
SIPS	Structured Interview for Psychosis-Risk Syndromes
SPI-A	Schizophrenia Proneness Instrument, Adult version
SPI-CY	Schizophrenia Proneness Instrument, Child & Youth
UTC	Unusual thought content
VTA	Ventral tegmental area
YouR study	Youth Mental Health Risk and Resilience study

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Authors Declaration

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I certify that the thesis presented here for examination for a MSc degree of the University of Glasgow is solely my own work other than where I have clearly indicated that it is the work of others (in which case the extent of any work carried out jointly by me and any other person is clearly identified in it) and that the thesis has not been edited by a third party beyond what is permitted by the University's PGR Code of Practice.

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1 Introduction

1.1 Schizophrenia prevalence

Schizophrenia is a chronic mental illness, defined by psychotic experiences of hallucinations and delusions, disorganised speech and behaviour, and impaired cognitive abilities (Patel et al., 2014). Schizophrenia affects 1 in 100 people worldwide (World Health Organization, 2013), and onsets in late adolescence to early adulthood. Schizophrenia is more prevalent in men than in women (Iacono & Beiser, 1992). Psychotic experiences are associated with higher levels of depression and distress (Heinze et al., 2018). Schizophrenia can be a highly debilitating condition and has been shown to lead to poor long term functional outcomes (Green, 2006), social isolation (Kalin et al., 2015), and significant decline in physical health (De Hert et al., 2011). Schizophrenia is associated with decreased life expectancy compared to the general population of between 12 – 15 years (Saha et al., 2007). This is also related to elevated suicide risk with as many as 10% of those diagnosed with schizophrenia dying from suicide, and as many as two to five times that making attempts throughout their lives (Siris, 2001).

1.2 Stages of schizophrenia progression

Traditional concepts of schizophrenia progression characterized the progression of schizophrenia into four clinical stages; premorbid, prodromal, psychotic and residual/recovery (Lieberman et al., 2001).

The premorbid stage is thought to start as early as in gestation, and generally lasts between one to three decades (Avramopoulos, 2018). The premorbid phase is associated with mild non-specific motor, social and cognitive impairments, and not all those who experience these symptoms will progress into later stages (Lieberman et al., 2001).

The prodromal phase is characterised by a progression from nonspecific behavioural changes to the onset of attenuated psychotic symptoms (APS) or basic symptoms (BS) (Lieberman et al., 2001). APS manifest like full psychotic positive and negative symptoms, but are present to a lesser degree by intensity, frequency and/or duration (Yung et al., 2005). BS are subjectively experienced disturbances across different domains of perception, thought processing, language, and attention (Schultze-Lutter et al., 2007). These are thought to be present between 1 to 5 years before the emergence of full psychotic symptoms (Häfner et al., 2003), though the length of this period varies across individuals. Significantly, those who do experience sub-threshold

symptoms, do not necessarily progress to the third phase (Nelson et al., 2016), and those who experience the progressive stage do not always experience APS or BS (Shah et al., 2017).

The psychotic stage is defined by onset of full psychotic symptoms. These are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM V) as the presence of at least two symptoms (hallucinations, delusions, disorganised speech, disorganised or catatonic behaviour, or negative symptoms) for at least six months continuously, with at least one month of active symptoms associated with social and occupational deterioration (American Psychiatric Association, 2013). It is hypothesized that the first two-three years following onset of psychosis is associated with significant and rapid deterioration of neurological processes (Birchwood et al., 1998). This is called the critical period theory of psychosis, and it is thought that this is the period in which effective intervention may control the pathophysiological progression of schizophrenia (Sheu et al., 2019).

Following first episode psychosis (FEP) the fourth clinical stage is the residual period. This stage has a diverse range of outcomes, but is defined by some lingering cognitive and symptomatic impairments. During the residual period, individuals often experience relapses, which are characterised by acute psychotic exacerbation (Emsley et al., 2013). The variation in the outcomes during the residual stage means some people experience multiple relapses, while others experience none.

More recent research on the clinical stages of schizophrenia has focused on the heterogeneity of progression (Ruiz-Iriondo et al., 2013). McGorry et al. (2006) proposed that schizophrenia progression should instead be viewed through a clinical staging model. Clinical staging models are commonly used in general medicine, in areas such as cancer, and rather than focus on diagnostic criteria, they instead focus on clinical outcomes and variables (Scott & Henry, 2017). The advantage of this approach is it allows for a more precise identification of the stage of the condition.

The model for schizophrenia proposed by McGorry and colleagues (2006) has eight stages; stages 0, 1a and 1b all describe progression from increased risk of psychotic experiences to moderate attenuated psychotic experiences. Stage 2 describes FEP experiences, and stages 3 a, b, c and 4 identify different trajectories of incomplete recovery, incomplete remission from FE, singular relapse, multiple relapse, and chronic psychosis, respectively. The difference in this model is the emphasis placed on the non-linearity of schizophrenia (McGorry et al., 2018).

1.3 Symptoms of schizophrenia

The main symptoms of schizophrenia can be divided into three categories; negative symptoms, positive symptoms, and disorganised symptoms (Arciniegas, 2015). Initially these sets of symptoms were divided into distinct types of schizophrenia, though both could be present in a single individual (Crow, 1985). Type I describes positive symptoms of schizophrenia, and Type II describing the negative symptoms, and if individuals reported cognitive impairments. This delineation has become less used in more recent research, favouring viewing the symptoms as clusters of symptoms, rather than separate types, to more accurately reflect the heterogeneous presentation of schizophrenia (Jablensky, 2010). Several studies for example Konopaske & Coyle (2015), argue that affective dysregulation should be considered a third separate cluster, describing symptoms such as flattening affect, depression, mania, anxiety and impulsivity, though this is currently considered as part of the negative symptoms in DSM V (American Psychiatric Association, 2013)

1.3.1 Negative symptoms

Negative symptoms were noted in early research into schizophrenia, though the precise groupings of these symptoms has been frequently changed (Galderisi et al., 2017). More recent research, using factor analysis and wider meta-analysis have divided negative symptoms into two subgroups: 1) amotivation and 2) diminished expression (Foussias et al., 2014). Amotivation describes a cluster of symptoms including inability to feel pleasure (anhedonia), a lack of interest in goal directed behaviour (avolition) or socializing (asociality), or a wider lack of interest in daily activities (apathy). Diminished expression is used to group two subtypes of symptoms: a) affect flattening, apathetic and unchanging facial expression and limited strength, tone or pitch of voice, and b) poverty of speech, a lack of additional unprompted content.

1.3.2 Positive symptoms

Positive symptoms describe experiences of hallucinations, delusions, and formal thought disorder, though the latter is sometimes considered as a separate third category of symptoms (McCutcheon et al., 2019). Hallucinations are defined as sensory perceptions experienced during consciousness in the absence of an external stimulus, and are primarily associated with damage to the visual system or psychiatric disorders (Rees, 2009). In schizophrenia, hallucinations can be experienced through any sensory system, i.e. visual, auditory, olfactory, gustatory and tactile. Delusions are ideas that are held with conviction by individuals, regardless of evidence or plausibility, that cannot be accounted for by a person's cultural or religious background, or level of intelligence (Kiran & Chaudhury, 2009).

1.3.3 Thought disorder

Formal thought disorders describes an impaired capacity to sustain coherent language (Rivkin & Barta, 2017) and describes a number of symptoms, including restricted quantity or significant vagueness (poverty of speech), tangentiality, distractibility or sudden loss of association (derailment). Other components of thought disorder include repeated, jumbled language (schizophasia), repeated word uses of self (perseveration) or others (echolalia), interrupted speech (blocking), unconventional word use (word approximations), inventing new words (neologisms), substitution of inappropriate word or word mispronunciation (paraphasic error) (Rivkin & Barta, 2017).

1.4 Cognitive deficits in schizophrenia

There are a wide range of positive and negative symptoms associated with schizophrenia, and individuals with schizophrenia can be highly heterogeneous in how they present (Andreasen et al., 1990). In comparison, impairment in cognitive deficits is a significantly more stable feature (Lieberman et al., 2001). These cognitive deficits are also found in those who do not transition (Sawada et al., 2017). These deficits compared to healthy controls remain even in the remission of psychotic symptoms (Settem et al., 2019), and are thought to be a significant contribution to the continued low functional outcomes for this group (Green, 2006).

1.4.1 Attention

Attention is defined as the cognitive process of selectively focusing on relevant stimuli and ignoring other information (Styles, 2006). Attention is not a single process, but consists of multiple sub-processes, including the ability to divide attention, selective attention (the ability to avoid distraction) and sustained attention (Baddeley, 1998; Baddeley, Baddeley, Bucks, & Wilcock, 2001). Meta-analysis has found that individuals with schizophrenia show deficits across all of these areas (Fioravanti et al., 2005), including in participants identified as being at clinical high risk for psychosis (CHR-P). Attention deficits in FEP and schizophrenia have been linked to poorer social and role functioning (Fu et al., 2017; Torgalsbøen et al., 2015)

1.4.2 Working memory

Working memory provides temporary storage and manipulation of sensory input which is involved in language comprehension, reasoning, and learning (Baddeley, 1992). Working memory impairment in individuals with schizophrenia has been of interest to research in cognitive deficits. In a meta-analysis of over 200 studies, working memory deficits in visuospatial and executive control were demonstrated robustly, though with significant group

differences based on duration of illness (Forbes et al., 2009). Working memory deficits in CHR-P populations also have been repeatedly measured (Gisselgård et al., 2018; Thermenos et al., 2016), and have been linked to longer symptom persistence (Broome et al., 2012).

1.4.3 Verbal fluency

Verbal fluency is the cognitive function that facilitates information retrieval from memory (Patterson, 2011). Verbal fluency needs executive control over cognitive processes of selective attention and inhibition, self-monitoring and internal response generation, and is essential for communication and social functioning. Verbal fluency is measured by testing semantic and phonemic fluency (Shao et al., 2014). Individuals with schizophrenia show deficits in both areas of verbal fluency, though the deficit compared to controls is more significant in semantic fluency measures (Henry & Crawford, 2005). Evidence of these deficits in verbal fluency remain, even when severity of negative symptoms and formal thought disorder are accounted for, though they are strong moderators (Galaverna et al., 2016). In CHR-P samples, deficits in verbal fluency are found in both semantic and phonemic measures (Hauser et al., 2017). More severe verbal fluency deficits have been positively associated with increased risk of transitioning, while lower cognitive impairments in domains of verbal fluency is positively associated with remission rates in CHR-P (Lee et al., 2014; Sabb et al., 2010).

1.4.4 Executive function

Executive function is a broad umbrella term for cognitive processes which operationalize and optimize other cognitive processes (Najdowski et al., 2014). Executive functions include inhibition, selective attention, cognitive inhibition, working memory, cognitive flexibility, adaptability and planning, though the exact definition has little consensus (Diamond, 2013). Executive functions are thought to be central to many cognitive processes, in particular to problem solving. Executive function deficits are common in those with schizophrenia and FEP (Fioravanti et al., 2005). There is evidence that executive functioning deficits are associated with deficits in social functioning, and possibly also with symptom severity (Mazurek & Mosiołek, 2018; A. E. Simon et al., 2003). CHR-P individuals also experience deficits in executive function, and it is hypothesized that these deficits start significantly before onset of psychosis (Bora & Murray, 2014).

1.4.5 Motor function

Motor function describes processes necessary for fine and gross motor movement, muscle coordination, muscle strength and balance (Schäppi et al., 2018). Initial research in

schizophrenia identified motor dysfunction as a symptom of anti-psychotic medication (e.g. clozapine) (Wang et al., 2019). However, research in drug naïve FEP and CHR-P populations showed motor dysfunction in fine motor and neurological soft sign measures(Gschwandtner et al., 2006). In schizophrenia, individuals showed deficits in motor coordination such as sequencing, sensory integration, motor coordination (neurological soft signs), signs of rigor and tremors (parkinsonism), and showed signs of abnormal involuntary movements (dyskinesia) (Schäppi et al., 2018). Even when antipsychotic medication is accounted for as a co-variate, these findings remain consistent (Wang et al., 2019). Motor dysfunction has been linked to symptom severity in CHR-P, FEP and schizophrenia populations, and in CHR-P is associated with an increased risk for transition (Callaway et al., 2014; Gebhardt et al., 2008; Wang et al., 2019).

1.4.6 Social cognition

Social cognition describes the mental processes through which people interpret and respond to others (Green et al., 2015). Individuals with schizophrenia show difficulties in identifying and understanding facial emotions (Kohler et al., 2010). These impairments are not found in assessment of non-affective face perception e.g. the age or sex of the face, suggesting it is specifically affect facial recognition that individuals with schizophrenia show deficits in (Darke et al., 2013). Deficits in this form of social cognition are associated with longer hospitalizations and longer time before seeking treatment (Kohler et al., 2010).

Emotion experiences and emotion regulation have been found to be diminished in individuals with schizophrenia (Taylor et al., 2012). Emotion experiences describes immediate responses to unpleasant and pleasant stimuli. Emotion regulation describes the two cognitive processes of emotion generation and emotion regulation (Gross, 2013). Findings in schizophrenia research shows there is increased negative response to neutral and pleasant experiences in those with schizophrenia (Horan et al., 2012). This deficit has also been found in CHR-P groups, and is associated with increased risk of transition (Corcoran et al., 2015)

1.4.7 Neuroimaging studies of cognitive deficits

Measures indicating cognitive differences in those with schizophrenia have also been found in neuroimaging studies. Magnetic Resonance Imaging (MRI) creates detailed anatomical images of the human brain through nuclear magnetic resonance (Yan et al., 2007). Meta-analysis of MRI studies on individuals with schizophrenia show that decreases in whole brain volume, in particular grey matter (Vita et al., 2012). These studies also show that this reduction continues

over time. These changes have also been noted to coincide with onset of psychosis (Chung & Cannon, 2015; Jung et al., 2012).

Functional Magnetic Resonance Imaging (fMRI) is an imaging method which measures regional changes in the brain's metabolism by measuring blood flow, assuming that increased blood flow is a result of increased neural activation (Glover, 2011). This is measured either from local cerebral blood flow, or from changes in blood oxygenation concentration (more commonly called blood oxygen level dependent(BOLD)) fMRI. Neural activation can be induced responses to cognitive tasks, or resting state changes in the brain. These allow measurement of neural activation of specific regions of the brain, and by comparing between groups, identify irregular activation patterns. Studies and meta-analyses of fMRI studies have consistently shown that schizophrenia is associated with aberrant fMRI-activity. In response to cognitive tasks individuals with schizophrenia show delayed temporal processing speeds, crucial for executive functioning, working memory and other essential cognitive processes (Alústiza et al., 2016). Meta-analysis of resting state studies also noted a significant hypoconnectiveness was observed in sensory networks, the auditory network (left insula, right superior temporal cortex), and somatomotor network (right precentral gyrus) (Li et al., 2019). This review also noted hypoconnectiveness in the prefrontal cortex (right medial prefrontal cortex, left, precuneus and anterior cingulate cortices), which is involved in decision making, executive function and working memory (Euston et al., 2012).

Magnetoencephalography (MEG) has enabled research to expand on the cognitive deficits in those with schizophrenia, by allowing measurement of near instantaneous responses of neural activity. MEG measures magnetic fields produced by the electric currents from the dendrites of the neurons during synaptic transmission. MEG also allows for a more precise localisation of activation and measurement of oscillatory neural activity in higher frequency ranges (e.g. alpha, beta, gamma) (Hinkley et al., 2010). This specificity in MEG has shown that there are lateralised auditory sensory deficits in those with schizophrenia (Thoma et al., 2003). Individuals with schizophrenia have shown deficits in sensory gating (Chen et al., 2018). Sensory gating is a cognitive mechanism to filter relevant from irrelevant information from sensory domains, deficits in this is associated with experiences of sensory overload, attentional difficulties and working memory difficulties (Chen et al., 2018). Other MEG studies have also been able to show timing deficits during facial processing (Rockstroh et al., 2006). In resting state measures,

individuals with schizophrenia showed stronger delta and theta power, but a reduction in alpha power compared to controls (Cañive et al., 1998).

1.5 Pathophysiological hypotheses for schizophrenia

Explanations for the mechanisms which underlie schizophrenia is an area that has been of significant interest in understanding the causes of schizophrenia (Stępnicki et al., 2018). Research in this area has significantly focused on neurochemical alterations as an explanation for what causes schizophrenia, and neurodevelopmental aberrations as an explanation for why this happens only to some individuals .

1.5.1 Neurochemical alterations

Several neurochemical types and cortical pathways have become focuses in trying to explain the mechanisms underlying schizophrenia. While there is some evidence for each of the proposed theories, the findings remain inconsistent and incomplete (Stępnicki et al., 2018). Recent research has aimed to address these by revising theories to create a theory which encompasses more of these findings.

1.5.1.1 Dopamine hypothesis

An early area of interest was in dopamine. Dopamine in the brain acts as a neurotransmitter, and functions by acting on dopaminergic (DAergic) receptors, classified as D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, D4). D1-like are primarily excitatory and D2-like are primarily inhibitory (Hasbi et al., 2011). Dopamine modulates central functions of the central nervous system (CNS), this includes reward and motivation, and higher cognitive functions of goal representation and working memory (Cools, 2008). Dopamine has three major pathways in the CNS: the nigrostriatal pathway, mesolimbic pathway and mesocortical pathway (Ikemoto, 2010). The nigrostriatal pathway transmits dopamine from the substantia nigra to the dorsal striatum, the mesolimbic pathway transmits from the ventral tegmental area (VTA) to the ventral striatum, and the mesolimbic pathway transmits from the VTA to prefrontal cortex (PFC).

Dopamine became of interest in psychosis research, following the discovery of the antipsychotic properties of the medication chlorpromazine (Gründer & Cumming, 2016). Chlorpromazine blocks D2 receptors and when administered to psychotic patients, reduced positive symptoms. The original dopamine hypothesis was proposed by van Rossum(1966), and said that D2 receptors were hyperactive in the mesolimbic pathway in schizophrenic individuals, and this caused the condition. This explanation did account for the positive symptoms of schizophrenia, but the original hypothesis did not offer explanations of the relationship to continued negative

symptoms and cognitive deficits in those who took these early anti-psychotic medications (Howes et al., 2015). Further limitations of the theory became clearer with the introduction of in-vivo studies, which showed that the early antipsychotic medications were not exclusively acting as D2 blocks (Farde et al., 1992), and in fact second generation anti-psychotics with the lowest level D2 occupancy were among the most effective.

A revised dopamine hypothesis was proposed by Davis, Kahn, Ko, and Davidson(1991), they focused on expanding the theory by studying the effects of other dopamine receptors, and the dopaminergic pathways. The revised hypothesis proposed that in addition to hyperactive dopamine D2 receptors in the mesolimbic pathways, there are hypofunctionality of dopamine D1 receptors in the mesocortical pathway. It also proposed that this created a disrupted feedback loop, where those with schizophrenia have reduced activity in the mesocortical area from the D1 receptors, which leads to disinhibition and overactivity in the mesolimbic pathway. This was an advance from the previous theory, and accounted for some of the observed results from in-vivo studies, however it too lacked a specificity, and the theory gave no clear framework as to how these conditions interacted to produce the symptoms of schizophrenia (Stępnicki et al., 2018). In addition, this version identified that certain dopamine receptors behaved differently for those with schizophrenia, but lacked an aetiological explanation for it.

1.5.1.2 Glutamate hypothesis

Glutamate is the main excitatory neurotransmitter in the CNS. Glutamatergic pathways link the cortex, limbic system, and thalamus, and make up 60-80% of the brains metabolic activity (Rothman et al., 2003). Glutamate receptors fall into two groups, ionotropic and metabotropic. This distinction marks how neurotransmitter signals when reaching the synaptic membrane bind with the receptor (Pankevich et al., 2011). Ionotropic receptors are fast acting and can produce large changes in current flow. One of the main glutamate ionotropic receptors is the N-methyl-D-aspartate (NMDA) receptor. NMDA receptors are thought to be central to learning and memory, and have been shown to be vital to neuroplasticity and recovery (Barco et al., 2006). Glutamate receptors has also been shown to regulate development and neurotoxicity (Howes et al., 2015).

The NMDA-R hypothesis of schizophrenia was developed following observations that NMDA receptors antagonists such as ketamine, dizocilpine and phencyclidine, induced psychotic like symptoms when administered to healthy participants (Stępnicki et al., 2018). The original glutamate hypothesis focused on a global deficit in glutamatergic neurotransmission, but this has

been developed to focus on a hypofunction of glutamate signalling in NMDA receptors (Stone et al., 2007).

Some evidence has supported the glutamate hypothesis (Howes et al., 2015); In animal studies, giving animals NMDA receptor antagonists resulted in neurotoxic changes in cortical brain regions, suggested to be similar to brain volume reductions found in schizophrenia. Post-mortem studies have noted disturbances in glutamatergic receptor density in the prefrontal cortex, thalamus and temporal lobes, though the findings have been inconsistent (Kapur & Seeman, 2002).

1.5.1.3 GABA hypothesis

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the CNS (Rudolph & Möhler, 2016). GABAergic interneurons play a central role in synchronization of oscillations in local networks and connection between different regions of the brain (Rudolph & Möhler, 2016). Abnormal synchronization across regions has been shown to be linked to cognitive deficits in attention, working memory and perception (Uhlhaas & Singer, 2006). The two main receptors for GABA are ionotropic ($GABA_A$ receptor) and metabotropic ($GABA_B$ receptor). $GABA_A$ receptor has been a focus of research into GABAergic interneurons because of its widespread presence in the CNS, and because multiple receptor modulators (barbiturates, benzodiazepines, and nonbenzodiazepines) bind at $GABA_A$ receptors, allowing for in-vivo studies to be more easily conducted (Wassef et al., 2003). The GABA hypothesis proposes that disturbances in GABA signaling in the cerebral cortex causes an imbalance between the excitation and inhibition, which leads to the cognitive deficits and symptoms of schizophrenia (Xu & Wong, 2018).

Post-mortem studies measuring GABAergic interneurons focused on GABA-synthesising enzymes in the PFC. There is consistent evidence to show that GAD67 (a GABA-synthesising enzyme) mRNA and protein shows reductions (Egerton et al., 2017; Tanaka, 2008). Given GAD67 is responsible for 90% of GABA production, this is thought to show strong evidence of a GABA deficit in the PFC. Animal studies have found injecting $GABA_A$ antagonist picrotoxin into rats create similar inhibition deficits as those with schizophrenia (Wassef et al., 2003). However, this activation from picrotoxin has also been linked to dopamine activation, and so if these animal studies can be assumed to measure only GABA dysregulation remains unclear. In-vivo studies also offer mixed results, some studies show $GABA_A$ reductions (Frankle et al., 2015), but meta-analysis show that these findings are inconsistent (Egerton et al., 2017). Clinical studies show that administration GABA agonists showed a reduction in schizophrenia

symptoms, but like animal studies, because of the interaction of dopamine in these GABA agonists, it cannot uniquely identify GABAergic interneurons role in schizophrenia.

1.5.1.4 Revised hypothesis of GABA-glutamate pathways

More recent pathophysiological hypotheses have focused on the relationship between glutamate and GABA pathways in schizophrenia. It is proposed that there is hypofunction in the glutamate NMDA receptors which are located at GABA interneurons, and that this imbalance trigger the generation of excessive mesolimbic dopamine activity (Schwartz et al., 2012). In this revised theory, glutamatergic and GABAergic dysregulation are the primary mechanism in schizophrenia, and dopaminergic dysregulation is a secondary consequence of this dysregulation. This imbalance between glutamate receptors and NMDA interneurons is thought to diminish the control of the PFC in schizophrenia (Balu, 2016).

This theory offers evidence to explain studies which reported findings of dopamine and NMDA activation e.g. studies measuring antipsychotics using dopamine antagonists have identified the activation of NMDA receptors (Abekawa et al., 2006) This finding showed dopamine-glutamate interactions occur intersynaptically and intraneuronally, supporting the linked role (Stępnicki et al., 2018).

In genetic studies, studies using rodents have shown that rodents which are bred to have hypofunctioning in the NMDA receptors show decreased inhibition to auditory and visual responses, increased social withdrawal, and decreased self-supportive behaviours compared to controls (Halene et al., 2009; Nakazawa et al., 2012). These changes mirror the decreased inhibition response and negative symptoms associated with schizophrenia. Mice with this genetic alteration also show a decrease in neural synchrony, which suggests a hyperactivation of the GABAgeric interneurons (Belforte et al., 2010). The evidence supports the potential for this relationship, but further research is needed in human studies and animal studies in larger mammals and primates.

1.5.2 Neurodevelopmental Theories of Schizophrenia

Research into neurodevelopmental aberrations in schizophrenia has traditionally focused on the neurodevelopmental hypothesis of schizophrenia. The neurodevelopmental hypothesis proposes that events during gestation and early life are the cause of schizophrenia (McGrath et al., 2003). Initially proposed by Weinberger (1987) this theory has been criticised for its unclear mechanisms on the precise roles between genetics and early life environmental experiences (McGrath et al., 2003). However, there is evidence for the role of genetic, prenatal and perinatal

risk factors that have been shown to have an effect on later onset psychosis (Jablensky, McNeil, & Morgan, 2017), and studies into the interactions between genetics and early environment have also shown a relationship to schizophrenia in later life (Misiak et al., 2018).

1.5.2.1 Genetic risk factors

Heritability rates for schizophrenia are estimated to be as high as 64 - 80% in twin studies (Hilker et al., 2018; Lichtenstein et al., 2009). Heritability rates are also higher in first degree relatives, and even in second degree relatives (Chou et al., 2017).

Identifying the precise genes conferring risk for schizophrenia has proven to be a significant challenge, however. This is because risk genes rarely involve a single gene, but rather a large number of genes with small individual effects. To address this question, genome wide association studies (GWAS) were initiated (Corvin et al., 2010) that offered an opportunity to consider single nucleotide polymorphisms (SNPs) across large population samples. SNPs are common variants of individual nucleotide sequences that are frequently observed in the population (>1%; Thapar & Cooper, 2013). In a study of >35000 subjects considering ~9.5 million SNP variants, they were able to identify 128 independent associations across 108 defined loci (Ripke et al., 2014). These included dopamine D2 receptors and glutamate receptors (Pers et al., 2016).

Copy number variation (CNV) describe duplications or deletion in specific regions of an individual's deoxyribonucleic acid (DNA), and are rare sequence variations (<1%; Thapar & Cooper, 2013). These variants can be inherited or can occur as *de novo* mutations. Building from the research of the GWAS study, the Psychiatric Genomics Consortium established a database of 41,321 participants to examine the role of specific CNVs in schizophrenia (Marshall et al., 2017). CNV deletions of locus' in 22q11.21, 2p16.3 (NRXN1), 15q13.3, 3q29, 16p11.2 distal, and 15q11.2 were all associated with schizophrenia, with an odds ratio(OR) between 1.8 – 67.7. CNV duplication of 16p11.2 proximal, 7q11.23 and 22q11.21 were associated with schizophrenia, with an OR of 0.15 – 16.1. Two CNVs of either duplication or deletion showed an increased risk for developing schizophrenia, in the 1q21.1 and 7p36.3 loci, with an OR of 3.8 and 3.5 respectively. These show significantly higher ORs than SNPS, which are generally <1.5 (Doherty et al., 2012). The high ORs could in part be due to the need for a relatively significant level to be present to be identified, as current measures of CNV lag behind GWAS study techniques, suggesting there might be other less frequent CNVs which also play a significant role in the development of schizophrenia (Avramopoulos, 2018).

1.5.2.2 Prenatal risk factors

In addition to genetic inheritance, perinatal factors can affect the risks of developing schizophrenia. Paternal age shows a non-linear relationship, but suggests that paternal age can be a risk factor (Miller et al., 2011). The review found a very small effect size for fathers < 25 years, a small effect size for fathers ≥ 35 years, and a small to medium effect size for fathers ≥ 50 years old, when compared to fathers between ages of 25 – 29 years old. Maternal age does not show a relationship with increased risk of developing schizophrenia. Maternal illness and foetal exposure to diseases including herpes, rubella, and certain microbial agents have shown mixed effect sizes, but appear to indicate foetal exposure to these diseases can increase likelihood of developing schizophrenia (Meli et al., 2012; Niebuhr et al., 2008; Yolken & Torrey, 2008). There is also some limited evidence for famine and maternal nutrition (Meli et al., 2012). Maternal deficits in certain vitamins have yielded strong associations. Mothers with iron deficiencies during pregnancy were associated with a four-fold increased risk for schizophrenia in the child (Brown et al., 2007).

Environmental factors during gestation also appear to show an increased risk factor for developing schizophrenia. Winter/spring seasons of birth has been shown to have a small but significant positive correlation, OR 1.07, with a population attributable risk of 3.3% (Davies et al., 2003). Being born in an urban environment, compared to a rural setting, has also been shown to have a significant risk factor, with a population attributable risk of 11.73% (Sørensen et al., 2014).

1.5.2.3 Perinatal risk factors

Complications during pregnancy and birth have been associated with increased risk of developing schizophrenia. Cannon, Jones, and Murray(2002) showed that complications in pregnancy, such as bleeding, diabetes, preeclampsia and certain blood issues (rhesus factors), were associated with OR of 1.69 – 7.75.

1.5.2.4 Childhood risk factors

The migrant status of an individual has shown to increase the risk of later developing schizophrenia for both first and second generation immigrants (2.3 – 2.7 incidence rates ratio (IRRs) and 2.1 – 4.5 IRRs respectively) (Bourque et al., 2011; Cantor-Graae & Selten, 2005). Both also observed increased IRRs in non-white populations, and Cantor-Graae and Selten (2005) noted an increased IRRs in immigrants in low/middle income countries, compared to high income countries (3.3 compared to 2.3 IRRs).

Abuse during childhood has been linked to schizophrenia incidence (Gallagher III & Jones, 2013; Seidenfaden et al., 2017) and there is evidence to suggest that the prevalence of certain types of childhood abuse are higher in schizophrenia populations (childhood sexual abuse, 26%, childhood physical abuse, 39% and childhood emotional abuse, 34%) (Bonoldi et al., 2013). Abuse during childhood has been calculated to have an OR of between 1.7 to 15, though several other variables including gender, depression, post-traumatic stress disorder, and cannabis use moderated these effects (Sideli et al., 2012).

Drug abuse, in particular cannabis, has been linked to increased risk for schizophrenia. Moore and colleagues (2007) showed that any use of cannabis was associated with an OR 1.41 for psychotic symptoms and with OR of 1.82 for schizophrenia. Experiences of psychotic symptoms, but not schizophrenia, increased significantly when studies focused on frequent users (OR 2.09 for psychotic symptoms, 1.82 for schizophrenia).

1.5.2.5 Limitations of the neurodevelopmental hypothesis of schizophrenia

The neurodevelopmental theory suggests that there is a relationship between genetics, early life experiences and later schizophrenia onset. However, it faces two significant limitations. First, there is a significant amount of evidence which shows that FEP individuals experience significant changes in global grey matter volume, and synapses connections (Cahn et al., 2009; Cahn et al., 2002; Stephan et al., 2006). If the neurodevelopmental disorder theory is correct, this significant change during onset should not occur, because the alterations should have been present since early infancy. This has resulted in some studies classifying schizophrenia as a neurodegenerative disorder (McGrath et al., 2003). Secondly, the neurodevelopmental hypothesis does not explain the evidence of environmental factors present in childhood and adolescence, which can increase an individual's risk of developing schizophrenia.

1.5.3 Alternative theories of neurodevelopmental aberrations

The hypothesis of neurodegeneration attempts to answer the evidence of the significant neurological changes during FEP and throughout the course of illness with schizophrenia. The hypothesis proposes that schizophrenia can be characterised as a chronic and progressive disorder of the nervous system, resulting in biochemical changes that lead to different clinical syndromes (Hardy & Gwinn-Hardy, 1998). In addition to addressing the significant changes observed in neuroimaging studies, this theory incorporates evidence of neurochemical alterations in supporting the hypothesis. Researchers also draw on evidence of the increased risk of relapse following treatment cessation and the mixed evidence for long term efficacy of medication as proof of the progressive neurodegeneration (Harrow & Jobe, 2013). This

hypothesis, while addressing issues of the neurodevelopmental theory, does face significant limitations. The neurodegenerative theory does not address the genetic and environmental factors that are shown to be predictive in later onset. In addition, recovery rates in schizophrenia are variable, and most evidence for this theory is based only on those classified as having chronic schizophrenia (Emsley et al., 2013; Pino et al., 2014).

The second hit model of schizophrenia has been proposed as an updated version to the neurodevelopmental model (McGrath et al., 2003). This theory proposes that early life experiences and genetics create alterations in the cerebral cortex. Later risk factors such as excessive synaptic pruning, or drug/alcohol abuse in adolescence and early adulthood, then act as a second 'hit'. The second hit can occur any time, though some versions of this theory proposed later onset of the second hit to result in lesser effects (Pantelis et al., 2003). This theory improves upon the original neurodevelopmental theory by incorporating the later risk factors and addresses the significant neurobiological changes measured before and during onset of psychosis. More recent research using this model proposes that rather than a binary model, a multi-hit threshold model where different environmental and genetic hits at key neurodevelopmental milestones offers a better understanding of the complex interactions leading to schizophrenia (Davis et al., 2016).

1.6 Treatment of schizophrenia

Treatment of schizophrenia has focused on three key areas; initiation of treatment, medical intervention and therapeutic intervention.

1.6.1 Duration of untreated psychosis

Initiation of treatment became of interest in schizophrenia research, following evidence that individuals who experience longer delays between onset of the psychotic experience and appropriate intervention reported poorer outcomes (Marshall et al., 2005). This is referred to as the duration of untreated psychosis (DUP).

Longer DUP has shown to have consistent significant negative functional impacts, with multiple reviews showing that those with long DUP experience negative clinical outcomes (Boonstra et al., 2012; Marshall et al., 2005; Perkins et al., 2005). Marshall and colleagues (2005) showed that individuals who had a long DUP were associated with worse functional outcomes (quality of life, overall functioning, social functioning, depression/anxiety) and worse symptomatic outcomes (positive symptoms, negative symptoms, disorganised symptoms) at baseline and during follow up. Those with long DUP were also shown to have a much lower rate of remission

and global functioning long term (Penttilä et al., 2014). Conversely, more recent studies have shown that reducing DUP can increase an individual's response to treatment (Murru & Carpiniello, 2018). Some evidence shows that longer DUP has been associated with deficits in some cognitive domains, including visual memory, working memory, and verbal memory (Amminger et al., 2002; Chang et al., 2013), though these findings have not been replicated in other studies (Rapp et al., 2013).

While DUP has shown as a good predictor of outcomes, it explains a relatively small percentage of the overall variance (Penttilä et al., 2014). Emerging literature also suggests that these findings may be as a result of lead-time bias, and that DUP better reflects stage of illness, not trajectory (Jonas et al., 2020). Additional limitations of DUP research have been identified by Register-Brown and Hong (2014). The authors noted that across the 132 studies, there was no standardised measure to estimate DUP. The most common method to collect data on DUP was using clinical interviews, though only 8% reported an inter-rater reliability (IRR). A second issue was that the definition for DUP varied between studies e.g. first psychiatric hospitalization, first antipsychotic treatment, first treatment of any form. The analysis found that despite this limitation DUP showed a consistent but small effect size (0.2 – 0.3) as a clinical measure of functional and symptomatic outcome, as well as remission rate.

1.6.2 Pharmacological interventions in schizophrenia

First generation antipsychotics, such as chlorpromazine and haloperidol, began to be used in the 1950's (Stępnicki et al., 2018). These drugs were effective in reducing positive symptoms by acting as dopamine antagonists targeting D_2 receptors, though this reduction in positive symptoms came with severe side effects (Peluso et al., 2012). First generation antipsychotics produced symptoms of psychomotor slowing, affective flattening and emotional quieting. This occurs because the medications act as antagonist to D_2 receptors throughout the CNS, not just the mesolimbic pathway (Li et al., 2016). This leads to the unwanted motor effects, and this effect in the prefrontal cortex is thought to exacerbate the negative symptoms of schizophrenia. The severity of these symptoms increased risk of nonadherence, relapse and hospitalization (Kishimoto et al., 2013).

Second generation antipsychotics, such as clozapine, olanzapine and risperidone, were thought to reduce side effects by reducing reliance on dopamine antagonists (Li et al., 2016). Second generation antipsychotics (atypical antipsychotics), target both dopamine (D_2 receptors), and serotonin ($5\text{-}HT_{2A}$ and $5\text{-}HT_{1A}$ receptors) (Stępnicki et al., 2018). These medications show similar levels of efficacy in reducing positive symptoms, though evidence of reducing negative

and cognitive symptoms has proven inconclusive (Conley & Kelly, 2007; Davies et al., 2007). One second generation antipsychotic, clozapine, has been shown to be more effective than first generation antipsychotics in treating treatment-resistant schizophrenia (Lieberman et al., 2005). Second generation antipsychotics showed reduced neurological symptoms, but have significant metabolic side effects, including rapid weight gain, insulin resistance and elevated blood pressure (Devlin & Panagiotopoulos, 2015). These symptoms create additional health risks and also have shown to decrease rates of adherence (Kishimoto et al., 2013).

Newer atypical antipsychotics, such as aripiprazole, brexpiprazole and cariprazine, are partial D_2 receptor agonists (Stępnicki et al., 2018). This is thought to act as a "dopamine stabiliser"; acting as an antagonist of the dopamine mesolimbic pathway, but as a functional dopamine agonist in the mesocortical pathway (Lieberman, 2004). Efficacy of third generation antipsychotics have similar rates to earlier antipsychotic medications in terms of reducing positive symptoms, but do not show evidence of reducing negative or affective symptoms (de Araújo et al., 2012). The advantage of third generation antipsychotics is significantly less severe side effects, though motor disorders such as akathisia, and metabolic side effects of weight gain, insomnia and nausea, are still present (Mailman & Murthy, 2010).

There remains little evidence that these medications are able to improve negative and cognitive symptoms, and as much of 30% of patients continue to experience treatment-resistant schizophrenia (Vita et al., 2019). Many patients also need to rely on long term use of antipsychotics, with relapse rates following discontinuation being between 62 – 91%, regardless of type or length of treatment (Emsley et al., 2013).

1.6.3 Psychological interventions in schizophrenia

1.6.3.1 Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) is one of the most common interventions used in schizophrenia (Bighelli et al., 2018). CBT focuses on challenging negative patterns of thought about the world and self (Rector & Cassin, 2010). In schizophrenia, this has been adapted to focus on positive symptoms (Ades et al., 2009). In terms of efficacy, results have varied but in a large meta-analysis Bighelli and colleagues (2018) found that overall CBT had a modest effect in reducing overall symptoms and positive symptoms (13.2%, 24.8% respectively). Techniques such as mindfulness have also shown some improvement on negative symptoms, though the results are not robust (Khoury et al., 2013).

CBT in conjunction with medication has been shown to increase rates of adherence to medication usage compared to medication alone (Guo et al., 2010). CBT shows a small but significant improvement in functioning levels, however this improvement was lost following treatment discontinuation (Laws et al., 2018). This same effect was found by the meta-analysis for distress levels, which decreases marginally during CBT administration, but was not maintained during the follow-up period. The study also noted no improvement on quality of life measures at any point during CBT treatment.

One area where CBT has been recently applied is in treatment-resistant schizophrenia patients. These are individuals with schizophrenia who are unresponsive to multiple types of antipsychotic medications, and represent a significant minority of the population (Lally et al., 2016). In this group, CBT has been shown to produce significant improvements in positive symptoms, negative symptoms and rates of depression during treatment and at follow up (Sensky et al., 2000)

1.6.3.2 Cognitive remediation

Cognitive remediation aims to improve the cognitive deficits associated with schizophrenia, and by extent improve functional outcomes (Ades et al., 2009). These measures focus on strategies to improve cognition through exercises and development of compensatory strategies to reduce effects of persistent cognitive impairments.

A meta-analysis of 26 studies (n = 1,151) showed that cognitive remediation measures can have a marked improvement, even after relatively short intervention periods (m = 12.8 weeks) (McGurk et al., 2007). The study found small but significant improvements across global cognition, attention/vigilance, processing speech, verbal working memory, verbal learning and memory, social cognition, reasoning and problem solving, but found no effect on visual learning and memory. With regards to secondary measures, the study noted a strong effect on general symptom improvement, and a moderately strong effect on functioning. The effects of cognitive remediation on symptom improvement has been of particular interest, and recent studies that targeted negative symptoms have noted small to moderate effects (Cella et al., 2017).

Recent research has begun to examine neural changes following cognitive remediation therapy. Matsuda, Makinodan, Morimoto, and Kishimoto (2019) found limited evidence of changes in activation patterns in the frontal brain regions, as well as volumetric changes following interventions. While these findings are positive, the evidence is still in preliminary stages as only 12 studies have so far investigated neurobiological correlates of remediation approaches.

1.7 Transition rates

Interventions still show only moderate and inconsistent improvements in those with schizophrenia (Bighelli et al., 2018; de Araújo et al., 2012). This has increased interest in early intervention and identifying those who are at increased risk for transition to psychosis (McGorry et al., 2006). One group are those with a genetic risk, such as having a first degree relative with schizophrenia. A more predictive model has been found when this genetic vulnerability is combined with considering sub-threshold symptoms. Studies which have looked at both have noted that in first degree relatives, those who report sub-threshold symptoms are at a significantly elevated risk for developing psychosis (Hormozpour et al., 2016; Tandon et al., 2012). Even independent of a genetic predisposition, individuals who experience sub-threshold symptoms are shown to be at a significantly elevated risk for transitioning to psychosis compared to those without (Riecher-Rössler & Studerus, 2017).These two groups have been primarily studied; and both groups are referred to as being at CHR-P.

CHR-P samples are generally studied in help-seeking samples, and the criteria to meet the DSM V diagnosis for Attenuated Psychosis Syndrome include behaviour and distress (Fusar-Poli et al., 2018). Non-help seeking CHR-P in some research are considered to be experiencing psychotic experiences (McGrath et al., 2015). Psychotic experiences are similar to subthreshold symptoms, but occur significantly less frequently, with a majority of those who report them experiencing between 1 – 5 psychotic experiences during their lifetime (Kelleher & Cannon, 2011). Recent research in community samples has demonstrated that there are individuals who report subthreshold symptoms at a significantly higher severity and frequency, meeting clinical definitions for CHR-P (Haining et al., 2019; McDonald et al., 2019; Mills et al., 2017). This has increased interest in research on community sample CHR-P, though research in the area is currently limited.

Research into improving predictive variables in CHR-P populations has focused across multiple domains including symptoms, environmental risk factors, and functioning. Mason and colleagues (2004) reported that unusual thought content, magical ideation, auditory hallucinations and negative symptoms of anhedonia and asociality were the most powerful in predicting transition, but these findings were not replicated (Thompson et al., 2011). Other studies have reported suspiciousness/paranoia as an additional predictor (Yung, Phillips, Yuen, & McGorry, 2004). Research which considered both prodromal APS and cognitive disturbances in BS found an increased risk for transition (Ruhrmann et al., 2010; Schultze-Lutter et al., 2012). Environmental factors, particularly use of drugs, has been also associated with increased risk for

transition in longitudinal studies, in both genetically vulnerable individuals and those who experienced sub-threshold symptoms (Cannon et al., 2008). Recent decline in functioning, in combination with symptom type or genetic risk has been shown to have predictive power across multiple meta-analyses (Fusar-Poli et al., 2013; Thompson et al., 2011).

There has been a significant decline in the rates of transition across CHR-P groups. A meta-analysis by Fusar-Poli and colleagues(2012) showed 22% of transitions after one year and 35.8% transitioning after 3 years, in contrast to earlier reports suggesting between 40 – 50% (Yung et al., 1998). Possible explanations for declining transition rates were methodological and definitional differences between studies . Rates of transition are also decreasing internally in longitudinal large scale studies (Yung et al., 2007) disputing the explanation of methodological differences for this effect. Some papers have suggested earlier detection may be creating "false positives" by identifying symptoms found in the prodrome of other conditions, such as obsessive thoughts or high paranoia (Simon et al., 2014). Comorbidity with axis II disorders have also been shown to account for declining rates of transition in some samples (Lim et al., 2018).Yung and colleagues (2007) similarly focused on earlier detection and intervention as creating a "dilution effect" by reducing rates of transition. However, this explanation was not supported and further analysis on this data set, with the study failing to find significant evidence for earlier intervention having an effect (B. Nelson et al., 2016). Neither were changes in treatment or changes in sample characteristics significant in explaining this decline (Hartmann et al., 2016).

Transition rates declining has not been found to mirror a decline in number of individuals reporting sub-threshold symptoms (B. Nelson et al., 2016). This has created more academic interest in CHR-P, and increased research into outcomes in this group.

1.8 Subthreshold symptoms in CHR-P

Subthreshold psychotic experiences are divided similar to schizophrenia symptoms into two categories; positive and negative symptoms (Yung et al., 2005). In addition, CHR-P characterized by self-reported cognitive changes, so-called basic symptoms, which can continue in those with schizophrenia (Schultze-Lutter et al., 2016). Nonspecific symptoms are also characteristic of the prodromal stage (Fusar-Poli et al., 2013). Shah and colleagues (2017) found that subthreshold symptoms are present in the majority (68%) of those who will go on to experience FEP, and non-specific symptoms were reported in both those who experienced subthreshold symptoms and those who reported no other subthreshold symptoms.

There are gender differences in CHR-P populations. Male participants with CHR-P have more severe negative symptoms, worse social functioning, report earlier onset of symptoms and longer duration of untreated symptoms (Barajas et al., 2015; Rietschel et al., 2015). Age of onset, regardless of gender, is also associated with worse functional outcomes (Häfner, 2000; Schultze-Lutter, Rahman, et al., 2015).

However, growing research into community samples show there are individuals who are not help-seeking, but which meet criteria

1.8.1 Nonspecific symptoms

Nonspecific symptoms in CHR-P describe a range a negative functional outcomes, including poor school and social functioning, and low psychological measures including anxiety symptoms and depressed mood (Lencz et al., 2004). These symptoms commonly precede onset of other forms of subthreshold symptoms (Schultze-Lutter, Rahman, et al., 2015). Nonspecific symptoms are not considered criteria for CHR-P (Lencz et al., 2004).

1.8.2 Negative symptoms

Negative symptoms are present in CHR-P individuals (Lencz et al., 2004) and fall into two distinct clusters: 1) diminished expression and 2) amotivation. Diminished expression describes experiences of affective flattening and poverty of speech, while amotivation describes symptoms of avolition, apathy, asociality and anhedonia. Despite not generally considered as an inclusion criteria for CHR-P, growing evidence shows that individuals who experience more severe negative symptoms, as well as APS, are more likely to transition than those without (Demjaha et al., 2012; Fusar-Poli & Borgwardt, 2007).

1.8.3 Attenuated psychotic symptoms

APS manifest like full positive psychotic symptoms, but are present to a lesser degree in intensity, frequency and/or duration (Fusar-Poli et al., 2013). In general, there are four clusters of APS positive symptoms: 1) unusual thought content (UTC) 2) non-bizarre ideas (NBI) 3) perceptual abnormalities (PA) 4) and disorganised speech (DS). UTC describes thoughts and beliefs characterised by strange, fantastic, or bizarre ideas, which range from atypical to severely distorted or illogical (Sinott et al., 2016). NBI describes delusions that are possible in real life, though they are atypical or improbable (Sinott et al., 2016). PA describe any perceptual experiences, which can be in the form of a general wider experience of distortions or illusions (e.g. hearing feeling muted), or specific hallucinations (e.g. hearing a voice) (Yung et al., 2005). Disorganised speech describes clusters of symptoms to do with how the participant uses

languages, either self-reported or objectively measured. Measures of APS differ slightly on groupings of these clusters, e.g. the Comprehensive Assessment of At-Risk Mental State (CAARMS) treats NBI as one set of symptoms, while the Structured Interview of Prodromal Syndromes (SIPS) splits NBI into two distinct categories of suspiciousness/persecutory ideas and grandiosity (Miller et al., 2003; Yung et al., 2005). To be considered to have an APS an individual must have a symptom in one of these categories which meets a severity threshold. In addition, the symptom must be present with a certain frequency and/or duration i.e. in CAARMS the frequency/duration level is at least once a month for more than an hour per occasion, or 3 times per week less than an hour per occasion. Some individuals experience full psychotic symptoms, but for brief periods of time (< 1 week) that rather than continuing into transition, remit without treatment (Yung et al., 2005). This CHR-P group meets criteria for brief limited intermittent psychotic symptoms (BLIPS).

1.8.4 Basic symptoms

BS are self-identified changes in thought processing, perception, language and attention (Schultze-Lutter et al., 2016). BS are mostly identified using the Schizophrenia Proneness Instrument, Adult/Child & Youth (SPI-A/SPI-CY) (Schultze-Lutter et al., 2015). This measure detects two BS categories; cognitive-perceptive basic symptoms (COPER) and cognitive disturbances (COGDIS). These groupings describe partially overlapping symptoms and experiences. COPER describes disturbances in thought and perceptual experiences. COGDIS describes disturbances in thought, language and some perceptual experiences. CHR-P may meet criteria for either or both COPER and COGDIS experiences, and both are determined by meeting the symptom criteria, and experiencing it at a reasonably frequent level (several times a month or more frequently). To meet COPER criteria, an individual must have first experienced these symptoms more than a year ago, while for COGDIS they can have emerged at any time.

Both sub-types of BS are thought to present before onset of psychosis, and be present during psychosis and in remission (Schultze-Lutter & Theodoridou, 2017). Several studies have identified BS as a distinct stage, the early at-risk mental state, which is characterised by the onset of these self-identified cognitive and perceptual changes. The late at-risk mental state is classified by presence of BS as well as APS and/or BLIPS (Bechdolf et al., 2012; Salokangas & McGlashan, 2008). Current theories (Fusar-Poli et al., 2013) assume that BS precede the onset of APS during the prodromal stage. It has been proposed that basic symptoms reflect the immediate symptomatic expression of the neurobiological processes underlying schizophrenia (Schultze-Lutter et al., 2016). Evidence of the significance of BS in risk of transition show that

COGDIS criteria has shown high predictability of transition within 4 years (54.9%; Schultze-Lutter, Michel, et al., 2015), and measurement of both BS and APS has shown to further increase predictability (Schultze-Lutter et al., 2012b).

In this conception of BS, it is hypothesised that attenuated and overt psychotic symptoms develop as a secondary phenomenon, resulting from poor coping strategies of emerging BS and associated stressors (Schultze-Lutter & Theodoridou, 2017; Schultze-Lutter, 2009; Schultze-Lutter et al., 2016). Currently only one study has been conducted to measure evidence of this relationship. The study was conducted on an FEP sample and found the predicted relationship of BS onset prior to APS onset only when level of education was accounted for. When this was not factored in, the study found a third of participants reported BS onset before APS (n = 27, 33.3%), a third reported them starting in the same month (n = 29, 35.8%) and a third reported BS onset after APS (n = 25, 30.9%) (Schultze-Lutter et al., 2010). Two explanations were offered for this disparity. One explanation for this disparity was the recall bias an individual might experience for APS symptoms, compared to BS which are more subjective. A second suggestion is that health care and higher education both have a socio-economic component to them. This means that in a help-seeking FEP sample, there is likely to be a higher level of wealthy individuals, and that this group is also more likely to attend college. The studies which initially pioneered the BS concept were also skewed in this manner (Schultze-Lutter et al., 2007a, 2008), and the paper suggests that a selection bias may account for why comparisons between groups showed different expected outcomes. A second study examining how non-specific subthreshold symptoms, as compared to the onset of APS and BS were affected by age of onset, found younger people (<18 year old) reporting fewer and shorter unspecified prodromal symptoms (Schultze-Lutter, Rahman, et al., 2015).

1.9 Cognitive deficits in clinical high risk for psychosis individuals

A meta-analysis of studies on neurocognitive deficits in CHR-P found evidence that they occur in multiple domains, including attention, working memory, processing speed, executive function, verbal fluency, visual memory, verbal memory and noting particularly robust impairments in symbol coding and visuospatial working memory (Bora et al., 2014). This study also considered CHR-P individuals with only a genetic vulnerability, but no APS or BS. In this group there was also impairment across all domains compared to controls. Compared to CHR-P groups with symptoms, the genetic risk group showed comparable results in other cognitive domains. CHR-P Individuals with both a genetic risk and APS symptoms showed more severe deficits in verbal memory and sustained attention. Other large reviews found comparable results

across most domains, but failed to find deficits in processing speed (Fusar-Poli et al., 2012). A study measuring cognitive deficits in CHR-P with BS found that the presence of COPER symptoms predicted cognitive deficits only in executive control and verbal memory (Frommann et al., 2011). It is proposed that this may indicate that BS generally precede neurocognitive impairments (Schultze-Lutter et al., 2016). In community samples, CHR-P were found to perform significantly worse in executive functioning and motor speed tasks, as well as overall diminished cognitive scores (Haining et al., 2019). Fusar-Poli et al., (2012) also noted deficits in social cognition, and found that they had larger effect sizes than other cognition measures. In particular deficits in discriminating between neutral and negative emotions have been observed (Corcoran et al., 2015). Individuals with worse facial affect was also associated with lower scores on spatial working memory and attention, compared to other CHR-P individuals (Yong et al., 2014). Difficulty identifying other people's facial expressions have also found in CHR-P compared to control (Piskulic et al., 2016) and are associated with worse functional outcomes (Matrunola, 2017) as well as increased risk of transition (Piskulic et al., 2016).

1.10 Outcome measures in CHR-P individuals

1.10.1 Remission

Only 22% of CHR-P individuals transition to psychosis (Fusar-Poli et al., 2012). In addition, a substantial number of participants meeting CHR-P criteria continue to experience sub-threshold symptoms over several years. (Beck et al., 2019) found that remission was around 50% at 2 – 3 year follow up, and this increased to 70% in studies after a 6 – 7.5-year period. While positive symptoms tend to remit at around 2 years, mood and anxiety symptoms tended to persevere for significantly longer durations (de Wit et al., 2014). There remain insufficient explanations into why there are differences in rates of recovery, and what the effect these long periods experiencing sub-threshold symptoms have on those who experience them.

1.10.2 Functional outcomes

APS and BS are associated with decreased functioning across multiple domains (Ruhrmann et al., 2010; Salokangas & McGlashan, 2008). These findings have also been demonstrated in community sample CHR-P (Haining et al., 2019). Studies show that individuals who experienced APS have significant impairments compared to controls in both role and social functioning at three year follow up (Addington, Cornblatt, et al., 2011). Explanations for the link between symptoms and functional decline refer to the impact of both negative and positive symptoms as significant contributors in functional impairments (Fulford et al., 2013; Salokangas & McGlashan, 2008).

Prevalence of co-morbidity in CHR-P has also been observed, with a number of studies finding a high prevalence of Axis-I diagnosis, particularly anxiety and affective disorders (Michel et al., 2018). This prevalence was present to approximately the same degree across remitted and non-remission CHR-P groups (63% and 67% respectively) (Beck et al., 2019).

1.11 Treatments

There are currently limited treatments and intervention options available for CHR-P individuals and their efficacy in reducing risk of transition and functional impairments have been modest (McFarlane et al., 2015).

1.11.1 Psychological intervention

Cognitive remediation has so far not shown significant effects in improving symptoms or reducing transition rates in CHR-P populations (Piskulic et al., 2015). CBT has shown to improve APS severity in CHR-P groups, but not transition rates (van der Gaag et al., 2012). Psychoeducation has shown to have some effects in improving role functioning, but not reducing risk of conversion to psychosis (McFarlane et al., 2015).

1.11.2 Medication

Second generation antipsychotic medications, such as amisulpride and risperidone, have shown effects on improving symptoms and reducing rates of transition (Phillips et al., 2009; Ruhrmann et al., 2007). There are concerns regarding unnecessary prescription of these medications, which have significant metabolic side effects (Devlin & Panagiotopoulos, 2015), and predicting those most at risk for transitioning still only shows an accuracy of 35% (Thompson et al., 2011).

1.11.3 Non-specific treatments

Non-specific interventions have grown more common in mental health services, designed to reflect the significant overlap in the early development of many disorders (Mei et al., 2019). Non-specific treatments such as nutritional supplements have shown to effect on prognostic outcomes at baseline and follow up (Amminger et al., 2015). Non-specific psychological interventions such as supportive counselling showed evidences of improvements of symptom severity equivalent to equivalent to CBT (Addington, Epstein, et al., 2011). The evidence of preventative studies suggests that the effects of these interventions are moderate, but stable across multiple studies (Nelson et al., 2020).

1.12 Duration of untreated prodromal symptoms

Duration of untreated prodromal symptoms (DUPrS) describes the onset of prodromal symptom until first intervention or until onset of FEP, though the definition of DUPrS varies across studies. Evidence shows that there are functional differences in the outcomes of FEPs for those who experience prodromal symptoms compared to those who do not (Shah et al., 2017).

Research into DUPrS has focused on two separate groups: 1) studies focused on DUPrS in FEP and transitioned populations, and 2) in CHR-P non-transitioned populations.

1.12.1 Duration of untreated prodromal symptoms in FEP

The most common approach to studying DUPrS is to examine FEP populations retrospectively, which was employed in 24 studies. However, not all studies provided details on length of duration, or measured duration of symptoms while an individual was FEP, which does not measure only DUPrS (Powers et al., 2019). There has also been very little standardisation in assessing duration (Powers et al., 2019). In more recent studies, there was use of structured interview tools, such as the Early Recognition Inventory (ERIraos) (Schultze-Lutter, Rahman, et al., 2015), but there was no consistency between papers. Most papers only considered APS (Huber et al., 1980; Malla et al., 2002; Powers et al., 2019; Rabiner et al., 1986; Shah et al., 2017) while only one also considered BS (Schultze-Lutter, Rahman, et al., 2015).

1.12.1.1 Outcomes of DUPrS in FEP samples

Transition rates

Rates of APS in FEP populations has been of interest in DUPrS research. One large study from the Personal Assessment and Crisis Evaluation (PACE) study measured DUPrS in those who converted to psychosis and found that 95% converted within 5 years of onset of symptoms (m = 61.02 months) (Powers et al., 2019). Not all studies have found this relationship, one study noted that duration of prodromal symptoms was only predictive in conjunction with other factors, such as family history and education (Huber et al., 1980).

Functional outcomes

Longer DUPrS is associated with lower general functional scores in FEP individuals (Keshavan et al., 2003). This finding remained true even when premorbid adjustment was accounted for, and was found at 1 and 2 year follow up. FEP individuals with longer DUPrS for BS also showed lower help-seeking behaviours compared to short DUPrS individuals (Schultze-Lutter, Rahman,

et al., 2015). This delay in help-seeking increases the length of DUP and can add significantly to rates of relapse and low functioning (Norman & Malla, 2001).

Symptomatic outcomes

In FEP studies, DUP is associated with lower rates of recovery (Perkins et al., 2005). The findings of these papers for the influence of DUPrS in FEP recovery has indicated there may be some effect. One paper found that shorter DUPrS was associated with lower levels of negative symptoms in FEP, specifically levels of anxiety (Malla et al., 2002). Relapse rates have also been shown to be associated with DUPrS (Rabiner et al., 1986)

1.12.2 Duration of untreated prodromal symptoms in CHR-P

Emerging data has highlighted that DUPrS in participants meeting CHR-P may confer a similar relationship with clinical and functional outcomes as observed in FEP (Zhang, Xu, Tang, Cui, Tang, et al., 2018). The term prodromal is used in this research, which denotes the early stage of a condition which progresses (Addington, 2003) . This cannot be assumed for CHR-P as a majority will not transition (Shah et al., 2017). However given evidence of the long term negative outcomes of experiencing subthreshold symptoms, even in those who do not transaction (Beck et al., 2019), research into the effect of longer duration of subthreshold symptoms in this population is still a necessary area of research.

research has ten studies explicitly focused on DUPrS in non-transitioned populations and its impacts on outcomes. All current research has been conducted in clinical CHR-P cohorts. There is currently no standardized tool to measures DUPrS. Instead all papers used self-reported data obtained from other instruments to establish DUPrS. These include SIPS, CAARMS and ERIraos.

1.12.2.1 Outcomes of DUPrS in CHR-P samples

Transition rates

Findings in CHR-P populations show some mixed evidence that DUPrS may be predictive for transition rates. (Zhang, et al., 2018b) examined a clinical population over one year to observe differences in conversion, but found no relationship between length of DUPrS and conversion.

Similarly, Carrión et al., (2016) and Zhang et al.,(2017) noted no relationship between the length of DUPrS and conversion, though both observed that the number of sub-threshold symptoms positively correlated with conversion rates. Two findings from the PACE study differed on these findings in a CHR-P sample. Yung and colleagues(2004) found that length of DUPrS to be

predictive of transition. Nelson et al. (2016) observed individuals with long DUPrS (> 1 year) had a significantly higher conversion rate (56%) compared to those with a shorter DUPrS (< 1 year; 32 %). In Nelson et al.(2016) individuals who entered treatment with shorter DUPrS also showed evidence that they did not reach same transition rate levels as those who entered treatment with longer DUPrS. One study measuring BS (Schultze-Lutter et al., 2007) found that dividing symptoms by length of DUPrS could increase prediction of risk of transition.

Functional outcomes

Four studies considered functional outcomes in CHR-P individuals with longer DUPrS. Functional decline was broadly shown to be linked to longer DUPrS. Zhang and colleagues(2018a) found a statistically significant impact of DUPrS on negative functional outcomes, but not functional recovery. Carrión et al., (2016) found that negative symptoms were associated with poorer social functioning, but positive symptoms were not associated with poor role or social functioning. Fusar-Poli et al. (2009) found that individuals experiencing BS showed a decline in GAF over a year follow up. Zhang, et al., (2018b) found that those with longer DUPrS experienced lower GAF scores overall than shorter DUPrS groups. Zhang et al.(2017;2018b) found this difference was more significant when the sample was divided into short and long duration. Individuals in the longer DUPrS group had significantly worse outcomes than short DUPrS. In measuring number of symptoms, longer DUPrS in APS was also associated with statistically more negative symptoms

Symptomatic outcomes

Only one paper in CHR-P research by tracked symptomatic changes in APS in relation to DUPrS (Zhang et al., 2018a). The study measured a cohort of CHR-P individuals over a two-year follow-up period and remission of APS was assessed. The paper did not find a statistically significant impact of DUPrS on symptomatic outcome.

1.13 Aims of the thesis

There is growing evidence to show that there is a significant population of CHR-P, who experience clinically defined CHR-P subthreshold symptoms of APS and BS (Schultze-Lutter, Michel, et al., 2015), but who do not seek early interventions (Mills et al., 2017). Online screening methods have allowed research to expand samples beyond help seeking groups, and recent evidence has shown the efficacy of these programs in detection of CHR-P from community samples (McDonald et al., 2019). In light of this, there is a need to expand research

in this area, and compare results of this group, to the more widely studied CHR-P help seeking group.

Using online screening methods to identify CHR-P individuals from a non-help seeking community sample, this thesis aims to address the identified gaps in the current literature on DUPrS. Three central questions are examined in the course of this text;

1. Does the assumed relationship of BS onset preceding APS onset occur in a CHR-P sample?

The current literature on duration of sub-threshold symptoms in CHR-P is still in preliminary stages, with significant gaps in the literature. One significant area is that to date only one study has measured the duration of BS compared to APS, and only in an FEP sample (Schultze-Lutter et al., 2010). The assumption that BS onset precede APS onset is central to the hypothesis that BS are the immediate symptomatic expression of the neurobiological processes, and that APS symptoms are a secondary consequence of poor coping to BS and associated stressors (Schultze-Lutter et al., 2016). This hypothesis is influential and commonly used in many areas of CHR-P research (Bechdolf et al., 2012;Fusar-Poli et al., 2013; Salokangas & McGlashan, 2008), but has not been validated in a CHR-P sample.

2. Is there an effect of duration of APS or BS, on functioning, and does this differ in those with longer or shorter duration?

Measures of the effect of DUPrS on functional outcomes have only begun to be explored, and only in clinical samples (Carrión et al., 2016; Fusar-Poli et al., 2009; Zhang et al., 2017; 2018b). This research aims to replicate these findings in a community sample, and explore the effect of BS duration on functioning measures.

3. Is there effect of duration of APS or BS, on cognition?

Other deficits found in CHR-P samples and the effect of duration of sub-threshold symptoms have been neglected e.g. only one study has measured the effect of DUPrS on cognition, and it was not reported in the main findings (Chon et al., 2015). This paper aims to address this deficit by examining the effect of APS and BS duration on multiple measures of cognition.

2 Methods

2.1 YouR study design

The data for this project was collected as part of the Youth Mental Health Risk and Resilience (YouR) study (Uhlhaas et al., 2017). This is a longitudinal, multisite project investigating the psychological and neurobiological predictors of emerging psychosis. This study is funded by the Medical Research Council (MRC). The YouR-study was approved by NHS Research Ethical Committee Glasgow and Greater Clyde.

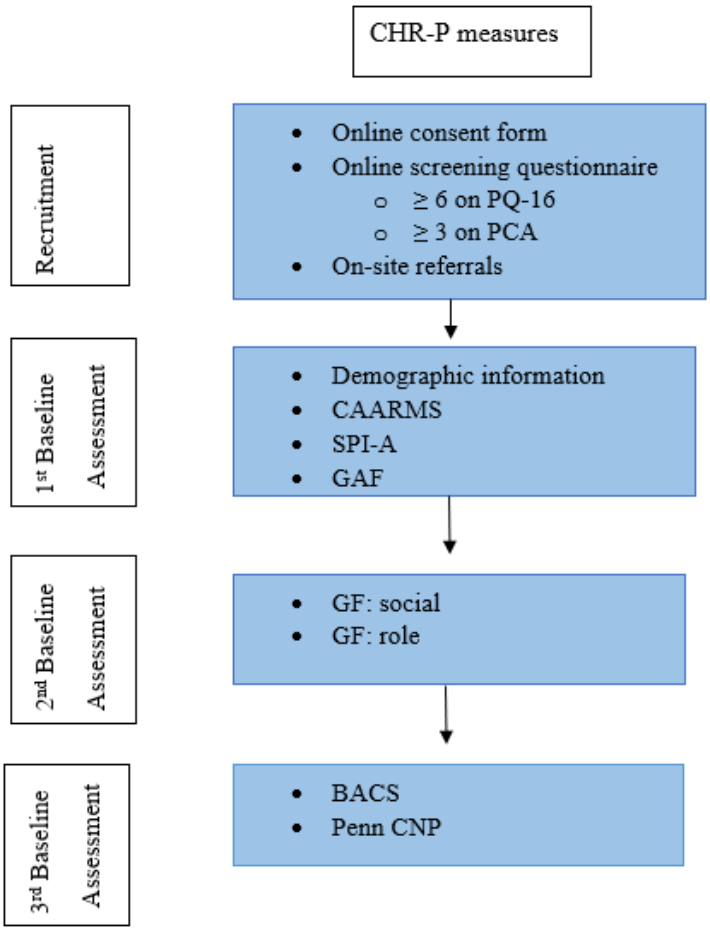
The YouR study collects multiple variables on CHR-P at baseline, including clinical measures, functioning and cognition measures, and neuroimaging measures including fMRI and MEG. Recruitment was continuously conducted throughout the year, once a participant met recruitment criteria they were immediately invited to a 1st baseline assessment to assess CHR-P state. Participants who met CHR-P criteria were then invited to 2nd baseline assessment at earliest convenient, generally between 2 – 3 weeks following initial screening. Subsequent baseline assessments follow this design and participant generally complete all four baseline assessments at 6 – 9 weeks from first assessment. A healthy control group was also collected who completed these baseline assessments. Follow up data using the same measures were collected every six months on the CHR-P group for the following three years, but not the healthy controls. For full details see (Uhlhaas et al., 2017).

The YouR study has been collecting data since 2016, and was still actively recruiting and screening CHR-P participants throughout 2018/2019. As part of the YouR research team, and to complete a thesis using the data, all researchers, including myself, assisted baseline demographic, clinical, functioning and cognitive assessments, neuroimaging procedures and completed follow up on participants. The control group was collected in 2016/2017 and does not have follow up data, so I did not participate in collecting this data.

Additional responsibilities throughout my year in the YouR study was to run recruitment, this included running an email campaign, acting as NHS liaison, and maintaining the recruitment website. My responsibilities also included scheduling initial screenings, baseline assessments and follow up assessments.

Not all measures collected in the YouR study were used in this current research, including fMRI and MEG imaging data and follow up data. The protocols of the YouR study used in this research are highlighted in Figure 1.

Figure 1. Flow chart of YouR study protocol measures used in the current research



2.2 Recruitment and participants

The CHR-P group was recruited from the general population and through clinical referrals from NHS-patient services. 92% were recruited from the general population, using flyers, transport advertisements and an email campaign. An email campaign was conducted across incoming first year students to colleges and universities in Edinburgh and Glasgow, and invited individuals to participate in an initial online pre-screening questionnaire (www.your-study.org.uk), The majority of recruited participants came from third level institutions (n = 129, 84.86%).

Informed consent was obtained online. Participants then completed the 16 item version of the prodromal questionnaire (PQ-16; Ising et al., 2012) as well as a 9 item-scale for the assessment of perceptual-cognitive anomalies (PCA). Participants were invited for clinical assessments if they endorsed six or more PQ-16 items, or 3 items on the PCA-scale.

Two inclusion criteria were identified in order for individuals to complete the online survey; they must be between 16 – 35 years old, and have normal/corrected to normal vision. Exclusion

criteria included having a diagnosed psychotic condition, or having any metal implants. Individuals who met criteria from the online survey were contacted for a first in person assessment. A portion of those who failed to meet any criteria were also contacted as a control group.

A total of 153 (107 female, 46 male) CHR-P individuals screened at baseline were used in this study. 135 (97 female, 38 male) of those completed the first three baseline assessments. A control group (n = 80, 61 female, 19 male) was collected of which 57 completed first three baseline assessments (40 female, 17 male). Most individuals were recruited from the general population, with 8 being collected from referral.

2.3 Demographic information

Demographic information was initially collected from the participant at baseline. This included age, years of education, citizenship, housing situation, specific learning difficulties, and family history of illness. Social factors including smoking, drinking and drug use was also recorded. Participants were asked about any instances of physical or mental illness in the last twelve months. If an incident of mental illness was reported, any diagnosis, medication and treatment was recorded. Suicidality and self-harm behaviours current and past were also assessed. Individuals who expressed current high suicidal ideation or intent were referred to appropriate services and excluded from the study.

2.4 Assessment of clinical high-risk status

Individuals who had met the pre-screening criteria were invited for an interview to determine CHR-P status. The two measures used were the CAARMS (Yung et al., 2005) and the SPI- A (Schultze-Lutter, Addington, et al., 2007). CAARMS was used to assess if a participant met at-risk mental state (ARMS) criteria, and shows a strong inter-rater reliability (IRR .85) (Yung et al., 2005). The positive scale of CAARMS was administered which included the following subscales: unusual thought content (UTC), non-bizarre ideas (NBI), perceptual abnormalities (PA) and disorganised speech (DS). Each of these are rated on a scale of 0 – 6 for intensity and frequency. In addition, the onset of the experience was recorded. Participants were asked to score their own distress regarding the experiences described on a scale of 0 (not distressed at all) to 100 (extremely distressed). A score for severity of positive symptoms was calculated using the summed scores of the product of intensity and frequency for each of the four subscales.

To meet CHR-P, participants needed to meet the criteria of at least one of the ARMS groups:

1. **Group 1: ARMS Vulnerability Group:** A family history of psychosis in a first degree relative or identified schizotypal personality disorder in the individual and a 30% drop in Global Assessment of Functioning (GAF) score from premorbid level, sustained for a month, occurred within past 12 months
2. **Group 2: ARMS Attenuated Psychosis Group:** Individuals who experienced subthreshold psychotic symptoms which started or worsened in the past 12 months. The experiences needed to have a global (intensity) score of ≥ 3 for UTC, NBI, PA and a global score of ≥ 4 in DS. In addition, the symptom needed to have a frequency score of ≥ 3 (frequency score 3 = "Once a month to twice a week, more than one hour per occasion, or 3 to 6 times a week - less than one hour per occasion").
3. **Group 3: ARMS Brief Limited Intermittent Psychosis Syndrome (BLIPS) Group:** Individuals who experienced a short period (< 1 week) of full psychotic experiences, which resolved without treatment. The experience needed to have a global score of 6 for UTC, NBI and DS, or a global score of 5-6 for PA. In addition, the symptom needed to have a frequency score of ≥4.

SPI-A was used to assess if a participant met COGDIS and/or COPER criteria. To meet SPI-A criteria, BS symptoms had to be present in the last three months. Symptoms were scored based on frequency (0 – 6) over the last three months. A score of moderate (3, several times in a month or weekly) to extreme (6, daily but not necessarily continuously) was considered as the symptom being present.

Table 1. List of COGDIS and COPER criteria, as identified in the SPI-A measure (Schultze-Lutter, Addington, et al., 2007)

COGDIS criteria *At least two of the following BS:*	COPER criteria *At least one of the following BS, which started over 12 months ago:*
Inability to divide attention (B1)	Thought interference (C2)
Disturbances of expressive speech (C5)	Thought blockage (C3)
Disturbances of abstract thinking (O3)	Disturbance of receptive speech (C4)
Captivation of attention by details of the visual field (O7)	Thought pressure (D3)
Thought interference (C2)	Unstable ideas of reference (D4)
Thought blockage (C3)	Thought preservation (O1)
Disturbance of receptive speech (C4)	Decreased ability to discriminate between ideas/perception and fantasy/true memories (O2)
Thought pressure (D3)	Derealization (O8)
Unstable ideas of reference (D4)	Visual perception disturbances (D5, F2-F3, O4.1-O4.10)
	Acoustic perception disturbances (F5, O5.1-O5.2)

2.5 Assessment of duration of prodromal symptoms

DUPrS was obtained retroactively from the CAARMS and SPI-A baseline screenings. This had previously been reported during interviews but not recorded in the dataset. As part of the current research for this thesis a dataset was created which included duration of each symptom reported for all CHR-P in the YouR study. Additional information including symptom subtype, age at onset of symptom, the life stage of the individual when the symptom onset and if a symptom was continuous or remitted were recorded.

Duration of symptoms was only recorded on items which had been scored as meeting APS or BS criteria. Neither CAARMS or SPI-A have a duration specific question in the measures, but both have duration specific requirements. To meet criteria of CAARMS symptoms must have started or become worse in the last year. To meet SPI-A COPER criteria, symptoms must have onset over 12 months ago. This meant participants were generally asked start dates of reported symptoms on CAARMS to gather this criterion, 77.57% of reported CAARMS items had a recorded duration, and 68.67% of SPI-A items. Only participants who reported a DUPrS were included in the analysis.

DUPrS is collected retroactively, which increases the risk of inaccurate recollection and reporting from participants. Only reported DUPrS where the participant was able to identify the month of onset, the year of onset (treated as January 1st of that year), or the age they were when the symptom onset (treated as date of birthday for that year), were included for analysis. Symptoms where the onset was not recorded, or the participant was unable to provide a defined onset time, were excluded. Duration was determined by the number of months from onset until the date of the baseline interview, in line with previous studies (Carrión et al., 2016; Chon et al., 2015; Nelson et al., 2016; Schultze-Lutter et al., 2010; Zhang et al., 2017; 2018a, b), the DUPrS for the present study was recorded in months.

2.6 Assessment of functioning

During the first baseline interview, the overall functioning of the participant in the last month was assessed using the global assessment of functioning (GAF). The GAF is a scale from 1 – 100 (1 being significantly inferior dysfunction and 100 being significantly superior functioning). This scale is further divided into 10 equal intervals, each with specific criteria over three areas of functioning; psychological, social and occupational. Two interviewers score the participants responses to questions about how their sleep, appetite, college work, employment, socialising with friends and family and mood have been in the last month. The GAF shows good IRR (0.89); (Startup, Jackson, & Bendix, 2002).

During the second baseline assessment Social and Role scales (GF: social and role; Cornblatt et al., 2007) were administered that assess role (occupational) functioning and social functioning of CHR-P individuals. The scales are measured separately and exclude psychological functioning e.g. subthreshold psychotic symptoms, to provide independent measures on these specific areas of functioning, rather than an overall assessment measured in GAF. For the GF role scale, participants are asked about their experiences in school/college/work/house work, depending on the age and occupation of the participant. Instances of failing exams or demotions at work are recorded, and how the participant feels they manage the pressures and demands of their occupation. The social scale focuses on friendships, family and romantic relationships, and instances of conflict and frequency of communication are recorded. To score the interviews, the two scales have a ten point range from 1 -10 (1 = extreme dysfunction, 10 = superior functioning) with each point on the range having defined features of the functioning levels for each point. A CHR-P individual would be expected to score between 6 – 8 on both the GF social and role scales, and the measures show high IRR (.956; Carrión et al., 2019).

2.7 Assessment of cognitive functioning

During the third baseline visit the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) and subtests from the Penn Computerized Neurocognitive Battery (Penn CNP; Moore, Reise, Gur, Hakonarson, & Gur, 2015) are administered.

The BACS assess six areas of neurocognitive functioning: 1) verbal memory, 2) working memory, 3) motor function, 4) attention and processing speed, 5) verbal fluency and 6) executive control. The BACS shows excellent test-retest reliability (interclass correlation coefficient (ICC) = 0.73). A seventh composite total score is calculated following completion of the task, and also shows strong test-retest reliability (ICC = 0.90) (Keefe et al., 2004).

The Penn CNP is a computer administered cognitive test battery (Moore et al., 2015) with high test-retest across domains (ICC > 0.6, Roalf et al., 2013). In the YouR study, the Penn Continuous Performance task which measures vigilance and visual attention, the Penn Letter N-Back test which measures working memory, and the Penn emotion recognition task which measures affect perception, were included

Table 2. Procedure and measures of the BACS and Penn CNP protocols used in the YouR study

Assessment	Name of task	Procedure	Time for task (in seconds)	Measure	Range
BACS					
Verbal memory	List learning (Version 1)	List of 15 words is read to participant and asked to recall as many as possible in any order. Procedure repeated five time.	-	Number of correct words recalled per trial, cumulated	0 – 75
Working memory	Digit sequencing task	Participants are read blocks of randomly ordered numbers, which steadily increase in amount during the trial. Participants are asked to order the number from lowest to highest	-	Number of correct responses	0 – 28
Motor speed	Token motor task	100 plastic tokens were spread out across a table. Participants were asked to place two tokens (one in each hand) into a container in the middle, and repeat as many as possible in the time given.	60	Number of tokens correctly placed in the container	0 – 100

Table 2 cont. below

Assessment	Name of task	Procedure	Time for task (in sec.)	Measure	Range
BACS					
Attention and Processing Speed	Symbol coding	Nine symbols matching to the numbers 1-9 were given as a key to the participant, and they were asked to translate the lines of the symbols into the numbers 1-9 as quickly as possible.	90	Number of correct symbols input	0 – 110
Verbal fluency	Semantic fluency	Participants were asked to name as many of a category (animals) as possible.	60	Number of different animals listed	∞
	Letter fluency	In two separate trials, participants were asked to name as many words starting with the letter (S, F)	60	Number of different words listed	∞
Penn CNP					
Vigilance and visual attention	Penn Continuous Performance task	A series of red vertical and horizontal lines composed of 7 segments flash in front of the participant(stimulus), followed by a blank screen. Participants press the space bar if the lines from a complete number or complete letters	.3/ stimulus 1/item 360 total	Number to true positive responses, response time of correct responses	0 - 360
Affect perception	Penn emotion identification task	Participants are shown a face, and must respond if they believe the facial expression is happy, sad, angry, fearful or neutral. This protocol is repeated 40 times. The faces are 4 men & 4 women each showing each expression	-	Correct responses, response time of correct responses	0 - 40
Working memory	Penn Letter N-Back test	A Letter flashes on the screen (stimulus) followed by a blank screen. Participants press space bar when one of the following pattern rules (0,1,2) are met: 0 = current stimulus is present, 1 = the same letter is repeated twice in a row, 2 = the letter shown before the previous letter, matches the current one	.5/ stimulus 2.5/item 337.5 total	Number to true positive responses, response time of correct responses	0 - 135

2.8 Statistical analysis

All statistical analysis were performed using R (R Core Team, 2019). Level of significance was set as 0.05 (two-tailed).

Three univariate measures were considered against the outcome measures: duration, gender and age at onset. DUPrS is the primary measure and is calculated by the number of months from onset until the date of the baseline interview. Gender and birth date are reported as demographic measures. Age of onset was calculated by subtracting age at baseline in months from months since onset of symptoms. These secondary measures were also considered in conjunction with duration to see the full effect of DUPrS on cognition and function measures.

To determine the effect of DUPrS on outcome measures, the CAARMS and SPI-A symptom with the longest continuous duration reported by each person was entered into the analysis, in line with previous studies in the field (Carrión et al., 2016; Chon et al., 2015; Nelson et al., 2016; Schultze-Lutter et al., 2010; Zhang et al., 2017; 2018a, b). In individuals who reported both APS and BS symptoms these were recorded separately.

To assess the relationship between onset of BS and APS, z-score transformations of the duration since the first onset APS and BS were conducted. This calculation was only done for individuals who had reported both. The z-scores were converted using the means and standard deviations of the duration of symptoms in the CHR-P group (APS and BS, conducted separately for the respective group). This method was applied to adjust for outliers (see Schultze-Lutter et al., 2010).

BACS and Penn CNP data was converted from raw data into standardized z-scores for each cognitive domain. The z-scores were converted using the means and standard deviations of the healthy control group, collected as part of the YouR study. For the BACS measures, the control group mean, and standard deviation were divided based on gender, and comparisons were also based against the respective genders. This is to keep in line with previous studies reporting significant gender differences in BACS measures scores (Keefe et al., 2004). The BACS composite score was calculated for each participant by averaging all six z-scores obtained on the cognitive measures, and then re-standardizing the average score by the same method discussed above (Keefe et al., 2004).

The overall variance explained by the models obtained through stepwise linear and logistic regressions was measured by the R^2 statistic.

3 Results

A summary of duration of all symptoms reported is in the appendix (Appendix Table 1). In line with previous literature, the analysis was conducted on the earliest onset sub-threshold symptom. This was determined from the reported symptom subtype with the longest duration, for APS and BS, separately.

Differences in demographic and functional information between individuals with APS and BS were analysed using Bartlett's test for continuous data, chi-square tests for categorical data, and non-parametric Kruskal-Wallis H tests for ordinal variables.

Table 3. Summary of Demographic and Clinical Variables in Relations to Duration of APS and BS.

	APS	BS	df	$K^2/H/X^2$	p
Number of participants	109	89			
Gender, f(%)	78(71.56)	60(67.42)	1	X^2 = 0.8	0.4
Age at baseline, median(range)	20(16-34)	21(16-34)	1	H = 0.2	0.6
Age at onset, median(range)	18(4-34)	17(5-30)	1	H = 0.3	0.6
years in education, median(range)	15(8-26)	15(10-26)	1	H = 0.4	0.6
UK citizen, N (%)			1	X^2 = 0.4	0.5
Mean duration, in months	43	53	1	K^2 = 0.6	0.2
Median duration, in months	27 (1-246)	42	1	H = 1	0.2
GAF, median (range)	58(21-89)	58(21-95)	1	H = 3	0.1
GF: Role, median(range)	8(4-9)	8(4-9)	1	H = 0.9	0.4
GF: Social, median(range)	8(5-9)	8(5-9)	1	H = 0.8	0.4
Medication, N(%)			1	X^2 = 0.2	0.6
Anti-psychotic	2(2)	1(11)			
Mood stabiliser	1(1)	0			
Anti-depressant	25(23)	18(20)			
Anti-convulsant	0	1(1)			
Other	10(9)	10(11)			
Multiple	16(15)	13(15)			
Diagnosis, N (%)			1	X^2 =0.3	0.6
Anxiety disorder	76(70)	56(63)			
Mood disorders	73(67)	58(65)			
Eating disorders	12(11)	7(8)			
Suicide risk	59(54)	48(54)			
Alcohol dependence/abuse	33(30)	25(28)			
Substance dependence/abuse	18(17)	10(11)			

Abbreviations APS = attenuated psychotic symptoms, BS = basic symptoms. X^2 = Pearson's Chi-squared test, K^2 = Bartlett test of homogeneity of variances, H = Kruskal-Wallis rank sum test.

No significant differences were found between participants who reported APS compared to participants who reported BS in age at baseline, age at onset, gender, years of education, citizenship, duration of symptoms, functioning, medication or diagnosis (Table 3).

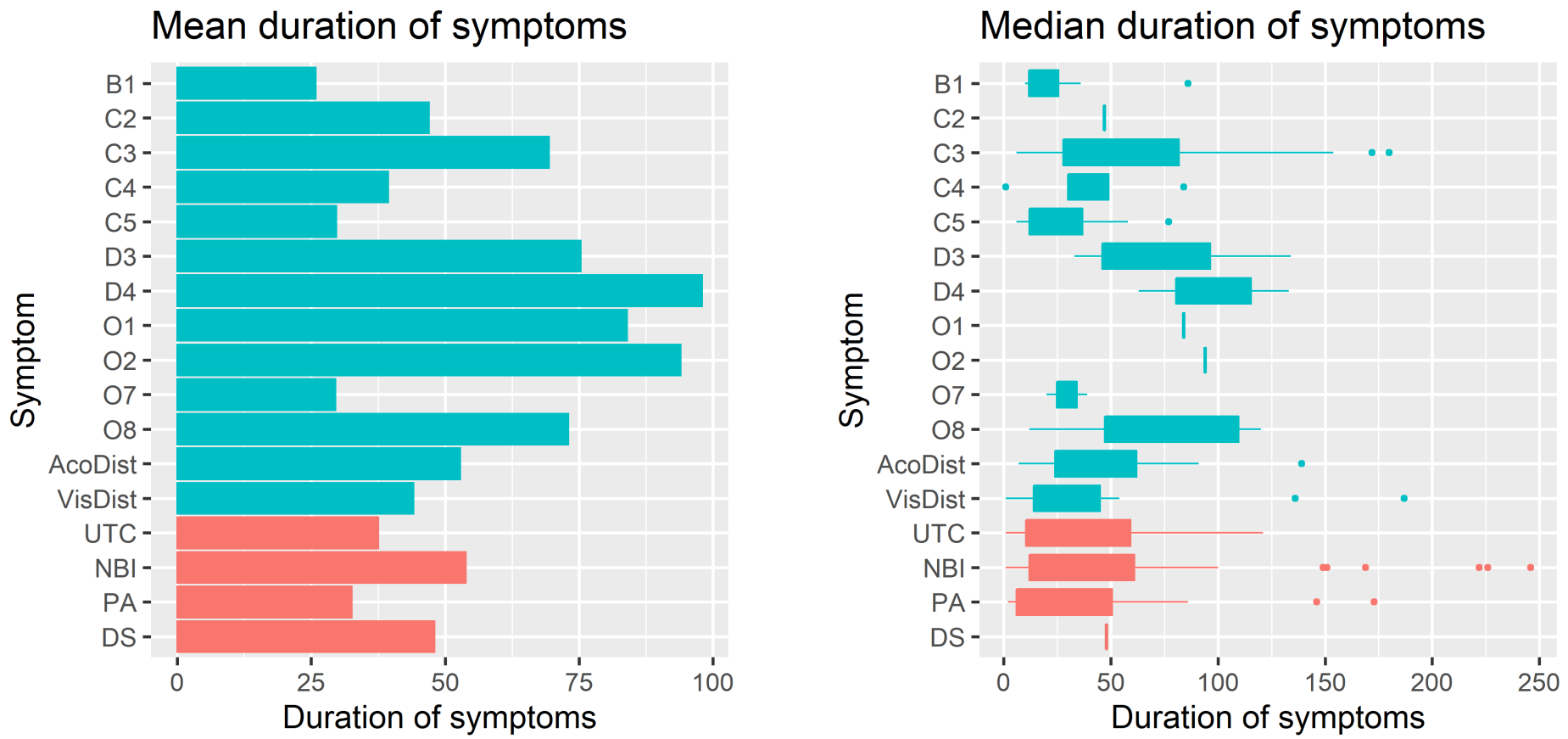
Table 4. Baseline CHR-P CAARMS and SPIA Symptoms

		Number of participants	Mean duration, in months	Median duration, in months (range)	Mean age at onset, in years	Gender f(%)
APS						
	Unusual thought content	20	37.55	24(1-121)	18.12	14(70)
	Non-bizarre ideas	49	53.84	42(1-246)	17.82	35(71.4)
	Perceptual abnormalities	39	32.59	12(2-173)	17.67	28(71.8)
	Disorganised speech	1	48	48	25	1(100)
BS						
	Inability to divide attention	8	25.88	15(10-86)	20.59	5(62.5)
	Thought interference	2	47	47	19.08	1(50)
	Thought blockage	20	69.45	50.5(6-180)	17.31	11(55)
	Disturbances in receptive speech	5	39.4	33(1-84)	15.92	5(100)
	Disturbances in expressive speech	10	29.7	24(6-77)	21.03	7(70)
	Thought pressure	3	75.33	59(33-134)	15.72	3(100)
	Unstable ideas of reference	2	98	98(63-133)	11.83	1(50)
	Thought perseveration	1	84	84	11	1(100)
	Decreased ability to discriminate…	1	94	94	8.17	1(100)
	Captivation of attention by details…	2	29.5	29.5(20-39)	18.54	2(100)
	Derealization	6	73	72.5(12-120)	16.17	4(66.67)
	Visual perception disturbances	12	44.08	19(1-187)	16.91	9(75)
	Acoustic perception disturbances	17	52.82	49(7-139)	16.19	10(58.2)

Abbreviations Captivation of attention by details... = Captivation of attention by details in the visual field, decreased ability to discriminate... = Decreased ability to discriminate between ideas and perception, fantasy and true memories

There was a large variation in the number of individuals who experienced different CAARMS symptoms (range = 1 – 49), similarly there was a significant difference in the number of individuals who experienced different SPIA symptoms (range = 1 – 20). There were notable differences in the duration of individual CAARMS symptoms (m = 32.59 – 53.84, med = 12 - 48) and SPIA symptoms (m = 25.88 – 98, med = 15 - 98) (Table 4).

Figure 2. Mean and median duration of first onset symptoms reported by CHR-P at baseline.



Blue = SPI-A symptom subtypes, Red = CAARMS symptom subtypes. Abbreviations: B1 = Inability to divide attention, C2 = Thought interference, C3 = Thought blockage, C4 = Disturbance of receptive speech, C5 = Disturbances of expressive speech, D3 = Thought pressure, D4 = Unstable ideas of reference, O1 = Thought preservation, O2 = Decreased ability to discriminate between ideas/perception and fantasy/true memories, O7 = Captivation of attention by details of the visual field, O8 = Derealization, AcoDist = acoustic perception disturbances, VisDist = visual perception disturbances, UTC = unusual thought content, NBI = non-bizarre ideas, PA = perceptual abnormalities, DS = disorganized speech.

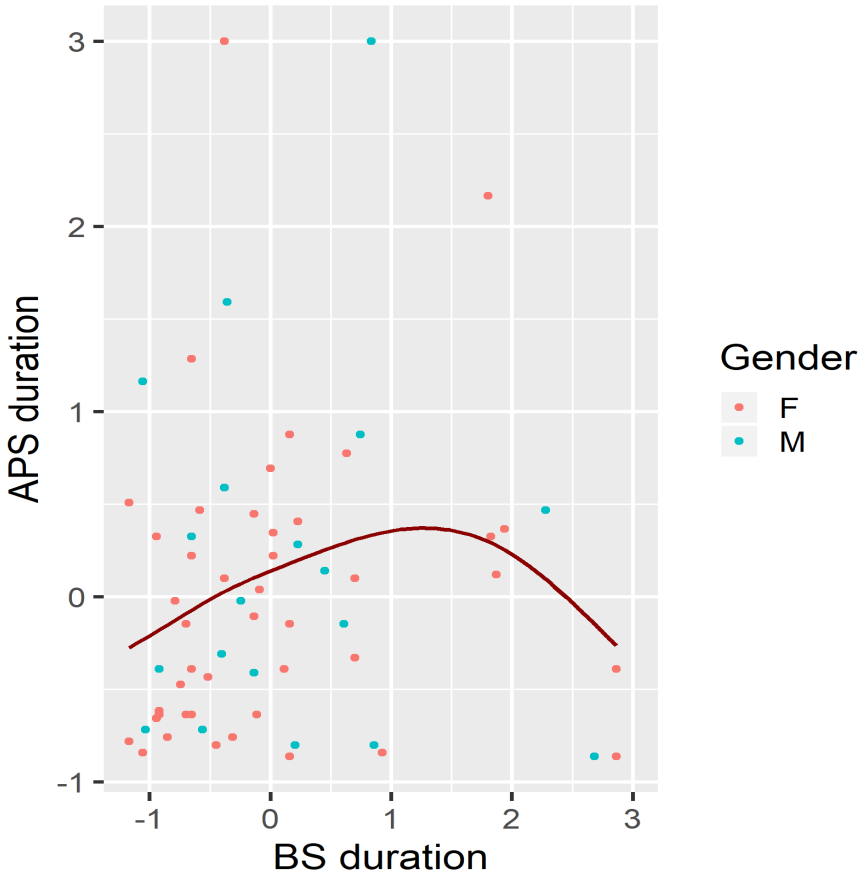
3.1 Relationship between attenuated psychotic symptoms and basic symptoms

Previous research has assumed that BS precede the onset of APS (Fusar-Poli et al., 2013; Häfner et al., 2003; Schultze-Lutter et al., 2016). To test if this relationship is found in the current CHR-P group, the first onset APS and BS symptom, in participants reporting both symptoms, were compared.

To adjust for outliers, the data was transformed to z-scores (see Schultze-Lutter, Ruhrmann, Berning, Maier, and Klosterkötter, 2010). Z-score transformations were calculated based on the earliest onset BS and APS, calculated from the reported month of onset to baseline interview date. As is standard in using z-scores, data points > ± 3 SD were rounded to ± 3 (Shiffler, 1988).

Analysis of the relationship between APS and BS onset was conducted using paired t-tests. Robust linear regression was also used to analyse a relationship between BS onset and APS onset as a measure which accounted for outliers.

Figure 3. Scatterplot and loess smooth line of the relationship between the duration of APS and BS



Abbreviations F = female, M = male, APS = attenuated psychotic symptoms, BS = basic symptoms

48.4% of the sample reported BS onset occurring prior to APS onset (n = 31), 37.5% reported APS onset prior to BS (n = 24), and 14.1% reported APS and BS onset (n = 9) occurring in the same month. In measures of time differences, no relationship was found between APS and BS onset (paired t-test: t = 0.02, df = 63, p = 1). The mean difference in the duration length was 0.0035 months (95%CI [-0.31 to 0.32]). Robust linear regression analysis which accounted for outliers also failed to find a relationship (robust regression: B = 0.056, SE = 0.082, t-value = 6.89, p = 0.5).

Secondary analysis was conducted that examined the relationship between short or long BS duration and onset of APS. This was conducted based off reported between group differences found in short and long duration of sub-threshold symptoms (B. Nelson et al., 2016; Zhang et al., 2017). This was conducted on the z-score transformation as >/< 1 (≈ 99.7 months). Short BS duration showed no significant relationship (paired t-test: t = -1, df = 50, p = 0.3, 95%CI [-0.287, 0.093]), even when outliers were accounted for (robust regression: B = 0.267, SE = 0.142, t-value = 1.879, p = 0.07). Long BS duration did show a relationship (paired t-test: t = 3, df = 4, p = 0.04, 95% CI [0.12 – 2.39]), which persisted when outliers were accounted for (robust regression: B = 0.310, SE = 0.032, t-value = 9.598, p = 0.002).

3.1.1 Influence of Gender, Age of onset and Education

Previous findings had reported an influence of age at onset and years of education on onset of BS and APS (Schultze-Lutter et al., 2010; Schultze-Lutter, Rahman, et al., 2015). In addition, evidence suggests that there are gender differences in duration of psychotic symptoms, with studies reporting that males experience longer duration of untreated illness (DUI) compared to females (Rietschel et al., 2015). Barajas et al., (2015) showed that this relationship also occurred in CHR-P groups, with male participants reporting earlier onset and longer sub-threshold symptoms.

3.1.1.1 Education

CHR-P were divided into groups based on level of education (3rd level/ no 3rd level) to measure if between group differences previously reported (Schultze-Lutter et al., 2010) occurred in this sample. Individuals not in 3rd level education reported no significant relationship between APS and BS onset (paired t-test: t = 0.4, df = 7, p = 0.7, 95% CI [-0.78, 1.14]), including when outliers were accounted for (robust regression: B = -0.037, SE = 0.195, t-value = -0.191, p = 0.9). Results for individuals in third level education similarly failed to show a significant effect (paired t-test: t = -0.1, df = 54, p =0.9, 95%CI: [-0.37, 0.33]; robust regression: B = 0.068, SE = 0.094, t-value = 0.722, p = 0.5).

3.1.1.2 Age at onset

CHR-P were divided by age at onset (>/< 18 years of age at onset of either symptom type). Neither group showed a significant relationship between APS and BS onset (paired t-test: < 18 years at onset: t= 0.1, df = 40, p =0.9, 95% CI [-0.4, 0.44]; > 18 years paired t-test: t= -0.1, df = 22, p =0.9, 95% CI: [-0.53, 0.48]), including when robust measures were used (robust regression: < 18 years at onset: B = -0.015, SE = 0.136, t-value = -0.113, p = 0.9; > 18 years at onset: robust regression: B = -0.016, SE = 0.085, t-value = -0.193, p = 0.8).

3.1.1.3 Gender

Male participants did not show a statistical relationship between APS and BS duration (paired t-test: t= -0.01, df = 18, p = 1, 95% CI: [-0.69, 0.68]) even when outliers were accounted for (robust regression: B = -0.055, SE = 0. 188, t-value = -0.293, p = 0.8). The same result was obtained for female participants (paired t-test: t= 0.04, df = 44, p =1, 95% CI: [-0.36, 0.37]) or onset (robust regression: B = 0.094, SE = 0.093, t-value = 1.021, p = 0.3).

Table 5. Summary of the paired t-tests and robust linear regressions conducted between APS-BS duration and onset.

	Paired t-test						Robust regression				
	n	**df**	**t**	**MD**	**p**	**95% CI**	**B**	**SE**	**t-value**	**F**	**p**
Whole sample	64	63	0.02	0.00	1	-0.31, 0.32	0.056	0.082	0.689	0.5	0.5
< 1	51	50	-1	-0.097	0.3	-0.28, 0.093	0.267	0.142	1.879	3	0.07
> 1	13	4	3	1.3	**0.04**	0.12, 2.39	0.310	0.032	9.598	112	**0.002**
Male only	19	18	-0.01	-0.004	1	-0.69, 0.68	-0.055	0.188	-0.293	0.09	0.8
Female only	45	44	0.04	0.007	1	-0.36, 0.37	0.094	0.093	1.021	1	0.3
< 18 years	41	40	0.1	0.02	0.9	-0.4, 0.44	-0.015	0.136	-0.113	0.01	0.9
> 18 years	23	22	-0.1	-0.026	0.9	-0.53, 0.48	-0.016	0.085	-0.193	0.04	0.8
No 3rd level education	9	7	0.4	0.18	0.7	-0.78, 1.14	-0.037	0.195	-0.191	0.04	0.9
3rd level education	55	54	-0.1	-0.021	0.9	-0.37, 0.33	0.068	0.094	0.722	0.5	0.5

Abbreviations n = number of participants, df = degrees of freedom, t = t-value, MD = mean difference, p = p-value, CI = confidence intervals, B = unstandardized estimate, SE = standard error, F =f test

3.2 Impact of duration of prodromal symptoms on functional outcomes

GAF is collected at baseline and completed by all 134 participants. 15 individuals did not complete a second baseline interview, so were excluded from analysis on role and social functioning

Linear regressions were used to conduct analysis between duration, gender, or age of onset and the GAF score. Multivariate linear regression was conducted to measure models of the interactions between duration and gender, and duration and age of onset, on GAF score.

The GF: Social and Role scale measures showed narrow ranges (social: range = 4 – 9, role: range = 5 – 9), meaning the measures failed to meet the assumptions of parametric measures. Quantile regressions were used to conduct analysis between duration, gender, and age of onset on role and social functioning. Multivariate multiple regressions in quantile regressions need larger samples of data (Koenker, 2005) than the current study, so were not conducted.

Table 6. Effect of duration of prodromal symptoms on functioning outcomes.

		B	SE	β	t	95% CI	R^2	p
APS								
	GAF	-0.015	0.023	-0.063	-0.65	-0.06, 0.03	-0.005	0.51
	GF: Role	0.000	0.004	-	0.00	-	-	1.0
	GF: Social	0.000	0.003	-	0.00	-	-	1.0
BS								
	GAF	-0.035	0.031	-0.121	-1.13	-0.10, 0.03	0.0033	0.26
	GF: Role	0.000	0.003	-	0.00	-	-	1.0
	GF: Social	0.000	0.002	-	0.00	-	-	1.0

Abbreviations GAF = global assessment of functioning, GF: Role = global functioning: role scale, GF: Social = global functioning: social scale, B = unstandardized estimate, SE = standard error, β = standardized estimate, t = t value CI = confidence intervals, p = p-value

Duration of APS or BS as a single main effect was not found to be significant in GAF scores, role functioning or social functioning (Table 6). Summary of effect of gender and onset are in the appendix (Appendix Table 2).

No significant effect was found by including gender or age of onset and APS duration on GAF scores. Similarly, no effect was found on either model with BS duration on GAF scores. Both measures are reported in the appendix (Appendix Table 3). Multivariate quantile regressions requires larger sample sizes (Koenker, 2005) than is available in the current study, so these models were not compared to GF: Role or Social measures.

Previous findings have reported differences in functioning depending on length of DUPrS (Nelson et al., 2016; Zhang et al., 2017, 2018b). To measure if this effect existed in this sample, symptom length was divided into short and long for APS and BS (Table 7). The separation was divided based on the median duration for APS (MED = 27 months) and BS (MED = 42 months).

Table 7. Effect of duration of prodromal symptoms on functioning outcomes, divided by symptom length.

		B	SE	β	t	95% CI	R^2	p
APS								
Short								
	GAF	-0.320	0.211	-0.206	-1.52	- 0.74, 0.1	0.0425	0.13
	GF: Role	0	0.039	-	0	-	-	1.0
	GF: Social	0.045	0.022	-	2.04	-	-	**0.047**
Long								
	GAF	0.011	0.033	0.047	0.34	- 0.054, 0.076	0.0022	0.74
	GF: Role	-0.0052	0.0045	-	-1.16	-	-	0.25
	GF: Social	0	0.0052	-	0	-	-	1.0
BS								
Short								
	GAF	-0.305	0.201	-0.228	-1.51	-0.71, 0.1	0.0518	0.14
	GF: Role	-0.029	0.022	-	-1.35	-	-	0.18
	GF: Social	-0.037	0.026	-	-1.40	-	-	0.17
Long								
	GAF	-0.014	0.040	-0.056	-0.36	-0.095, 0.066	0.0031	0.72
	GF: Role	-0.0072	0.0052	-	-1.39	-	-	0.17
	GF: Social	-0.0072	0.0052	-	-1.38	-	-	0.18

Abbreviations GAF = global assessment of functioning, GF:Role = role functioning, GF:Social = social functioning, B = unstandardized estimate, SE = standard error, β = standardized estimate, t = t value CI = confidence intervals, p = p-value

Divided by duration, shorter APS was associated with slight negative effects on social functioning (B = 0.045, p = 0.047), though this finding was not significant in the long APS group (B = 0, p = 1.0) (Table 7). No significant effect of APS or BS duration was found for any other measure of functioning. Summary of effect of gender and onset are in the appendix (Appendix Table 4).

3.3 Impact of duration of prodromal symptoms on cognitive functioning

16 CHR-P participants did not complete the third screening and were excluded from the analysis on cognition measures. Cognition data was converted from raw data into standardized z-scores. The z-scores were converted using the means and standard deviations of the healthy control group. For the BACS measures, the control group mean, and standard deviation were divided based on gender, and comparisons were also based against the respective genders, in line with previous research (Keefe et al., 2004). The BACS composite score was calculated for each participant by averaging all six z-scores obtained on the cognitive measures, and then re-standardizing the average score by the same method discussed above (Keefe et al., 2004).

F-tests were conducted to compare cognition scores between of CHR-P to healthy controls, Cohen's d was used to measure effect size.

Table 8. Results of individuals with APS and BS in Neurocognitive and Social Cognitive Measures compared to a healthy control group.

	Controls (n = 57)		**CHR-P (n = 136)**		**df**	**F**	**(95%) CI**	**p**	**Cohen's d**
	M	**SD**	**M**	**SD**					
BACS									
Verbal memory	0	1	-0.23	1.22	56	1	0.92, 2.23	0.1	-0.2
Working memory	0	1	-0.07	1.26	56	2	0.99, 2.41	**0.05**	-0.06
Motor speed	0	1	-0.79	1.12	56	1	0.78, 1.89	0.4	-0.73
Attention & processing speed	0	1	-0.49	1.16	56	1	0.84, 2.05	0.2	-0.44
Verbal fluency	0	1	-0.14	0.62	56	0.8	0.49, 1.19	0.2	-0.29
Executive function	0	1	-0.04	1.36	56	2	1.1, 2.8	**0.01**	-0.033
BACS composite score	0	1	-0.64	1.51	56	2	1.4, 3.4	< **0.001**	-0.46
Penn CNB									
Emotion recognition accuracy	0	1	-0.16	1.00	56	1	0.62, 1.50	0.9	-0.15
Emotion recognition RT	0	1	0.43	1.28	56	2	1.0, 2.5	**0.03**	0.36
Working memory accuracy	0	1	-0.29	1.15	56	2	1.1, 2.8	**0.01**	-0.3
Working memory RT	0	1	-0.09	0.80	56	0.7	0.41, 1.00	**0.05**	-0.1
Attention accuracy	0	1	-0.37	1.29	56	2	1.0, 2.5	**0.04**	-0.3
Attention RT	0	1	-0.13	0.88	56	1	0.6 1.5	0.8	-0.18

The CHR-P group showed significant differences compared to healthy controls, and performed worse in all measures of working memory, executive function, attention accuracy and BACS composite score (Table 8). CHR-P preformed slightly statistically better than controls in the emotion recognition task in reaction time scores (Table 8).

Univariate MANOVAs were conducted to examine any effect duration of subthreshold symptoms, gender, or age of onset had on measures of cognition. Multivariate MANOVAs were conducted to measure the models of the interaction between duration and gender, and duration and age of onset, on neurocognitive measures. Bonferroni correction was applied to adjust for multiple comparisons.

3.3.1 Impact of attenuated psychotic symptom duration on Cognitive Outcomes

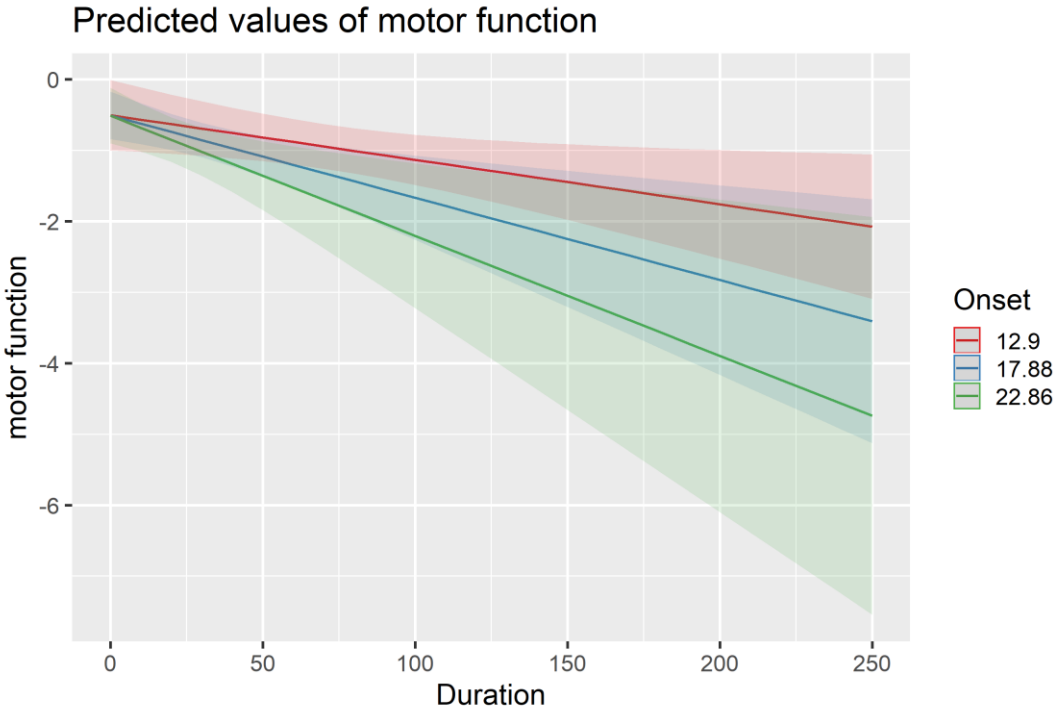
Table 9. Analysis of the Effect of APS Duration on Cognition

	B	**SE**	**β**	**t**	**95% CI**	**R^2**	**p**
BACS							
Verbal memory	0.000	0.002	0.000	0.00	-0.005, 0.005	0.000	0.997
Working memory	0.001	0.003	0.062	0.56	-0.004, 0.007	0.003	0.58
Motor speed	-0.005	0.002	-0.17	-1.96	-0.009, 0.000	0.038	**0.05**
Attention & processing speed	-0.001	0.002	-0.04	-0.4	-0.006, 0.004	0.002	0.66
Verbal fluency	-0.002	0.001	-0.07	-1.38	-0.004, 0.007	0.019	0.17
Executive function	0.000	0.003	0.036	0.15	-0.005, 0.006	0.000	0.88
BACS composite score	-0.001	0.003	-0.05	-0.44	-0.007,0.005	0.002	0.66
Penn CNP							
Emotion recognition accuracy	0.001	0.002	0.035	0.34	-0.003, 0.005	0.001	0.73
Emotion recognition RT	0.003	0.003	0.124	1.22	-0.002, 0.008	0.015	0.23
Attention accuracy	0.000	0.003	-0.09	-0.17	-0.006, 0.005	0.000	0.86
Attention RT	-0.003	0.002	-0.17	-1.7	-0.007, 0.001	0.029	0.09
Working memory accuracy	-0.002	0.002	-0.08	-0.77	-0.007, 0.003	0.006	0.44
Working memory RT	-0.001	0.002	-0.05	-0.48	-0.004, 0.003	0.002	0.63

Abbreviations: RT = reaction time, B = unstandardized estimate, SE = standard error, β = standardized estimate, t = t value CI = confidence intervals, p = p-value

Longer APS duration was associated with worse motor speed scores, and explained 4% of the variance in the sample (Table 9). The findings showed very marginal negative effects, and the findings are moderately significant (B = -0.005, p = 0.05, 95%CI [-0.009, 0.000]). Summary of effect of gender and onset are in the appendix (Appendix Table 5.1).

Figure 4. Interaction effect of duration of APS and age of onset on motor speed



Onset age divided into three quantiles (25th, 50th, 75th), reported in years.

A model including APS duration and age at onset of APS symptoms was found to be significant for motor speed. The remaining findings are reported in the appendix (Appendix Table 6.3). The model accounted for 9% of the variance in the sample and was significant (p = 0.04). This finding indicates that those who were older at the onset of symptoms were more affected by longer APS duration compared to individuals who were younger when symptoms onset, and this interaction resulted in worse motor speed scores (B = -0.001, p = 0.05, 95%CI [-0.0021, 0.0002])

No significant relationship was found between APS duration and cognition measures when gender was added to the model (Appendix Table 6.1).

3.3.2 Impact of basic symptom duration on cognitive outcomes

Table 10. Analysis of the Effect of BS Duration on Cognition

	B	SE	β	t	95% CI	R^2	p
BACS							
Verbal memory	-0.012	0.020	0.0072	-0.59	-0.006, 0.006	0.0097	0.56
Working memory	0.013	0.017	0.14	0.75	-0.002, 0.010	0.0154	0.46
Motor speed	0.020	0.018	-0.13	1.09	-0.006, 0.005	0.0318	0.28
Attention & processing speed	0.006	0.018	0.1	0.33	-0.003, 0.009	0.0031	0.74
Verbal fluency	0.020	0.010	0.29	2.01	-0.003, 0.004	0.0341	**0.05**
Executive function	-0.008	0.024	-0.097	-0.35	-0.008, 0.005	0.0102	0.73
BACS composite score	0.010	0.022	0.065	0.47	-0.005, 0.009	0.0062	0.64
Penn CNP							
Emotion recognition accuracy	0.000	-0.020	0.003	-0.18	-0.006, 0.005	0.0004	0.86
Emotion recognition RT	-0.003	-0.108	0.003	-0.96	-0.010, 0.003	0.0117	0.34
Attention accuracy	0.002	0.081	0.003	0.72	-0.004, 0.009	0.0066	0.48
Attention RT	-0.020	-0.196	0.017	-1.22	-0.008, 0.002	0.0385	0.23
Working memory accuracy	-0.002	-0.081	0.003	-0.72	-0.008, 0.004	0.0065	0.48
Working memory RT	-0.001	-0.051	0.002	-0.45	-0.005, 0.003	0.0026	0.65

Abbreviations: RT = reaction time, B = unstandardized estimate, SE = standard error, β = standardized estimate, t = t value CI = confidence intervals, p = p-value

Shorter BS duration was associated with worse verbal fluency scores (B = -0.02, p = 0.05) and explained 3% of the variance in the sample (Table 10). Effect of gender and age of onset are reported in the appendix (Appendix Table 5).

A model including gender and duration of BS failed to find significant effect of the model on most cognition measures, which is reported in the appendix (Appendix Table 6.2). Two measures using this model found an effect from this interaction term; verbal fluency and working memory accuracy (Table 11).

In the verbal fluency measure, the whole model was significant ($p < 0.0001$), including when adjusted for multiple comparisons. The model showed in male participants shorter BS was associated with worse verbal fluency (B = -0.037, p = 0.0041) compared to female participants (Table 11). This model explained 71% of the variance of the scores in verbal fluency between participants. However, the main effect showing significance in this model was not duration, and gender as a single main effect explained 58% of the variance (Appendix Table 5.1).

In the working memory accuracy measure, the whole model explained 6% of the variance, but was not significant ($p < 0.5$) (Table 11). One measure in the interaction was significant, and showed when the variance created by gender was accounted for, longer duration showed a marginal negative effect on working memory accuracy ($B = -0.011$, $p = 0.05$). The interaction was near significance, and showed that male participants performed relatively worse compared to female participants ($B = 0.012$, $p = 0.6$).

A model of the interaction between BS duration and age of onset also showed significance in BACS composite score, but failed to find an effect on any other measure of cognition. These finding are reported in the appendix (Appendix Table 6.4). The model explained 12 % of the variance, but was not significant ($p < 0.5$) (Table 11). Short BS duration was shown to have a negative relation to BACS composite scores ($B = -0.201$, $p = 0.04$). The interaction was also significant ($p = 0.05$), and showed that those who were younger when symptoms onset were more effected by longer BS duration compared to individuals who were older when symptoms onset, and this interaction resulted in this group having worse overall BACS scores ($B = -0.001$, $p = 0.05$, 95%CI [-0.0021, 0.0002]) (Table 11).

Table 11. Analysis of the Effect of BS Duration and Gender/Age of Onset on Cognition

	B	**SE**	**β**	**t**	**Pr(>|t|)**		**R^2**	**p**
BACS								
Verbal fluency								
Duration	0.037	0.009	0.13	3.94	**0.0004**			
Gender	1.740	0.264	0.92	6.6	< **0.0001**	}	0.714	< **0.0001**
Duration*Gender	-0.037	0.012	-0.12	-3.1	**0.0041**			
BACS composite score								
Duration	0.201	0.096	-0.079	2.11	**0.04**			
Onset	0.184	0.114	-0.141	1.62	0.12	}	0.122	<0.5
Duration*Onset	-0.010	0.005	0.043	-2.07	**0.05**			
Penn CNP								
Working memory accuracy								
Duration	-0.011	-0.395	0.005	-1.96	**0.05**			
Gender	-0.388	-0.149	0.457	-0.85	0.40	}	0.061	< 0.5
Duration*Gender	0.012	0.453	0.006	1.88	0.06			

Abbreviations: B = unstandardized estimate, SE = standard error, β = standardized estimate, t = t value CI = confidence intervals, p = p-value

4 Discussion

The main aim of the current study was to examine the duration of prodromal symptoms in a non-help seeking population to establish differences and similarities in DUPrS with previous data from help seeking CHR-P samples. To this end, the duration length of APS and BS onset as well as their effects on outcome measures were investigated.

Three key questions were asked: -

1. Does the assumed relationship of BS onset preceding APS onset occur in a CHR-P sample?

2. Is there an effect of duration of APS or BS, on functioning, and does this differ in those with longer or shorter duration?

3. Is there effect of duration of APS or BS, on cognition?

Three key findings emerged from this study. First, this study failed to find evidence for BS onset preceding APS onset in this CHR-P sample, despite the current hypothesis of BS reflecting immediate symptomatic expression of the neurobiological processes underlying schizophrenia, and APS being a secondary consequence of poor coping to BS (Schultze-Lutter et al., 2016). Secondly, this study failed to find a main effect of DUPrS on either outcome measure. The study finding no effect of DUPrS on functioning contrasts with DUP research which has reported consistent evidence that longer DUP is associated with worse outcomes (Penttilä et al., 2014). This difference between findings may offer validation to current theories regarding the critical period theory of psychosis. The study failed to find an effect of duration on cognition, which was inconsistent with some previous findings of DUP (Rapp et al., 2013), but consistent with findings on DUPrS (Chon et al., 2015). Finally, this study suggested preliminary evidence that in community CHR-P samples, duration of symptoms is significantly longer then in clinical studies.

4.1 The relationship between basic symptom onset and attenuated psychotic symptom onset in a CHR-P sample.

This is the first study to consider the relationship between BS and APS onset in a CHR-P sample. The previous study on this measure in an FEP sample (Schultze-Lutter et al., 2010) reported BS onset prior to APS. The current study found no significant relationship between BS onset and APS onset ($p = 1.00$, 95% CI = [-0.31, 0.32]) even when outliers were accounted for. Accordingly, this study does not confirm the current hypothesis that BS are the manifestation of

psychosis-risk and that APS are secondary consequence of poor coping mechanisms in response to the BS (Schultze-Lutter et al., 2016)

While there was no overall relationship, there was some evidence of a moderate trend when considering short and long duration of BS symptoms separately. Only the long BS duration sample showed a statistically significant relationship of BS onset preceding APS onset. Analysis for between group differences based on gender, age at onset, and years of education all failed to find evidence of BS onset preceding APS onset in any of the groupings. All measures had narrow confidence intervals around a null value, suggesting strong evidence that BS onset had no relationship to APS onset.

Overall these findings challenge the hypothesis of BS occurring prior to APS. In fact, APS onset preceded BS onset in a significant portion of the sample (37.5%, n = 24), and there was no significant evidence for a time difference between BS and APS onset across the sample. These findings were consistent when variables previously reported to effect recall of DUPrS, age at onset and years of education, were accounted for. The findings of the current paper challenges the central assumption that APS constitute a response towards more fundamental BS (Schultze-Lutter, 2009).

Secondly, this analysis differs from the currently used staging model of the CHR-P state. This model classifies presence of only BS as the early at-risk mental stage, and presence of both BS and APS as the late at-risk mental stage (Fusar-Poli et al., 2013). The findings of this paper appear to suggest that the assumed stages of this model do not reflect the trajectory of all those who experience APS and BS.

There are a number of potential explanations for the difference between the expected hypothesis and the findings of this study. One possibility is that the hypothesis of BS representing immediate symptomatic changes to the underlying biological processes, and APS being secondary responses (Schultze-Lutter et al., 2016), may not be accurate. This hypothesis was not primarily developed from neurobiological research. Rather, the hypothesis of BS was developed by Huber and Gross (1989), and was based on evidence of presence of BS being correlated to higher rates of transition, and the continued presence of BS in those with schizophrenia. Their research has been validated, showing that presence of BS is associated with higher rates of transition in CHR-P samples (Schultze-Lutter, Michel, et al., 2015), and that BS remain even in remission from psychosis (Schultze-Lutter & Theodoridou, 2017).

These findings only show indirect evidence of the fundamental role of BS. Research into the neurobiological mechanisms of BS, and its role in APS and schizophrenia, is currently in the preliminary stages and has not conclusively shown evidence for this theory(Schultze-Lutter et al., 2016). The current study failing to validate these findings may offer preliminary evidence that this hypothesis, while observing a valid finding of the prevalence of BS in all stages of psychosis, may not have accurately assumed the role of BS in APS.

However, previous research has shown evidence for BS onset preceding APS in an FEP sample (Schultze-Lutter et al., 2010), and appeared to support the hypothesis. A second explanation may be a difference between the groups studied in the current study and previous research. The hypothesis, and subsequent findings validating this relationship, were both conducted on FEP samples. In contrast, this study was completed on a CHR-P sample, the majority of whom did not transition (≈93% at 12 month follow up).

The differences in the findings between the studies may be related to the risk of transition, with the current study representing a sample who are not at significant risk for transition. It is possible this between group difference in reported APS and BS onset may reflect different trajectories for those at genuine risk for psychosis, compared to those who will remit from CHR-P. This explanation does not provide a mechanism for how APS develops prior to BS, suggesting that while this between group difference may be significant, the current findings still produce evidence which does not confirm the current hypothesis describing APS as a response to BS.

4.2 The impact of duration of prodromal symptoms on functional outcomes in short and long duration groups

Functional deficits are a frequently reported outcome in CHR-P samples (Fulford et al., 2013; Salokangas & McGlashan, 2008) and are prevalent even in non-transitioned samples (Beck et al., 2019). Longer DUP and DUPrS have previously been found to have negative effects on functional outcomes (Penttilä et al., 2014; Zhang, et al., 2018a,b)

The current study found no significant effect between APS and BS duration on role or social functioning. The only previous study to use GF: Role and Social as a measure compared to duration on a CHR-P sample (Carrión et al., 2016) also reported no effect of APS on functioning. Their study did find a relationship with the duration of negative symptoms .

Based on previous findings which reported differences between short and long duration of symptoms (Nelson et al., 2016; Zhang et al., 2017; 2018b), the current study divided the sample into short and long duration of APS and BS and compared these groups with functioning. When

the current sample was divided into short and long duration of APS and BS, in the short APS duration sample, duration was modestly associated with improvement in social functioning (B = 0.045, p =0.047), but this was not the case in the long APS duration group (B = 0, p = 1.0). No effect of duration was found on role functioning, in either the short or long duration sample. No effect of BS duration was found on social or role functioning, even when divided into short and long duration samples.

The current study found no association between longer duration of APS or BS on GAF scores. These findings remained consistent when the sample was divided into short and long duration. APS and BS duration in CHR-P samples has previously been reported to have a significant effect on GAF scores, with longer DUPrS associated with lower GAF scores (Fusar-Poli et al., 2009; Zhang, et al., 2018b). Fusar-Poli et al., (2009) found that a sample of individuals with reported BS at baseline followed up over 12 months showed a significantly lower GAF score compared to baseline. These effects were not explained by type of symptom or age of participant, but instead identified as being significantly correlated to the duration of the symptoms being present for the 12 months (β=70.375, p=0.008). Zhang and colleagues (2018b) reported that when a sample was divided into long and short APS (>/<3 months), longer APS duration was associated with lower reported GAF scores, but failed to find an effect on present GAF scores in individuals with short or long DUPrS.

While findings are inconsistent between samples, in general previous studies have reported DUPrS to show some effect on GAF scores and functioning, while the current study found no evidence for a relationship between duration of APS or BS and functioning measures. A potential explanation for the different findings between previous research and this study may be a difference between samples. Previous research on the effect of DUPrS on functional outcomes has all been conducted on clinical CHR-P samples (Carrión et al., 2016; Fusar-Poli et al., 2009; Zhang, et al., 2018a,b). In comparison the CHR-P YouR cohort is a non-help seeking sample, the majority of whom are currently in 3rd level education. This may mean that the study has a bias in favour of recruiting high functioning CHR-P participants. However, the CHR-P YouR cohort does show lower functioning compared to controls in the study (Haining et al., 2019).

Overall, the inconsistent findings on the effect of longer DUPrS (Carrión et al., 2016; Fusar-Poli et al., 2009; Zhang, et al., 2018a,b), and the failure of the current study to find an effect of duration of APS or BS on any functioning measures is in contrast to previous DUP research. Research in DUP has consistently found evidence showing longer DUP has a moderate negative

effect on functional outcomes (Marshall et al., 2005; Murru & Carpiniello, 2018; Penttilä et al., 2014).

One explanation for this difference between DUP and DUPrS findings may be in relation to the critical period theory of psychosis. This theory proposes that the first 2-3 years following onset of psychosis is associated with significant and rapid deterioration of neurological processes (Birchwood et al., 1998). It has been hypothesized the negative effects of longer DUP occur because of this delay in treatment during this critical period (Crumlish et al., 2009). Within this theory, DUPrS occurs prior to the critical period, and the different effect of DUPrS, compared with DUP, may demonstrate that the critical period only occurs following the first experience of a full psychotic symptom.

However, the theory of a critical period as only occurring after onset of the first full psychotic experience has been disputed, with evidence showing that earlier intervention in CHR-P can improve outcomes in those who transition (Fusar-Poli et al., 2013; Malla et al., 2018). In addition, Longer DUPrS is associated with lower general functional scores in FEP individuals (Keshavan et al., 2003). The findings of this paper might provide preliminary support this theory, by demonstrating even in samples with significant lengths of DUPrS (>27 months APS or > 42 months BS, ≈ > 2 years or >3.5 years), the duration does do not appear to have a significant negative effect on functioning in a low transition rate sample, compared to a transitioned FEP population.

A second explanation may be related to a difference in sample, this study is the first study to examine duration of subthreshold symptoms in a community sample, not a help-seeking clinical sample. Previous studies on community sample CHR-P observed lower levels of symptom severity (Mills et al., 2017). This study failing to replicate previous findings of the relationship between duration and functioning may potentially indicate other differences between these groups. This may have important implications for future research; there is a currently an understudied group of individuals in the community, who experience symptoms at a frequency comparable to clinical CHR-P samples (Haining et al., 2019; McDonald et al., 2019; Mills et al., 2017), but who may represent a differing population, and where current research of the trajectory and outcomes of CHR-P may not apply.

4.3 The impact of duration of prodromal symptoms on cognition

Cognitive deficits are a significant and stable feature of schizophrenia and CHR-P (Giuliano et al., 2012; Harvey & Bowie, 2003). In FEP and schizophrenia, longer DUP is associated with

deficits in visual memory, working memory and verbal memory (Amminger et al., 2002; Chang et al., 2013), though findings have been inconsistent (Rapp et al., 2013). Analysis of the effect of duration of APS as a single main effect on cognitive measures has only been conducted in one study (Chon et al., 2015), while a second study conducted measures of DUI (which includes DUPrS and DUP) (Rapp et al., 2013). Neither found a significant effect of DUPrS on cognition.

The present study found that duration of APS had no main effect on the majority of neurocognitive and social cognition measures. Only one marginal main effect was found, that motor speed was negatively affected by longer duration (B = - 0.005, p = 0.05). Analysis of the effect of BS on cognition also showed no effect across the majority of the measures. One measure found longer BS duration was associated with slight improvements in verbal fluency scores (B = 0.02, p = 0.05). Chon et al., (2015) measured visual attention, verbal fluency, executive function, cognitive flexibility and theory of mind, a measure of social cognition. Their study failed to find a significant effect of APS duration on any of the reported measures. The current study similarly failed to find an effect of APS duration of executive function, attention, verbal fluency or social cognition. The only marginal significant finding, working memory, was not tested in previous research. Chon and colleagues (2015) did not analyse duration of BS as a main effect, and so the findings of BS duration having a marginal effect on verbal fluency could not be compared. Overall both studies showed no significant evidence for DUPrS having an effect on cognition.

Research on DUP had noted a significant effect of independent variables of gender, age of onset and higher premorbid IQ that should be accounted for when analyzing the effect of DUP on outcome measures (Amminger et al., 2002). However, interaction models including gender and duration of APS or BS showed no significant effect across most models, despite significant between group differences being expected in some cognition measures (Keefe et al., 2004). Similarly, few models including age of onset and duration of APS or BS showed significance, despite evidence showing age of onset as a differential in outcomes between CHR-P groups (Häfner, 2000). The few models which were significant, showed very marginal effects on the cognition measures.

The current research found limited evidence of any impact of the duration of APS or BS on neurocognitive measures. This occurred even when significant covariates of gender and age of onset (Häfner, 2000; Keefe et al., 2004) were accounted for. Rapp et al., (2013) failed to replicate findings reporting DUP having an effect on cognition. Their study then conducted a review of literature in the area, and found that across 18 studies measuring this relationship, only 5 reported

significant effects. Rapp and colleagues (2013) suggested that the lack of evidence for an effect of DUI on cognition measure might support the theory of psychosis as a neurodevelopmental disorder. This theory suggests that the cognitive deficits in schizophrenia precede the onset of symptoms (McGrath et al., 2003; Weinberger, 1987) and therefore cognition might have no connection to DUI. This study may be considered consistent with these findings.

A different explanation by Goldberg et al., (2009), proposed that the lack of evidence for longer DUP having an effect on cognition, compared to the significant evidence of longer DUP having a negative effect on response to treatment, might provide evidence for two different psychological mechanisms. In this theory, psychotic experiences are conceptualized as learned behaviors which become more difficult to treat the longer, they are consolidated. In comparison, neurocognitive functioning is conceptualized as being comprised of moment-to-moment information processing, which is not dependent on the duration of the psychotic symptoms to be associated with deficits. This explanation could also be applied to DUPrS, and provide an alternative justification for the current study failing to find any significant effect of DUPrS on cognition.

4.4 Length of DUPrS in non-help seeking sample

Five previous studies have provided information on the DUPrS in CHR-P sample. Nelson and colleagues (2016) were reporting on the duration of APS of a cohort collected as part of the PACE study. This large longitudinal sample was broken down based on year of screening, to compare between differences of duration of sub-threshold symptoms. Yung et al., (2004) was also reporting on the duration of APS in the PACE sample, but did not create a between group design. Zhang et al., (2018a) reported on duration of APS in a CHR-P screened at the Shanghai Mental Health Centre. Carrión et al., (2016) reported on a sample gathered as part of the Recognition and Prevention (RAP) program, analyzing duration of positive and negative sub-threshold symptoms in a CHR-P group. Chon and colleagues (2015) analyzed duration of APS symptoms in a CHR-P sample collected as part of an ongoing longitudinal study in the Seoul Youth Clinic.

Two papers have studied duration of BS in a CHR-P sample (Fusar-Poli et al., 2009; Klosterkötter et al., 2001). However, neither study reported on the duration of the BS for the CHR-P sample. This means that comparisons between BS duration in previous findings and this current CHR-P sample cannot be done as part of this research.

Table 12. Duration of APS symptoms reported in previous work on DUPrS, compared to the YouR study.

	Cohort collected	Mean duration, in months	Median duration, in months	Range
YouR study	**2016 – 2019**	**43**	**27**	**(1 - 246)**
Carríon, et al., (2016)	2000 – 2006	40.15	24.77	(2 - 192)
Chon, et al.,(2015)	2005 – 2013	18.42	12.00	(1 - 60)
Nelson, et al.,(2016)	1995 – 1997	18.57	13.12	(0 - 243)
	1998 – 2000	16.09	6.00	(1 - 183)
	2001 – 2003	10.41	6.07	(6 - 69)
	2004 – 2006	14.83	8.00	(16 - 78)
Yung, et al., (2004)	1995 – 1999	14.33	6.00	(0 - 134)
Zhang, et al., (2018a)	2011 – 2013	-	3.7	-

This evidence seems to support the possibility that a non-help seeking population experiences longer APS duration than previously reported durations of help-seeking CHR-P samples. The findings of the YouR study show that there is a sample of CHR-P who can be detected from community samples (McDonald et al., 2019), but that they may experience longer DUPrS than clinically referred CHR-P samples.

One explanation for the longer mean and median duration of APS found in the YouR study, compared to previous findings, might be awareness of the general public of services from which the studies recruit. A majority of the previous CHR-P duration studies are based as part of larger mental health service programs i.e. the PACE study and the Shanghai Mental Health Centre (Nelson et al., 2016; Yung et al., 2004; Zhang et al., 2017;2018a, b). This means that there is likely wider awareness of these recruitment sites as mental health services. In comparison the YouR study recruited from a community sample, and received minimal CHR-P referrals (n = 8). The YouR study is tied to NHS Glasgow and Greater Clyde, but the screening and study took place in the psychology department at University of Glasgow, which may lack the same name recognition as previous clinically based studies. This could mean there was a delayed awareness of the YouR study in participants and may explain a difference in APS duration between the studies.

A second explanation may be the focus of the previous studies on early intervention. A significant area of research in many of the previously reported help-seeking samples was the validity of earlier intervention methods in reducing transition rates (Chon et al., 2015; Nelson et al., 2016; Yung et al., 2004). This meant a priority of the studies was widespread outreach of the

programs, and earlier recruitment in younger samples. In comparison, while the YouR study used recruitment methods (flyers, emails, advertising), the aim of the study was not related to earlier targeted interventions. Instead recruitment followed a more open approach, inviting participants to a screening, following self-motivated responses to the online questionnaire. Evidence for the difference between study motivation may be observed in the difference in the ranges of durations reported in earlier clinical CHR-P samples (Carrión et al., 2016; Nelson et al., 2016; Yung et al., 2004). These showed wider ranges of longer duration closer to the YouR study. This similarity is not observable in the YouR study compared to more recently published papers (Chon et al., 2015; Zhang, et al., 2018a) . Nelson et al., (2016) proposed that the reason for this change over time in help seeking samples was an improvement in access to supports for CHR-P samples. Their study failed to find significant evidence earlier intervention as an explanation for the variance however ($p = 0.19$).

In consideration with other findings from community samples, a different explanation for these difference in duration of symptoms may point to differing populations. As discussed above, this current study failed to replicate clinical CHR-P studies which showed duration of subthreshold symptoms negatively affected functional outcomes, which added to current studies which show community samples show lower levels of symptom severity and higher levels of functioning (Mills et al., 2017). The longer durations experienced by this current community sample may be an additional difference between community and help-seeking clinical samples, and further demonstrate a differing trajectory or underlying process. Research into community CHR-P samples are only in the preliminary stages, but the differing findings of this paper may suggest a need for further research to assess the significance of these differences, and illuminate the reasons for this divergence between samples.

4.5 Strengths and limitations

Three key strengths of the current study. Firstly, the YouR study is a longitudinal study measuring a range of outcomes of those at-risk for psychosis, and recorded both APS and BS. This allowed this current paper to be the first paper on DUPrS in a CHR-P sample to report on both duration of APS and BS in one sample.

Secondly, the analysis conducted on the duration of APS and BS showed stable null findings between onset of BS compared to APS onset, suggesting that even in a moderate sized sample, these findings may reflect significant evidence that these is not a relationship.

Finally, the YouR study is a CHR-P sample (n = 154) recruited from a community population. Previous evidence on a community CHR-P sample found only 50% had shown help-seeking behavior (Mills et al., 2017). This suggests the participants in this study may represent a CHR-P sample not detected in clinical studies.

There are several limitations to the current findings. Firstly, duration was measured as a retroactive self-reported experience. This means the sample is vulnerable to recall bias (Schultze-Lutter et al., 2010; Schultze-Lutter, Rahman, et al., 2015). This is of particular concern in a CHR-P sample, who are already vulnerable to cognitive deficits which might affect recall (Emre Bora & Murray, 2014). In addition, during data collection interviewers were not specifically instructed to collect estimates of duration. This meant there was missing data and some of the YouR CHR-P sample were excluded from analysis (APS: n = 31, BS: n = 30). A standardized tool or protocol in place on future studies may address this.

Secondly, no measure of negative symptoms or nonspecific symptoms were recorded. This meant analysis on duration of negative symptoms could not be conducted. This is of particular importance in comparing this work with previous findings on the effect of DUPrS on functioning, where duration of negative symptoms, but not positive symptoms have been identified as causing negative effect on functioning (Carrión et al., 2016). CHR-P subthreshold symptoms are highly heterogeneous across the population (Fusar-Poli et al., 2013), and it is important in future research to also use tools to measure negative and nonspecific symptoms, in addition to APS and BS.

Thirdly, as this study was conducted in a CHR-P sample, a majority of whom do not transition, the use of prodrome does not accurately reflect the trajectory of this cohort. The decision to include this was based off previous CHR-P research (e.g. Nelson et al., 2016), to allow for comparison. However, similar to earlier models of schizophrenia which classified stages of schizophrenia as progressive (Lieberman et al., 2001), language in research is important in how it shapes understanding, and there is a need to adjust the terminology used. Future research would be better suited to referring to DUPrS as duration of subthreshold symptoms, or other terms which more fully encompass the differing trajectories of symproms for CHR-P.

In terms of evaluating the significance of the findings, the sample who reported both APS and BS symptoms was small (n = 64), but only slightly smaller than the previous study on this question (n = 79; Schultze-Lutter et al., 2010). This suggests there is some validity in interpreting the analysis of the whole group which showed non-significance. In interpretation of between group differences, the study reports on some small group sizes. In particular the size of the

samples becomes significant in interpreting the findings on long BS duration. In this subgroup there was a significant effect, with to BS onset preceding APS onset (M.D = 1.3 months, p = 0.04). This sample only includes 8 data points, making conclusions from this sample less reliable. In addition, while the robust regression analysis of this measure also reported significant results (B = 0.31, p = 0.002), this measure downweights outliers. All data points in this analysis had already been converted to z-scores to account for outliers, meaning that significant variation in a small sample had been removed before this significant result was found. This all suggests that this finding provides limited evidence for any effect.

Comparison with other studies appears to be potentially limited, for three reasons. Firstly, the sample had a significant gender imbalance, and had significantly more female participants compared to male participants. One reason may be the pool the subjects were collected from also had a gender imbalance, one of the main recruitment sites for the YouR study, University of Glasgow, reports a 41% male undergraduate population (Scottish Funding Council, 2017). A second explanation may be a difference between genders in response to the digital recruitment method, with female participants showing more willingness to engage with the website. Previous studies on e-health services had noted a higher usage among women compared to men (Smail-Crevier et al., 2019). This is an important variable that should be accounted for in future research, and there is a need for research focusing on male engagement with online mental e-health.

A second limitation of comparing this study to other measures is the high level of functioning in the sample. Recruiting and performing baseline assessments of functioning primarily from a currently studying 3rd level cohort is at risk for a sample bias towards high functioning individuals. This is different from other clinical cohorts, who do not primarily recruit in this way and may find CHR-P with lower functioning as a result. This becomes significant in both the reported functioning, and scores in cognition. Cognitive deficits have been shown to be associated with worse functional outcomes (Carrión et al., 2013). This may mean the current sample being high functioning also indicates lower levels of cognitive deficits than would be found in clinical CHR-P samples. Previous studies on the YouR dataset did observe decreased levels of functioning and cognition compared to controls (Haining et al., 2019), but higher the clinical samples. This suggests that while the presence of subthreshold symptoms does appear to be related to lower levels of functioning and cognition in a community sample, these findings may not be directly comparable. Replication of these current findings in a community sample that is not predominantly in 3rd level education might address these functioning and cognition disparities.

Finally the YouR study has a significantly lower transition rate (≈7%), compared to the average of previously reported findings (22%; Fusar-Poli et al., 2012). This raises questions of if the CHR-P sample recruited from the community sample are actually at significant risk for psychosis, or comparable to clinical samples. Previous studies on community samples have noted the cohort have less severe positive, negative and general symptoms, and higher functioning scores compared to clinical samples (Mills et al., 2017). This suggests there is a risk for a between group difference of vulnerability for transition to psychosis between the YouR study and other clinical studies. This is significant in assessing the difference in the findings of the current research with previous research on BS compared to APS onset, which was analyzed in an FEP sample (Schultze-Lutter et al., 2010). However, follow up data collection on the YouR study has not been completed, and 2 year follow up is showing an increasing transition rate. Further follow-up data are still required for our cohort of CHR-P participants to determine who will develop psychosis. Preliminary evidence the persistence of APS in our sample suggest that the clinical trajectories may be similar to existing CHR-P samples. In addition, the frequency and severity of reported symptoms in this sample are comparable to clinical CHR-P samples, and dissimilar to general population psychotic experiences, which generally only occur between 1 – 5 times during a lifetime (Kelleher & Cannon, 2011). This suggests that while these samples may not be direct comparisons, there are sufficient similarities between groups to classify this community sample as CHR-P.

4.6 Future research

There is a need for more standardization between studies of DUPrS on CHR-P populations. Studies currently differ on screening methods, and length of follow up on CHR-P samples (Beck et al., 2019; Powers et al., 2019). A specific tool designed to assertion DUPrS of symptoms in CHR-P, or an addition of duration as a standardized measure to current screening methods of sub-threshold symptoms (e.g. CAARM; Yung et al., 2005) would allow for more research to be conducted in larger samples for the effect of DUPrS on outcomes. Analysis of DUPrS in this way could be particularly utilized in studies on younger populations. These studies might produce more accurate recall of symptom onset, and if followed up could act as a prospective study of onset of later symptoms, rather than exclusively a retrospective study that is the standard in analyzing DUPrS currently.

Very few studies currently collect data on BS duration (Fusar-Poli et al., 2009; Klosterkötter et al., 2001), and this current study is the first to report on duration both APS and BS duration in one population. Evidence shows that presence of both APS and BS increases risk for transition (Schultze-Lutter, Michel, et al., 2015), a frequently measured outcome in DUPrS research

(Carrión et al., 2013; Chon et al., 2015; Nelson et al., 2016; Yung et al., 2004; Zhang et al., 2017; 2018b). Future research which measured BS could potentially find evidence regarding the role of BS duration on risk of transition. This approach to future research could also help clarify the findings of the current study. The findings of this study failed to replicate the previously reported findings of BS onset occurring prior to APS (Schultze-Lutter et al., 2010), which could have significant implications for several key hypotheses about sub-threshold symptoms in CHR-P . Larger studies of clinical and non-help seeking CHR-P samples which collect duration on both APS and BS data could lend clarity to the differences between the previously reported findings and the findings of this papers.

The current study found a significant number of participants (37.5%, n = 24) who reported APS symptom prior to BS onset. There is a need for research focused on participants who report these findings. Larger sample sizes comparing between group differences of those who report APS onset preceding BS, compared to those who report BS onset preceding APS onset, might offer significant avenues in determining the role of BS in underlying neurobiological processes. In particular, studies measuring differences in transition rates and utilizing neuroimaging data might provide significant information in determining how these different reported patterns of symptom onset occur.

This study found a longer duration of CHR-P compared to previously reported lengths found in clinical samples. Further research is needed on community CHR-P samples, to observe if they represent a sample who are undetected but at risk for transition, or if there is a larger than previously assumed number of individuals who experience APS and/or BS, but are not at risk for transition to psychosis. In particular, there is a need to assess the effect of sub-threshold symptoms on this sample.

The current study found that despite significant duration lengths reported by the participants, that duration did not play a significant role in functioning outcomes or cognition measures. However, this sample still showed lower levels of functioning and poorer performance on cognition measures (Haining et al., 2019). There is a need for further research into what aspect of these sub-threshold symptoms results in these worse outcomes, if the continued length of symptoms does not appear to have a significant effect.

4.7 Conclusions

The current research offers interesting preliminary findings into the value of studying duration of prodromal symptoms. The most significant evidence was found in the failure to confirm a hypothesis of APS as secondary outcomes to the neurobiological changes that are symptomatically shown in BS onset (Huber & Gross, 1989; Schultze-Lutter & Theodoridou, 2017; Schultze-Lutter, 2009; Schultze-Lutter et al., 2016). This finding demonstrates a need for further research in this area on a CHR-P sample to further validate either the present study, or the previous findings which did find evidence for the hypothesis (Schultze-Lutter et al., 2010). Answering the questions produced by this paper with regards to the validity of the hypothesis could yield significant findings in future CHR-P research.

The lack of significant findings on the effect of duration of APS and BS on functioning and cognition also produces interesting evidence. These findings appear to add additional validity to hypothesized theories of a critical period of psychosis (Birchwood et al., 1998), and the neurodevelopmental theory of schizophrenia (McGrath et al., 2003). Both theories are dependent on measures of duration to validate the assumptions of the theory, but currently few studies have been conducted to validate them within the prodromal period.

The difference in duration between non-help seeking CHR-P samples and previously reported help-seeking CHR-P samples produces interesting evidence that there may be differences between these samples beyond recruitment methods. This is supported by the differing findings on the effect of duration of subthreshold symptoms on functioning in this sample compared to clinical samples. Research explaining these differences is currently limited, but this study offers preliminary evidence that beyond symptom severity, there may be different trajectories in non-help seeking CHR-P samples.

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Appendices

Appendix table 1.

List of all symptoms and duration of symptoms reported by participants in the YouR study.

	Number of participants	Mean duration, in months	Median duration, in months	Mean age at onset, in years	Gender f(%)
APS					
Unusual thought content	38	29.5	24	18.07	28(73.3)
Non-bizarre ideas	63	44.52	27	18.15	47(74.6)
Perceptual abnormalities	59	26.8	12	18.63	43(72.88)
Disorganised speech	6	39.5	43	17.54	2(33.33)
BS					
Inability to divide attention	21	22.24	12	18.91	14(66.67)
Thought interference	5	31	47	17.82	3(60)
Thought blockage	34	56.21	36	17.61	23(67.65)
Disturbances in receptive speech	17	25.53	24	17.17	15(88.23)
Disturbances in expressive speech	26	35.35	21	19.21	17(65.38)
Thought pressure	9	62.22	52	17.74	8(88.89)
Unstable ideas of reference	6	49.17	42	16.57	3(50)
Thought perseveration	3	52.67	62	15.61	3(100)
Decreased ability to discriminate..	9	51.33	55	14.17	4(44.44)
Captivation of attention by details..	5	23.8	24	15.62	4(80)
Derealization	15	47.33	42	13.39	11(73.33)
Visual perception disturbances	23	36	18	17.26	15(65.22)
Acoustic perception disturbances	30	41.5	35	17.64	21(70)

Abbreviations APS = attenuated psychotic symptom, BS = basic symptoms, Captivation of attention by details.. = Captivation of attention by details in the visual field, Decreased ability to discriminate.. = Decreased ability to discriminate between ideas and perception, fantasy and true memories

Appendix table 2.

Table of the effect of gender/age of onset on functional outcomes.

Table 2.1 Effect of gender on functioning outcomes.

		B	SE	β	t	R^2	p
APS							
	GAF	2.440	2.450	0.096	1	0.00917	0.32
	GF:Role	1.000	0.577	-	1.73	-	0.09
	GF:Social	0.000	0.450	-	0.00	-	1.0
BS							
	GAF	3.721	0.137	2.903	1.28	0.00436	0.20
	GF:Role	1.000	0.547	-	1.83	-	0.07
	GF:Social	0.000	0.530	-	0.00	-	1.0

Table 2.2. Effect of age of onset on functioning outcomes.

		B	SE	β	t	R^2	p
APS							
	GAF	-0.015	0.023	0.223	-0.64	0.0039	0.52
	GF:Role	0.000	0.004	-	0.00	-	1.0
	GF:Social	0.000	0.002	-	0.00	-	1.0
BS							
	GAF	0.000	0.015	0.003	0.14	0.0002	0.89
	GF:Role	0.000	0.004	-	0.00	-	1.0
	GF:Social	0.000	0.003	-	0.00	-	1.0

Appendix table 3.

The effects of duration and gender/duration and onset of APS and BS on GAF scores

	B	SE	β	t	p	R^2	P
APS							
Duration	-0.027	0.034	-0.115	-0.8	0.42		
Gender	0.983	3.281	0.039	0.3	0.77	0.0152	0.655
Duration*Gender	0.028	0.046	0.097	0.61	0.55		
Duration	0.005	0.064	0.022	0.08	0.94		
Onset	0.599	0.299	0.262	2	**0.05**	0.0574	0.101
Duration*Onset	0.001	0.005	0.075	0.32	0.75		
BS							
Duration	-0.056	-0.195	0.056	-1	0.32		
Gender	1.971	0.073	4.602	0.43	0.67	0.0352	0.387
Duration*Gender	0.032	0.110	0.067	0.47	0.64		
Duration	0.036	0.126	0.093	0.39	0.70		
Onset	0.636	0.248	0.475	1.34	0.18	0.0406	0.32
Duration*Onset	-0.003	-0.149	0.005	-0.54	0.59		

Appendix table 4.

Table of the effect of gender/age of onset on functional outcomes, samples divided into short and long duration.

Table 4.1 Effect of gender on functioning outcomes.

	B	SE	β	t	R^2	p
APS						
Short						
GAF	0.086	2.279	0.004	0.03	0.0000	0.98
GF:Role	0	0.78	-	0	-	1.0
GF:Social	0	0.019	-	0.00	-	1.0
Long						
GAF	4.240	3.550	0.162	1.19	0.0261	0.24
GF:Role	1	0.61	-	1.63	-	0.11
GF:Social	0	0.059	-	0	-	1.0
BS						
Short						
GAF	2.010	4.700	0.066	0.43	0.0044	0.67
GF:Role	-1	0.69	-	-1.44	-	0.16
GF:Social	0.000	0.41	-	0.00	-	1.0
Long						
GAF	5.430	3.470	0.235	1.57	0.0552	0.12
GF:Role	1	0.449	-	2.226	-	0.032
GF:Social	1	0.56	-	1.8	-	0.08

Table 4.2. Effect of age of onset on functioning outcomes.

	B	SE	β	t	R^2	p
APS						
Short						
GAF	0.232	0.329	0.097	0.7	0.0094	0.48
GF:Role	0	0.051	-	0.00	-	1.0
GF:Social	0.000	0.019	-	0.00	-	1.0
Long						
GAF	0.808	0.376	0.284	2.15	0.0804	0.036
GF:Role	-0.051	0.053	-	-0.95	-	0.34
GF:Social	0	0.059	-	0.00	-	1.0
BS						
Short						
GAF	-0.305	0.201	-0.228	-1.51	0.0518	0.14
GF:Role	-0.071	0.056	-	-1.275	-	0.21
GF:Social	0	0.041	-	0.00	-	1.0
Long						
GAF	-0.014	0.040	-0.056	-0.36	0.0031	0.72
GF:Role	1.000	0.059	-	0.00	-	1.0
GF:Social	0.000	0.055	-	0.00	-	1.0

Appendix table 5

linear regressions of the effect of gender/age of onset on neurocognitive outcomes.

Appendix table 5.1

Table of effect of gender on cognition

	B	SE	t	R^2	p
APS					
BACS					
Verbal memory	-0.078	0.260	-0.3	0.0009	0.77
Working memory	0.654	0.274	2.38	0.0559	**0.02**
Motor speed	-0.084	0.257	-0.33	0.0011	0.75
Attention & processing speed	0.608	0.252	2.42	0.0574	0.02
Verbal fluency	0.957	0.083	11.6	0.5830	< **0.0001**
Executive function	0.035	0.305	0.11	0.0001	0.91
BACS composite score	0.747	0.321	2.33	0.0536	**0.02**
Penn CNP					
Emotion recognition accuracy	0.440	0.208	2.11	0.0445	**0.04**
Emotion recognition RT	-0.267	0.274	-0.97	0.0098	0.33
Attention accuracy	0.099	0.294	0.34	0.0012	0.74
Attention RT	0.218	0.196	1.11	0.0127	0.27
Working memory accuracy	0.063	0.264	0.24	0.0575	0.81
Working memory RT	0.082	0.185	0.44	0.0021	0.66
BS					
BACS					
Verbal memory	0.024	0.435	0.05	0.0000	0.96
Working memory	0.252	0.378	0.67	0.0122	0.51
Motor speed	0.218	0.398	0.55	0.0082	0.59
Attention & processing speed	0.432	0.388	1.11	0.0333	0.27
Verbal fluency	1.073	0.151	7.09	0.583	< **0.0001**
Executive function	-0.239	0.524	-0.46	0.0058	0.65
BACS composite score	0.452	0.468	0.96	0.0252	0.34
Penn CNP					
Emotion recognition accuracy	0.481	0.220	1.99	0.0485	0.05
Emotion recognition RT	-0.239	-0.084	-0.74	0.0070	0.46
Attention accuracy	0.432	0.154	1.38	0.0239	0.17
Attention RT	-0.192	-0.085	-0.52	0.0071	0.61
Working memory accuracy	0.279	0.107	0.95	0.0115	0.34
Working memory RT	0.047	0.025	0.22	0.0006	0.83

Appendix table 5.2

Table of effect of age of onset on cognition

	B	SE	t	R^2	p
APS					
BACS					
Verbal memory	0.063	0.023	2.75	0.0732	**0.01**
Working memory	0.100	0.030	3.35	0.1110	**0.001**
Motor speed	0.007	0.023	0.31	0.0010	0.76
Attention & processing speed	-0.005	0.024	-0.19	0.0004	0.85
Verbal fluency	-0.003	0.012	-0.29	0.0009	0.77
Executive function	-0.021	0.028	-0.75	0.0058	0.46
BACS composite score	0.018	0.030	0.59	0.0037	0.55
Penn CNP					
Emotion recognition accuracy	-0.005	0.020	-0.27	0.0008	0.79
Emotion recognition RT	0.200	0.025	0.79	0.0065	0.43
Attention accuracy	0.047	0.027	1.75	0.0308	0.08
Attention RT	0.007	0.018	0.4	0.0017	0.69
Working memory accuracy	0.008	0.024	0.31	0.0010	0.76
Working memory RT	0.028	0.017	1.65	0.0277	0.10
BS					
BACS					
Verbal memory	0.109	0.047	2.29	0.128	**0.03**
Working memory	-0.010	0.044	-0.22	0.00134	0.83
Motor speed	-0.084	0.045	-1.88	0.089	0.07
Attention & processing speed	-0.013	0.046	-0.29	0.00235	0.77
Verbal fluency	0.014	0.027	0.53	0.0076	0.60
Executive function	-0.045	0.061	-0.74	0.015	0.46
BACS composite score	-0.028	0.055	-0.51	0.00709	0.62
Penn CNP					
Emotion recognition accuracy	0.000	0.002	0.02	0.0000	0.99
Emotion recognition RT	0.074	0.282	2.59	0.0795	**0.01**
Attention accuracy	0.022	0.087	0.77	0.0076	0.44
Attention RT	0.027	0.099	0.6	0.0097	0.55
Working memory accuracy	-0.021	-0.090	-0.79	0.0080	0.43
Working memory RT	0.027	0.152	1.36	0.0232	0.18

Appendix table 6

The effect of duration and gender/duration and age of onset on cognition measures

Appendix table 6.1

Multivariate regression of the effect of APS duration and gender on cognition measures.

	B	SE	t	Pr(>|t|)	R^2	p
BACS						
Verbal memory						
Duration	0.002	0.003	0.61	0.54		
Gender	0.124	0.349	0.36	0.72	0.0094	0.83
Duration*Gender	-0.004	0.005	-0.9	0.37		
Working memory						
Duration	0.006	0.004	1.56	0.12		
Gender	0.993	0.364	2.73	0.01	0.0802	**0.05**
Duration*Gender	-0.006	0.005	-1.28	0.20		
Motor speed						
Duration	-0.002	0.003	-0.6	0.55		
Gender	0.094	0.336	0.28	0.78	0.0555	0.15
Duration*Gender	-0.005	0.005	-1.15	0.25		
Attention and processing speed						
Duration	0.000	0.003	-0.05	0.96		
Gender	0.613	0.338	1.81	0.07	0.0575	0.13
Duration*Gender	0.000	0.005	-0.04	0.97		
Verbal fluency						
Duration	-0.001	0.001	-0.66	0.51		
Gender	0.918	0.111	8.29	**0.00**	0.5850	< **0.0001**
Duration*Gender	0.001	0.002	0.47	0.64		
Executive function						
Duration	0.003	0.004	0.66	0.51		
Gender	0.247	0.409	0.6	0.55	0.0067	0.89
Duration*Gender	-0.004	0.006	-0.77	0.44		
BACS composite score						
Duration	0.003	0.004	0.75	0.46		
Gender	1.067	0.428	2.49	**0.01**	0.0673	0.09
Duration*Gender	-0.007	0.006	-1.17	0.25		
PennCNP						
Emotion recognition accuracy						
Duration	0.000	0.003	0.06	0.95		
Gender	0.361	0.279	1.29	0.20	0.0515	0.17
Duration*Gender	0.002	0.004	0.54	0.59		
Emotion recognition RT						
Duration	0.001	0.004	0.36	0.72		
Gender	-0.362	0.365	-0.99	0.32	0.0255	0.49
Duration*Gender	0.003	0.005	0.57	0.57		
Attention accuracy						
Duration	0.003	0.004	0.83	0.41		
Gender	0.426	0.392	1.09	0.28	0.0190	0.61
Duration*Gender	-0.007	0.006	-1.3	0.20		
Attention RT						
Duration	-0.003	0.003	-1.24	0.22		
Gender	0.141	0.261	0.54	0.59	0.0378	0.30
Duration*Gender	0.001	0.004	0.21	0.84		
Working memory accuracy						
Duration	0.000	0.004	-0.05	0.96		
Gender	0.191	0.353	0.54	0.59	0.0111	0.79
Duration*Gender	-0.003	0.005	-0.67	0.51		
Working memory RT						
Duration	0.002	0.002	0.82	0.41		
Gender	0.323	0.245	1.32	0.19	0.0296	0.42
Duration*Gender	-0.005	0.003	-1.58	0.12		

Appendix table 6.2

Multivariate regression of the effect of BS duration and gender on neurocognitive outcomes.

	B	SE	t	Pr(>|t|)	R^2	p
BACS						
Verbal memory						
Duration	0.002	0.003	0.61	0.54		
Gender	0.124	0.349	0.36	0.72	0.0094	0.83
Duration*Gender	-0.004	0.005	-0.9	0.37		
Working memory						
Duration	0.006	0.004	1.56	0.12		
Gender	0.993	0.364	2.73	0.01	0.0802	**0.05**
Duration*Gender	-0.006	0.005	-1.28	0.20		
Motor speed						
Duration	-0.002	0.003	-0.6	0.55		
Gender	0.094	0.336	0.28	0.78	0.0555	0.15
Duration*Gender	-0.005	0.005	-1.15	0.25		
Attention and processing speed						
Duration	0.000	0.003	-0.05	0.96		
Gender	0.613	0.338	1.81	0.07	0.0575	0.13
Duration*Gender	0.000	0.005	-0.04	0.97		
Verbal fluency						
Duration	-0.001	0.001	-0.66	0.51		
Gender	0.918	0.111	8.29	**0.00**	0.5850	< **0.0001**
Duration*Gender	0.001	0.002	0.47	0.64		
Executive function						
Duration	0.003	0.004	0.66	0.51		
Gender	0.247	0.409	0.6	0.55	0.0067	0.89
Duration*Gender	-0.004	0.006	-0.77	0.44		
BACS composite score						
Duration	0.003	0.004	0.75	0.46		
Gender	1.067	0.428	2.49	**0.01**	0.0673	0.09
Duration*Gender	-0.007	0.006	-1.17	0.25		
PennCNP						
Emotion recognition accuracy						
Duration	-0.002	-0.090	-0.44	0.66		
Gender	0.350	0.160	0.91	0.37	0.0511	0.26
Duration*Gender	0.002	0.106	0.44	0.66		
Emotion recognition RT						
Duration	0.004	0.123	0.6	0.55		
Gender	0.291	0.102	0.58	0.57	0.0428	0.34
Duration*Gender	-0.010	-0.334	-1.37	0.17		
Attention accuracy						
Duration	0.001	0.037	0.18	0.86		
Gender	0.329	0.118	0.66	0.51	0.0320	0.48
Duration*Gender	0.002	0.068	0.28	0.78		
Attention RT						
Duration	-0.033	-0.321	-1.29	0.21		
Gender	-0.638	-0.281	-0.82	0.42	0.0567	0.56
Duration*Gender	0.024	0.274	0.69	0.50		
Working memory accuracy						
Duration	-0.011	-0.395	-1.96	**0.05**		
Gender	-0.388	-0.149	-0.85	0.40	0.0613	0.18
Duration*Gender	0.012	0.453	1.88	0.06		
Working memory RT						
Duration	-0.003	-0.147	-0.71	0.48		
Gender	-0.105	-0.054	-0.3	0.76	0.0073	0.91
Duration*Gender	0.003	0.138	0.56	0.58		

Appendix table 6.3

Multivariate regression of the effect of APS duration and age of onset on neurocognitive outcomes.

	B	SE	t	Pr(>|t|)	R^2	p
BACS						
Verbal memory						
Duration	0.010	0.007	1.38	0.17		
Onset	0.100	0.030	3.35	**0.00**	0.1110	**0.01**
Duration*Onset	0.000	0.001	-0.73	0.46		
Working memory						
Duration	0.011	0.008	1.29	0.20		
Onset	0.049	0.034	1.43	0.16	0.0258	0.48
Duration*Onset	-0.001	0.001	-0.95	0.34		
Motor speed						
Duration	0.008	0.007	1.02	0.31		
Onset	-0.001	0.030	-0.02	0.98	0.0854	**0.04**
Duration*Onset	-0.001	0.001	-1.98	**0.05**		
Attention and processing speed						
Duration	0.012	0.008	1.53	0.13		
Onset	0.010	0.031	0.33	0.74	0.0424	0.25
Duration*Onset	-0.001	0.001	-1.92	0.06		
Verbal fluency						
Duration	-0.007	0.004	-2.02	**0.05**		
Onset	-0.027	0.015	-1.77	0.08	0.0563	0.14
Duration*Onset	0.000	0.000	1.42	0.16		
Executive function						
Duration	0.011	0.009	1.18	0.24		
Onset	-0.005	0.037	-0.13	0.89	0.0271	0.46
Duration*Onset	-0.001	0.001	-1.4	0.17		
BACS composite score						
Duration	0.016	0.010	1.69	0.09		
Onset	0.046	0.039	1.18	0.24	0.0399	0.28
Duration*Onset	-0.001	0.001	-1.18	**0.24**		
PennCNP						
Emotion recognition accuracy						
Duration	0.004	0.006	0.62	0.54		
Onset	0.004	0.026	0.16	0.87	0.0048	0.93
Duration*Onset	0.000	0.000	-0.58	0.57		
Emotion recognition RT						
Duration	0.006	0.008	0.74	0.46		
Onset	0.054	0.033	1.62	0.11	0.0476	0.20
Duration*Onset	0.000	0.001	0.01	0.99		
Attention accuracy						
Duration	0.007	0.009	0.84	0.40		
Onset	0.072	0.036	2.01	**0.05**	0.0428	0.25
Duration*Onset	0.000	0.001	-0.52	0.60		
Attention RT						
Duration	-0.005	0.006	-0.78	0.44		
Onset	-0.015	0.024	-0.64	0.53	0.0335	0.36
Duration*Onset	0.000	0.000	0.13	0.90		
Working memory accuracy						
Duration	0.006	0.008	0.75	0.45		
Onset	0.011	0.032	0.34	0.74	0.0190	0.61
Duration*Onset	-0.001	0.001	-1.1	0.27		
Working memory RT						
Duration	0.001	0.005	0.25	0.80		
Onset	0.034	0.023	1.52	0.13	0.0305	0.40
Duration*Onset	0.000	0.000	-0.06	0.95		

Appendix table 6.4

Multivariate regression of the effect of BS duration and age of onset on neurocognitive outcomes.

	B	SE	t	Pr(>|t|)	R^2	p
BACS						
Verbal memory						
Duration	0.010	0.007	1.38	0.17		
Onset	0.100	0.030	3.35	**0.00**	0.1110	**0.01**
Duration*Onset	0.000	0.001	-0.73	0.46		
Working memory						
Duration	0.011	0.008	1.29	0.20		
Onset	0.049	0.034	1.43	0.16	0.0258	0.48
Duration*Onset	-0.001	0.001	-0.95	0.34		
Motor speed						
Duration	0.008	0.007	1.02	0.31		
Onset	-0.001	0.030	-0.02	0.98	0.0854	**0.04**
Duration*Onset	-0.001	0.001	-1.98	**0.05**		
Attention and processing speed						
Duration	0.012	0.008	1.53	0.13		
Onset	0.010	0.031	0.33	0.74	0.0424	0.25
Duration*Onset	-0.001	0.001	-1.92	**0.06**		
Verbal fluency						
Duration	-0.007	0.004	-2.02	**0.05**		
Onset	-0.027	0.015	-1.77	0.08	0.0563	0.14
Duration*Onset	0.000	0.000	1.42	0.16		
Executive function						
Duration	0.011	0.009	1.18	0.24		
Onset	-0.005	0.037	-0.13	0.89	0.0271	0.46
Duration*Onset	-0.001	0.001	-1.4	0.17		
BACS composite score						
Duration	0.016	0.010	1.69	0.09		
Onset	0.046	0.039	1.18	0.24	0.0399	0.28
Duration*Onset	-0.001	0.001	-1.18	**0.24**		
PennCNP						
Emotion recognition accuracy						
Duration	0.006	0.248	0.72	0.40		
Onset	0.023	0.117	0.59	0.56	0.0103	0.85
Duration*Onset	0.000	-0.256	-0.87	0.39		
Emotion recognition RT						
Duration	-0.004	-0.151	-0.46	0.65		
Onset	0.056	0.213	1.11	0.27	0.0863	0.075
Duration*Onset	0.000	0.185	0.65	0.52		
Attention accuracy						
Duration	0.008	0.287	0.85	0.40		
Onset	0.059	0.229	1.16	0.25	0.0307	0.5
Duration*Onset	0.000	-0.109	2 -0.37	0.71		
Attention RT						
Duration	0.007	0.068	0.09	0.90		
Onset	0.044	0.161	0.45	0.65	0.0446	0.66
Duration*Onset	-0.001	-0.256	-0.34	0.74		
Working memory accuracy						
Duration	0.001	0.027	0.08	0.94		
Onset	-0.020	-0.084	-0.42	0.67	0.0347	0.44
Duration*Onset	0.000	-0.185	-0.64	0.53		
Working memory RT						
Duration	-0.001	-0.034	-0.1	0.92		
Onset	0.024	0.138	0.7	0.49	0.0248	0.59
Duration*Onset	0.000	0.065	0.22	0.82		