BLUNTED AFFECT, SOCIAL WITHDRAWAL AND SUICIDE IN SCHIZOPHRENIA

by

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Abstract

Completed suicide in schizophrenia remains a significant unanswered challenge, requiring new perspectives and novel investigation. This thesis examines how previously under-investigated symptoms, including blunted affect and social withdrawal, may be associated with suicidal behaviour in people with schizophrenia. For this study, a multidisciplinary approach was used incorporating philosophy, psychiatry, and neuroimaging. I begin with Chapter 1, in which I give a philosophical consideration of why we should not regard suicide as an irrational action in schizophrenia. My arguments are based on the idea that overwhelming feelings and suffering such as isolation and of not belonging, which relate to negative symptoms including blunted affect, could be sufficient reasons for someone to end their life and therefore could be considered as rational acts. In chapter two, I present a systematic review on the negative symptom of blunted affect in suicide in schizophrenia, aiming to show the gaps in existing evidence and current knowledge. In summary, this highlights that blunted affect is likely to influence suicidal behaviour in the presence of depression, anxiety, or hopelessness. Following the systematic review's findings, a primary data chapter then focuses on quantitative examination of suicidal behaviour in first-episode psychosis (FEP) patients examining the associations between blunted affect, social withdrawal, and suicidal behaviour in FEP. Specifically, a mediational analysis demonstrated that blunted affect and social withdrawal are associated with suicidal behaviour when hopelessness acts as a mediator. To further enhance our understanding of suicidal behaviour in people with schizophrenia, I present a second data chapter conducting a functional Magnetic Resonance Imaging (fMRI) study, which compared brain function in patients with

FEP and high vs low suicidal behaviour during an emotional face response task, aiming to explore whether there are any differences in brain function between the two groups. Findings demonstrate that patients with high suicidal behaviour reported reduced activation in the prefrontal cortex: specifically, the Medial Frontal Gyrus and Anterior Cingulate Gyrus, in response to presentation of emotional faces; areas related to decision making and executive function. The summary and discussion chapter includes implications such the mechanisms of blunted affect and social withdrawal and how high scores on such symptoms might impact patient's brain function, as well as early identification of suicide risk, and implications for treatment that focus on social connectedness and recovery. The novelty this thesis presents, focuses on the multidimensional examination of under-examined factors such as blunted affect and social withdrawal, that might play an indirect role to the development of suicidal behaviour. The symptoms of blunted affect and social withdrawal might lead to suicide when risk factors such as hopelessness act as mediator. Lastly, high scores on these symptoms might potentially be related to underlying brain dysfunction; however, this in itself does not automatically equate to suicide being irrational. Findings in this thesis could be seen as evidence which might lead to better identification of risk, and prevention of suicidal behaviour in people with schizophrenia.

Dedication

Στον Θεό που μου χάρισε πολύτιμο χρόνο και μια ατίθαση περιέργεια ώστε να αναζητήσω την αλήθεια και να ερευνήσω τον άνθρωπο.

Στην μεγάλη μου οικογένεια, που μου έμαθε τη σημασία της δημιουργίας και της πίστης,

Στις πατρίδες μου Ελλάδα και Κύπρο που με έκαναν να συνειδητοποιήσω ότι η αθανασία προϋποθέτει δημιουργία, η ευτυχία ηθική, και το όραμα πάθος.

Σε όλους όσους αποφάσισαν να φύγουν.

“Suicide is connected with a general state of extreme depression and exaggerated sadness, causing the patient no longer to realize the bonds which connect him with people and things about him. Pleasures no longer attract”

Émile Durkheim, Suicide: A Study in Sociology,1897

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my grandparents Christos and Meri, Panayiotis and Maria, who taught me the beauty of being young and alive and to my uncle and aunt Drs Petros and Niki Kokkinos who showed me that a genuine vision has the power to transform peoples' lives. Nothing would be possible without the loudness and perseverance of my big family and friends!

Declaration

This thesis has been written for submission as a partial fulfilment of the requirements for the University of Birmingham. This thesis is my own work, carried out under the supervision of Professor Rachel Upthegrove, Professor Lisa Bortolotti, Dr Renate Reniers and Dr Pavan Mallikarjun. Authorship of published papers are and will be shared with my supervisors. This thesis has not been submitted for a degree at any other institution.

Publication and abstracts related to this thesis

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2019: Blunted affect and suicide in people with schizophrenia: A systematic review, 4th Suicide & Self-harm, Research Forum at University of Glasgow (Talk)

2019: Social Isolation and suicide in young people in the UK, 4th Suicide & Self-harm, Research Forum at University of Glasgow (Poster).

2018: Blunted affect and suicide in people with schizophrenia: A systematic review, British Association of Psychopharmacology, Imperial Collage London (Poster).

2018: Lack of emotional expression and suicide in schizophrenia, Schizophrenia International Research Society Conference, Italy (Poster).

2018: Suicide risk factors in schizophrenia, Postgraduate Research Conference, University of Birmingham (Poster).

2017: The symptom of blunted affect and its importance in clinical practice, National Institute of Mental Health, Prague, CZ (Talk).

2017: Suicide risk factors in schizophrenia, on 9th Young Psychiatrists Meeting, Prague, CZ (Talk).

Statement of contributions to thesis

The results, analyses and interpretations presented in this thesis represent the work of the author, developed in discussion with my PhD supervisors, Professor Rachel Upthegrove and Professor Lisa Bortolotti and Dr Renate Reniers. The body of research comprising the thesis was conducted in collaboration with many others whose specific contributions are acknowledged following. Two chapters in this thesis present a subset of data collected from two different studies at University of Birmingham.

I have presented the theoretical accounts and my arguments in chapter 3 under the supervision of Professor Lisa Bortolotti who also contributed to the publication in chapter 3.

For the data search for systematic review presented in chapter 4, I thank the library staff at the Barberry, The National Centre for Mental Health, who also helped me accessing papers from different electronical libraries.

Chapter 5 presents a subset of the data collected within a cross sectional research project, First Episode Psychosis- Autism (FEP-A) examining the clinical and neurobiological overlap between autism and psychosis, which has been conducted at the School of Psychology at University of Birmingham in partnership with Birmingham and Solihull Mental Health NHS Trust in 2014. The FEP-A study was designed by Professor Stephen Wood, Professor Rachel Upthegrove and Dr Katharine Chisholm. In FEP-A data I was responsible for creating the hypotheses, organising, and cleaning the data, data analysis and interpretation of data in chapter 5.

Chapter 6 presents data collected from a pilot study, Biological correlates of dimensional symptoms of psychosis (BioPoP) started in 2015 which aimed to examine the clinical and neurobiological markers of dimensional symptoms of psychosis. The BioPoP study was designed by Professor Rachel Upthegrove, Professor Stephen Wood and Dr Pavan Mallikarjun. I was responsible for collection of the clinical assessments and neuroimaging data and the administrative duties of the study, data entry and analysis. For chapter 6 I was responsible for generating the hypothesis, cleaning, and analysing the clinical and brain imaging data and interpretation.

Other individuals contributed to the broader FEP-A and BioPoP projects, and are acknowledged as follows:

- For contributions to participant recruitment, data collection, and/or data entry in FEP-A: Katherine Chisholm, Mirabel Pelton, and Mariam Iqbal.
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All chapters have been written by the author.

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List of Abbreviations

AQ = Autism-Spectrum Quotient

BHS =Beck Hopelessness Scale

CTQ = Childhood Trauma Questionnaire

DA = Dopamine

DOI = Duration of Illness

DSM =Diagnostic and Statistical Manual of Mental Disorders

DUP = Duration of Untreated Psychosis

EIS = Early Intervention Service

FEP = First Episode Psychosis

FEP-A = First Episode Psychosis - Autism

G16 - PANSS = General Symptom Item 16 Active social avoidance

MINI = MINI - International Neuropsychiatric Interview

N1 - PANSS = Negative Symptom Item 1 Blunted affect

N2 - PANSS = Negative Symptom Item 2 Emotional withdrawal

N4 - PANSS = Negative Symptom Item 4 Passive apathetic/social withdrawal

NHS = National Health System

NS = Negative Symptoms

PANSS = Positive and Negative Syndrome Scale

PFC = Prefrontal Cortex

PS = Positive Symptoms

PSP = Personal and Social Performance

ROI = Region of Interest

SB = Suicidal Behaviour

SBQ-R = Suicidal Behaviour Questionnaire – Revised

SIAS = The Social Interaction Anxiety Scale

SPQ = Schizotypal Personality Questionnaire

UHR = Ultra-high risk

WHO = World Health Organization

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CHAPTER 1: INTRODUCTION

1. Schizophrenia

The historical roots of schizophrenia begin over 100 years ago when Emil Kraepelin coined the term “dementia praecox”. Based on his clinical observations, he defined “dementia praecox” as a biological illness caused by anatomical or toxic processes with a deteriorating course. He was the first person who also distinguished between “dementia praecox” and “manic depression” as the two forms of psychosis (1). However, this is not the major reason Kraepelin is still a person research refers to. His clinical observations helped him to revise his theory and to suggest that specific combinations of symptoms can define a specific mental disorder in relation to the course of mental disorders (2). This is still relevant today as approximately 50% of the people who meet criteria for one mental disorder also endorsed symptoms that meet criteria for another or more additional disorders (3).

A few years later, in 1911, Eugen Bleuler, a Swiss psychiatrist, added a milestone in psychiatry re-naming ‘dementia praecox’ to Schizophrenia. In 1911, in his book, he writes: “I call dementia praecox ‘schizophrenia’ because (as I hope to demonstrate) the ‘splitting’ of the different psychic functions is one of its most important characteristics” (4). The change Bleuler made is not about the name he gave to a psychiatric disorder, rather to the whole concept of definition, classification, and symptomatology of schizophrenia. The separation of affective disorders from schizophrenic psychosis as two distinct entities has been the foundation of psychiatry for more than a century now (2). However, over the last decades these two conditions have been considered to be on a continuum rather than as two entirely distinct disorders as Bleuler suggested. Accurately dating schizophrenia is not possible since it is a condition which has evaded a clinical definition until

relatively recently. Intriguingly, presentation of schizophrenia symptoms seems to have existed since ancient times. In 400 BC, Hippocrates suggested that mental conditions such as madness (schizophrenia is used as a later term for it), mania and neurosis are basically problems which occur because of neurochemical imbalances in the brain.

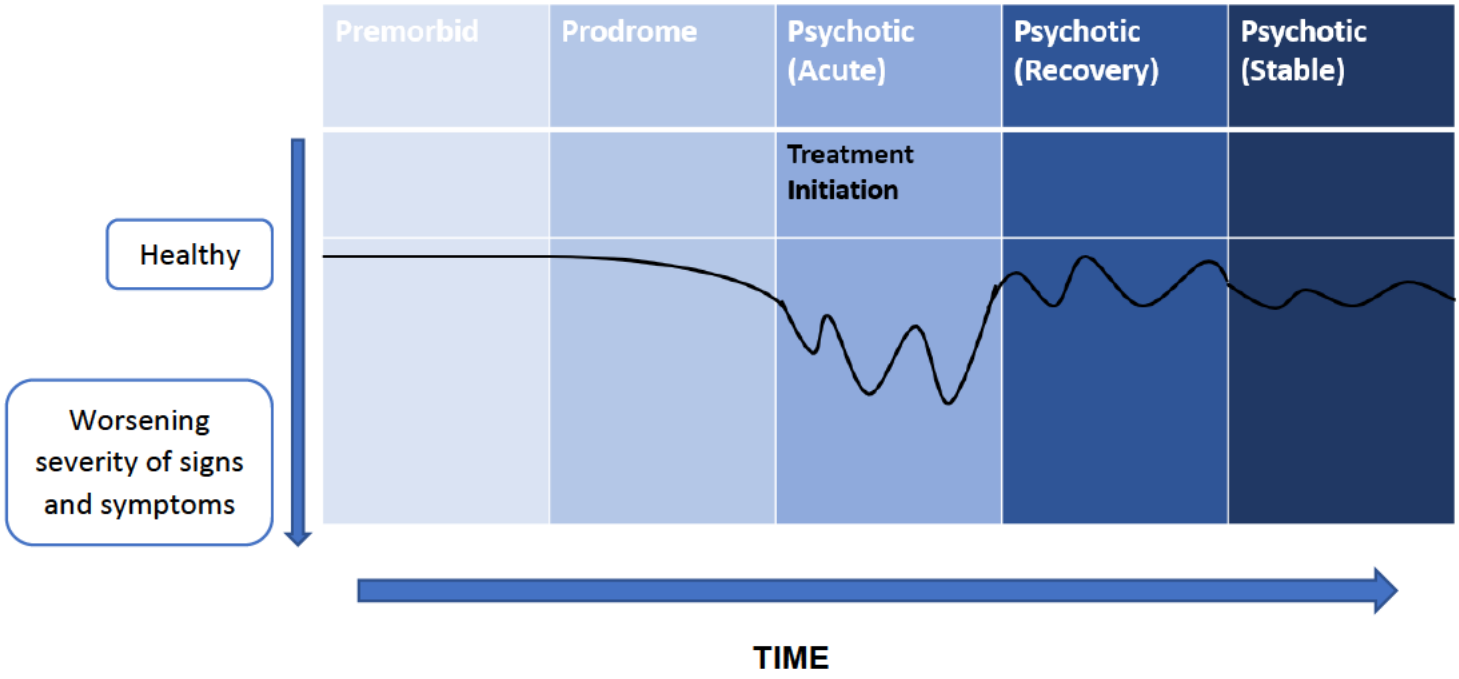
The existence of schizophrenia over the years makes it as one of the biggest challenges in clinical and social research. The implications of it in society, economy and medical practice are huge. The consequences of schizophrenia are vast, affecting not only the public sector of each country but also the financial costs and the general quality of life of people. Foremost, the cost obstructs the social and personal development of each patient. It has been observed that many people with schizophrenia tend to stay at home with their families (5). Moreover, social isolation, unemployment, inability to communicate and build relationships, lack of education and the need for professional support (5) are consequences of schizophrenia which result in it being one of the main challenges in recent research and global health.

Schizophrenia is reported as one of the top 10 disabling conditions worldwide for young people. It is suggested that more than 1% of the general population is experiencing schizophrenia (7). In the United Kingdom, the total burden of schizophrenia exceeds the amount of £11 Billion per year (8) and it is estimated that up to 7500 new cases of schizophrenia arise each year in UK (11). The financial cost of schizophrenia arises in part due to the loss of productivity related to functional impairment, which affects some people's independent living skills and social, educational, and work performances. These stem from cognitive impairments, emotional disturbances, loss of motivation, compulsive voices and delusions,

distortion of thought, poor speech and language, psychomotor diminishment and self-harming features those people might experience (11).

Financial cost is not the only challenge in public health. Another important factor to consider is the onset of schizophrenia, which begins during adolescence. Lay et al., (12) and Ropcke and Eggers (13) in their 12-year and 15- year follow-up study, respectively, reported that the mean age of onset of the first psychotic episode is 16 years. Neuroimaging studies focusing on the age range of ultra high risk (UHR) individuals suggest that the mean age of the first psychotic episode is 19 years (14). The UHR is the stage of imminent and high of developing a first episode of psychosis, and the identification of individuals in this state helps significantly to delay the onset of FEP or even to prevent the onset of a psychotic disorder (15). The peak age of onset of schizophrenia ranges between 16–25 years, and it is preceded by a prodromal phase of symptoms or attenuated symptoms which are the first indicators showing that the individual is at enhanced risk of developing a psychotic episode or disorder (16). According to the National Alliance on Mental Illness, US, the prodromal phase also includes odd behaviours and a decline in functioning at school or work (see Figure 1.1).

Figure 1.1 Stages of Illness



(This is a modified figure from Lieberman and First, 2018. Original source:, (17)*)*

These challenges have led mental health services and psychiatric services to create multidisciplinary teams, which aim to integrate unique skills to meet the individuals'/patient's needs. It is no coincidence that the engagement of philosophical work with scientific processes, which was introduced during the 20th century, developed comprehensive accounts on the conceptual structure of psychiatry. The particular engagement has contributed to a more dynamic workplace where values and theories are connected with evidences, data and observations (18). Phenomenological theories about disturbances of the self and disorders' classification, reconnect the nature of the mind with the field of neuroscience; and the thought clarity with psychopathology and psychiatric nosology aspects (19).

Psychology is another area relevant to the understanding of schizophrenia. In psychological research we find relatively new accounts introducing cognition as a fundamental way people receive environmental stimulus. The impact the environment has on cognitive function is also highlighted/acknowledged. Social sciences use compassion–focused approaches to examine and assess patients and the field of biotechnology develops applications which represent the neural function of the brain and its dysfunctions using simulators. Neuroscience provides new neuroimaging techniques and many other ways for identifying neural dysfunction in certain brain areas such as Prefrontal Cortex (PFC), whereas economic sciences study the national financial costs, family, social and Health Services costs to provide solutions. To sum up, evidence suggests that such complex challenges affect many sectors in life, including health, society, economy and even politics, and therefore adopting a complimentary avenue of research might be the most efficient way to unfold such complexities.

1.2 Symptoms in Schizophrenia

1.2.1 Positive Symptoms

Schizophrenia is characterized by a multiplicity of symptoms that are complex and diverse that affect many fundamental mental activities (20). The most accepted classification is the one which divides symptoms into positive and negative, a terminology originated by the neurologist Hughlings Jackson (21). He defined positive symptoms as the result of a pathological insult to a higher level of brain functioning. According to his writings, (1984), the positive mental symptoms such as

illusions, hallucinations, delusions, and perceptual disorders are the outcome of brain dysfunction. The term positive is due to the fact these symptoms reflect an excess or distortion of the normal function (22). Positive symptoms are proposed to be excessive behaviour generated by neurophysiological systems that have been disinhibited by the original lesion (21).

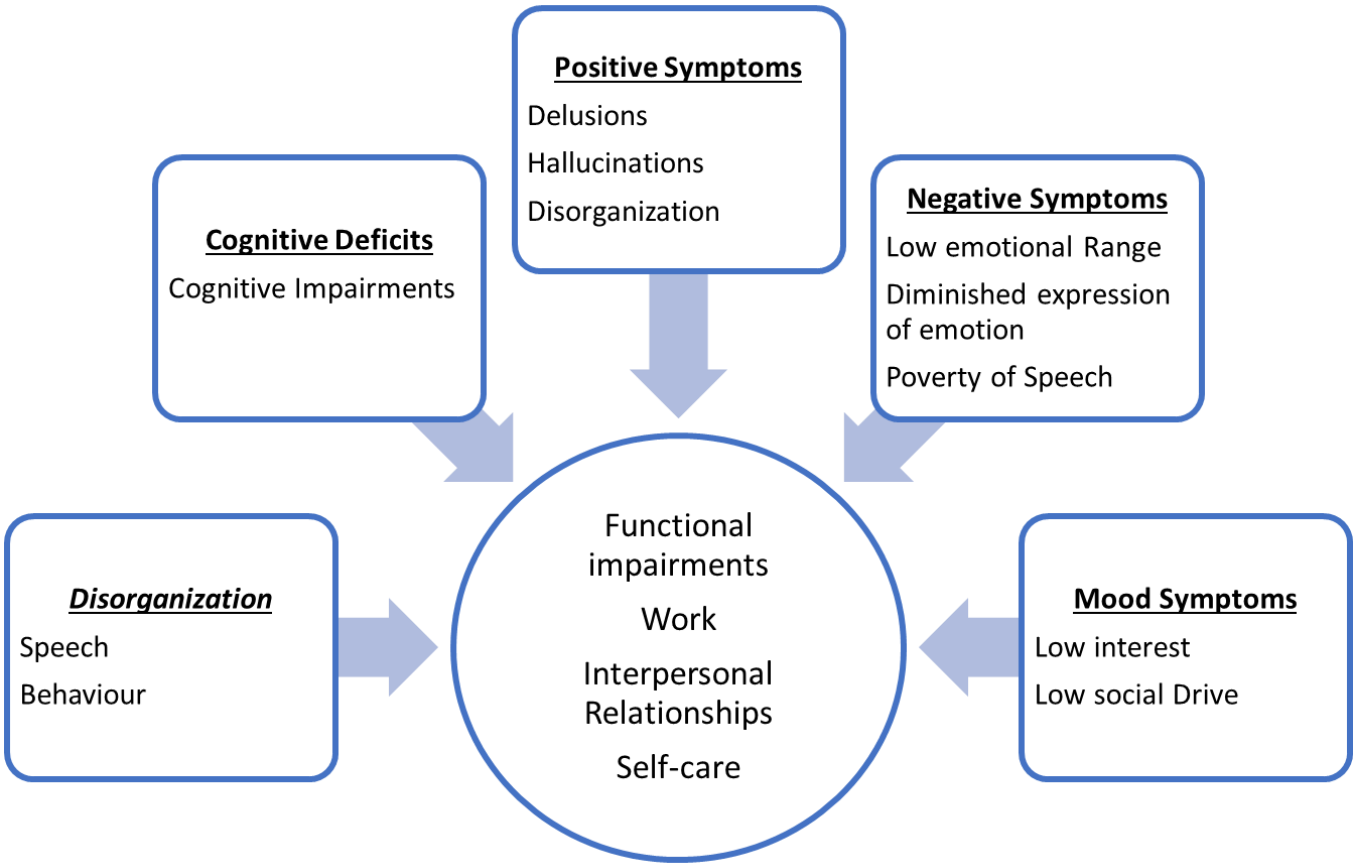
1.2.2 Negative Symptoms

In a contrast, negative symptoms represent the reduction in an individuals' performance according to a variety of functions. In much of the literature, negative symptoms are defined as ‘‘involving primarily an absence of normal functions’’ (19). Namely, negative symptoms reflect the diminution of normal function (22). Negative symptoms in schizophrenia are: blunted affect (lack of emotional display), loss of motivation, alogia (poverty of speech and content), apathy and avolition (lack of motivation, physical anergia, poor hygiene), anhedonia (diminished ability to experience positive emotions from pleasant events) (23), social withdrawal and poor psychomotor movement (24). Current studies suggest negative symptoms tend to persist longer (see Figure 1.2) and are more difficult to treat as antipsychotic treatments are overall effective in positive symptoms only (7). This differentiation of positive and negative symptoms has become a key factor for understanding the behavioural signs in patients and treating schizophrenia.

Unlike other conditions, schizophrenia is a condition in which dysfunction in many areas might be present simultaneously with several symptoms, including negative symptoms and emotional dysfunction. Kraepelin and Bleuler considered

disturbances in affect or emotional disturbances as primary symptoms in schizophrenia (25). However, nowadays, DSM-V (2013), categorises emotional impairment under the umbrella of negative symptoms. Under these terms, emotional disturbance refers to the negative symptoms which affect emotion function and expression. One of the negative symptoms strongly associated with emotion dysfunction is blunted affect which concerns emotion expressiveness (26).

Figure. 1.2 Symptoms clusters of schizophrenia



(This is a modified figure from Marder, 1999. Original Source: (27))

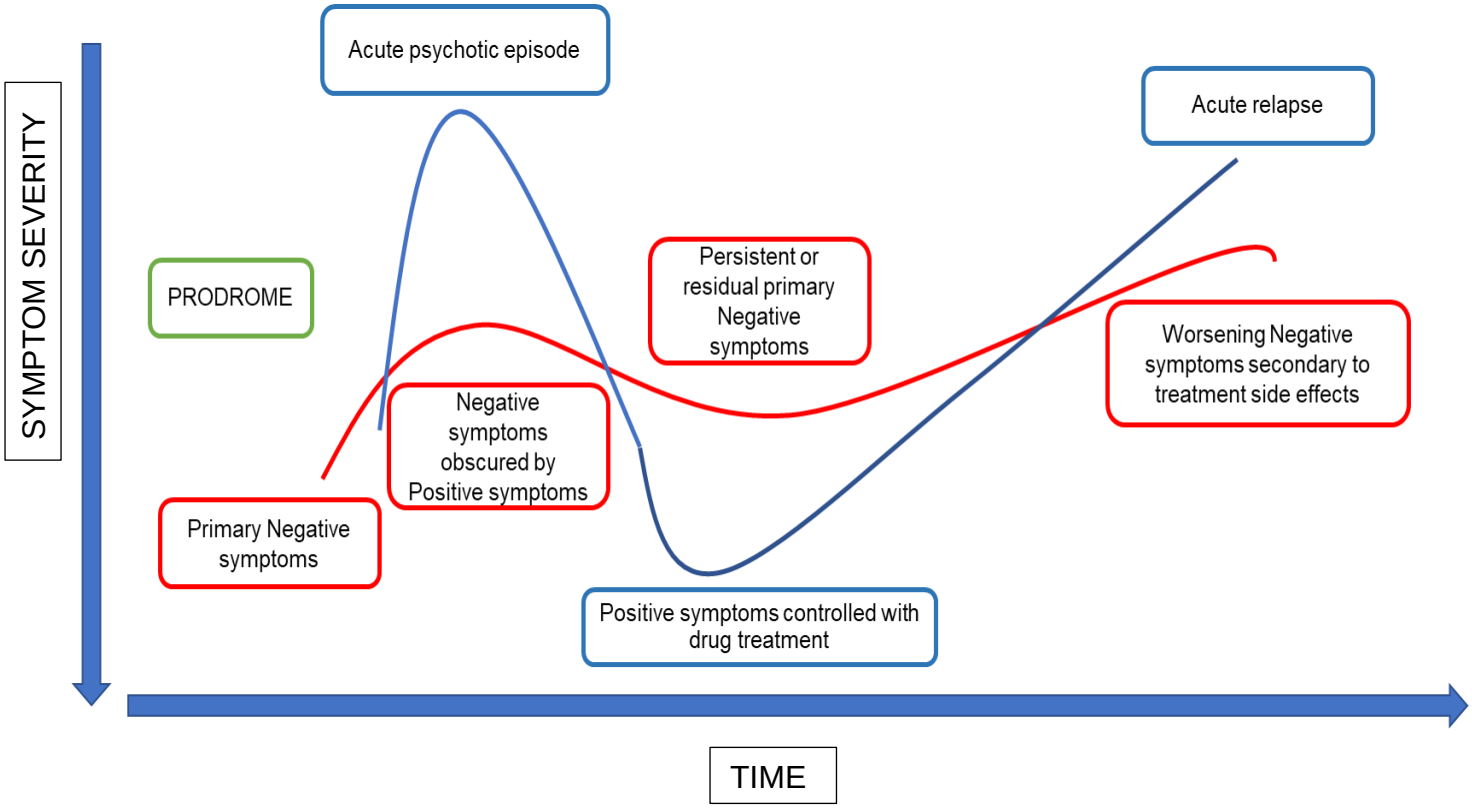
1.2.3 Primary and Secondary Negative Symptoms

Carpenter and colleagues (28) while examining the timing and duration of negative symptoms, suggested that negative symptoms need division into primary and secondary symptoms, as they do not present as a homogeneous entity.

The fundamental distinction between primary and secondary negative symptoms is that primary (deficit or enduring) negative symptoms are intrinsic to schizophrenia (29,30). Primary negative symptoms are part of the disorder itself. In contrast, secondary negative symptoms refer to negative symptoms that occur in association with, or are caused by, positive symptoms, neuroleptic – drug effects, depression, social/environmental deprivation, or chronicity (26,27). Primary symptoms are present during or between positive symptoms performance while secondary symptoms may not be persistent (see Figure 1.3).

This distinction seems to offer reliability in grouping negative symptoms and analysing the nature of each category (31,32). However, the attempt to disentangle the relation between primary and secondary symptoms remains quite complex and difficult to apply clinically, because of the potential challenges, clinicians might face in terms of the patients' clinical presentation.

Figure 1.3 Expression of Positive and Negative symptoms over time



(This is a modified figure from Möller, 2007. Original Source: (33)*)*

1.3 Depression in Schizophrenia

Depression is another common feature in schizophrenia. Findings suggest that depression rates in schizophrenia range from 7% - 75%, with an average rate of 25%. The rate of depression remains poorly understood since the cohort status, illness chronicity, assessment methods and medication contribute to the variability of the final estimation (34). Depression in schizophrenia relates to impaired functioning, weight loss or gain, anhedonia, dysphonic mood, impaired tolerance to normal stress and guilt (35). However, existing findings report that negative symptoms, such as

psychomotor retardation, lack of energy, diminished interest and activities, inability to form relationships with other people, sleep disturbances and loss of concentration, seem to be significantly associated with depression in schizophrenia (34,36).

1.4 Blunted affect and Emotion dysfunction in Schizophrenia

Blunted affect is the major negative symptom and the main interest of this thesis. Oorschot and colleagues (37), examining emotional experiences in negative symptoms in schizophrenia found that approximately one-third (33,2%) of the patients who experience negative symptoms in schizophrenia experience blunted affect. Blunted affect reflects a deficit of emotional and affective expression, a tendency to keep emotions hidden and unknown from others, together with a reduction in the intensity of an individual's displayed emotional response (11). The presentation of blunted affect, thus, is highly prevalent in patents who lack facial emotional expression (38). Studies that examine the affective experience in schizophrenia have used several clinical assessments such as Brief Psychiatric Rating Scale (BPRS), Schedule for the Assessment of Negative Symptoms (SANS), Emotional Blunting Scale (EBS) and Affective Flattening scale (AFS). All the above provide useful information on the symptoms of blunted affect, apathy, emotional shallowness and how these negative symptoms contribute to the decreased social functioning and interpersonal disengagement observed in individuals (39). These studies have observed that people with schizophrenia do not lack emotional and affective experience, as we might wrongly assume. Instead, they experience strong emotions in the presence of relative events. Namely, there is no difference in emotional experience in people with and without blunted affect (11,40,41). It is highly

important, thus, to highlight that blunted affect concerns the lack of the expression and exhibition of the emotional experience rather than the lack of the development of these emotions or even the content of patients' emotions.

Studies documented that patients with schizophrenia showing less outward emotional expression and high levels on emotional blunting compared to people without schizophrenia (42,43). It has been reported that difficulties in several expression modalities such as spontaneous emotional expression, smiling or gesture are also present in schizophrenia patients (44). Difficulties in emotion expression are not limited to the lack or reduced facial expression and therefore they have a critical role in patients' function and performance. Emotion abnormalities and emotional blunting are strongly related to social role and exposure, to the intention to communicate with others, to forming relationships and to being socially active (45).

Although people with blunted affect may experience sadness or fear with the same intensity, they cannot display this facially to the same extent (46,47). Darwin, in his writings on the expression and emotion in man and animals (48), explained that people with facial deficits remain motionless and passive with a pale face, and they seem like they are ‘‘drowned from their own weight’’(49). People with blunted affect often look inactive and static. Following the facially displayed cues, we can estimate the social situation of the person and therefore we gain an understanding of how socially active the person is. In other words, one's dysfunction on emotion expression may make it harder to other people to recognise his/her emotions and therefore, can lead people to develop certain social behaviours towards that person, due to the signals the first person gives to the later. One behaviour people might show to those who present a diminished or lack of emotion expression may be a

reluctance to interact with them or wrong judgments about them (i.e. assumptions of someone not being in distress or feeling emotion, as this is not as readily displayed facially). Such behaviours can make a person with schizophrenia vulnerable to social and emotional isolation as they start narrowing their network (47).

Blunted affect is an emotion impairment in schizophrenia that does not function independently and may interact with other negative symptoms such as anhedonia, alexithymia (the inability to identify one's feelings), social isolation and social withdrawal, affective non-responsibility and possibly with lack of empathy (50). Mueser et al., (51) found a link between facial emotion recognition and social competence, suggesting the idea that facial display affects our social life and roles. Consistent to presented findings, Hooker and Park in their study (52) identified that patients who reported emotion recognition deficits had more problems in social behaviour compared to those who did not report emotion recognition deficits, suggesting that the ability to express emotions, affects the ability to recognise others' emotions, improve social performance and ultimately exhibit a healthy social behaviour.

Further studies on emotion impairments in schizophrenia suggested that emotion dysregulation may trigger or add to the development of delusions. The idea that emotion disturbances might have a direct association to delusions is based on the cognitive models of psychosis development. In the case of anomalous conscious experiences (such as hearing voices or thought insertion) the adverse life events the patient might experience can trigger emotional changes. Such changes, though, seem to influence the content and perpetuate the occurrence of the delusions or voices (53). Fowler et al., (54), explain that hallucinations and delusions are likely to

mirror the content of emotional distress or depressive feelings the patient might experience and therefore, patients who struggled managing emotional distress (mainly patients who experienced anxiety and depression) were more likely to develop acute psychotic symptoms (55,56). This might happen because the processes between social anxiety, worry and persecutory ideation in schizophrenia have been suggested to have clear similarities and overlap (57).

Targeting such emotion and social difficulties might present a significant and novel strategy for improving our understanding on how individuals experience these difficulties. In turn, improved understanding might lead to the development of new pathways for effective treatments and interventions such as suicide prevention interventions in schizophrenia. Findings on emotion impairments in schizophrenia such as blunted affect introduce not only the potential link between emotion expression and social behaviour but also the fact that emotion impairment remains a largely unmet challenge in the treatment of schizophrenia.

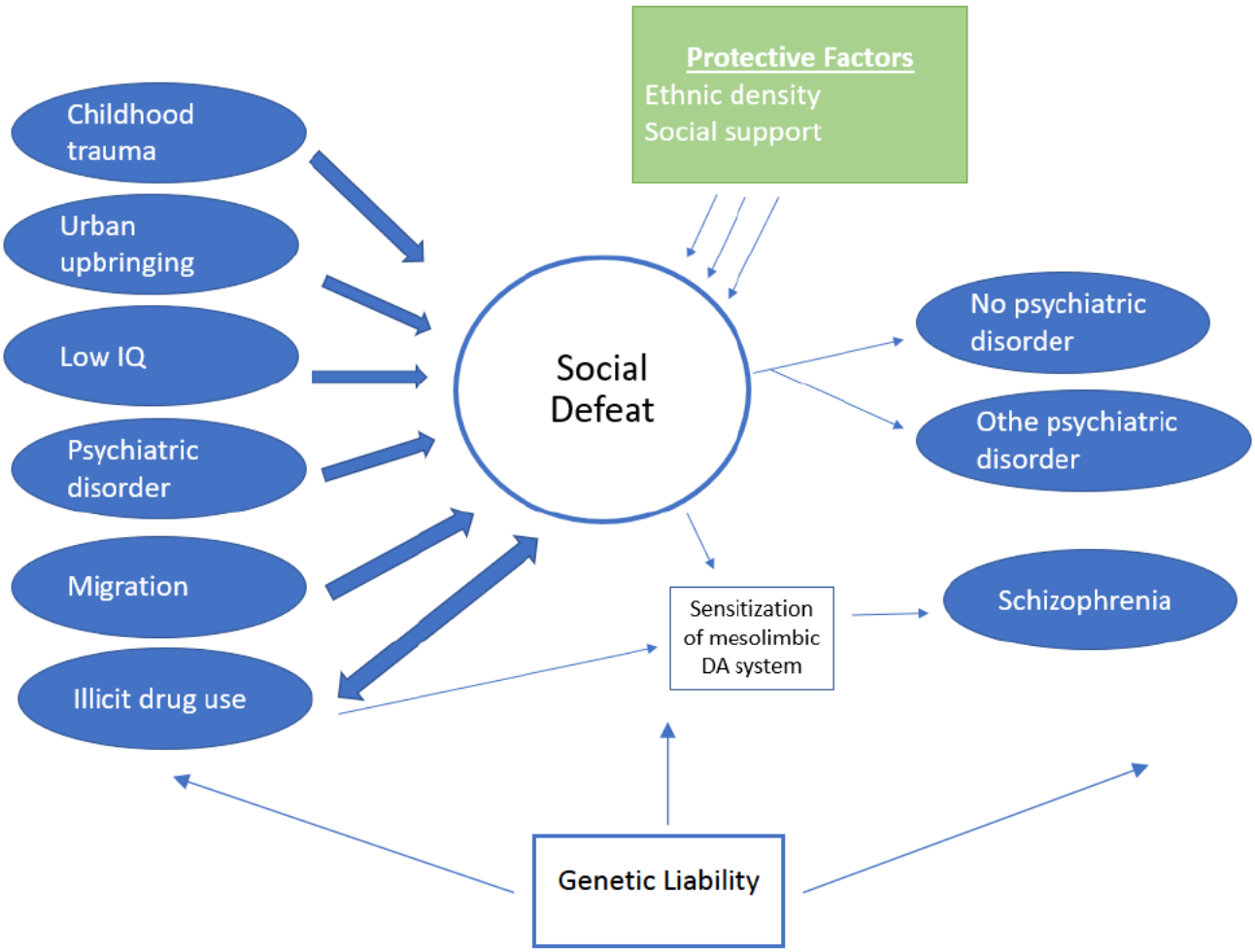
1.5 The role of social defeat in schizophrenia

As mentioned above schizophrenia is a multifactorial condition, and therefore existing literature provides different accounts on schizophrenia mechanisms. The two most prevalent attempts to explain the pathogenic mechanisms and origins of schizophrenia include the dopamine (DA) and neurocognitive hypotheses. Most recently, a cognitive approach of understanding the development of schizophrenia and psychotic symptoms gained interest from the research community (55). However, these accounts have not been satisfactorily integrated (58) as they seem

to act independently, which raises concerns since we know that brain systems and functions interact with each other.

On the other hand, the relatively new social-defeat or social exclusion hypothesis seems to integrate and explain the links to DA and cognitive hypothesis more satisfactorily and efficiently compared to previous hypotheses regarding schizophrenia origins. The social defeat hypothesis posits that the experience of social defeat or social exclusion may lead to changes to the dopamine system (DA hypothesis) which is either increased or decreased activity of the dopamine related brain systems. Social defeat has also significant effects on cognitive function, particularly on intelligence, (59) as socially isolated people report relatively less use of intelligence processing, because intelligence is tool people use to navigate the complex social structure, context and dynamics of human communities. Therefore, the lack of interaction with communities reduces the utility of intelligence. The idea of social defeat hypothesis is essentially broader than that of social withdrawal, as it also refers to other factors that contribute to the development of social defeat. Such factors include: being excluded from the majority group, urban upbringing, migration, childhood trauma, low intelligence, and drug abuse which have been reported as potential factors to contribute to schizophrenia development (60) (see Figure 1.4).

Figure 1.4 Schematic illustration of the experience of social defeat as the common mechanism underlying 6 major schizophrenia risk factors



(This is a modified figure from Selten et al., 2013. Original Source: (30))

Read et al., (61) in their review reported that several psychological and biological mechanisms related to social dysfunction and exclusion can increase the risk for psychosis through childhood trauma, including abuse and neglect. Cantor-Graae's (62) review which attempted to provide a biopsychological model of schizophrenia risk factors suggested that social deprivation, social adversity, poor education, and long periods of unemployment are associated with social isolation, social exclusion,

and risk of developing schizophrenia. More interestingly, these factors and particularly childhood trauma and neglect, seem to contribute not only to schizophrenia development but also to the suicidal behaviour in schizophrenia. In his study, Roy (63), reported that patients who had attempted suicide had significantly higher scores on Childhood Trauma Questionnaire (CTQ) for physical, emotional and sexual abuse and emotional and physical neglect, compared to those who had never attempted suicide. This might suggest that childhood trauma and neglect should be regarded as distal risk factors for suicidal behaviour. In other words, they should be considered as factors that are the foundation on which prevalent schizophrenia risk factors like substance abuse, stress or acute psychotic experiences are built on.

The experience of social isolation or exclusion, though, should not be considered as a specific cause of schizophrenia as many people exposed to such experiences develop other psychiatric disorders such as depression or social phobia, or none at all, and therefore, it is unlikely to be regarded a necessary or sufficient cause. In contrast, it should be considered as complementary to other hypotheses and models of schizophrenia development reporting proximal risk factors. This thesis focuses only on two main negative symptoms of blunted affect and social withdrawal and attempts to understand the general role of social isolation and social withdrawal in schizophrenia development.

As mentioned above, blunted affect and social withdrawal refer to the capacity to infer internal emotional states from facial expressions, social cognition, emotion regulation skills and expression of emotion. Targeting these symptoms in research might deepen our understanding of social behaviour, a fundamental question in

schizophrenia research. Moreover, understanding the significance of these symptoms might induce research into new pathways on how to manage and cope with social adjustment and challenges in our environment. The inability to express emotion and interact socially (46) might lead to problems regarding social role and to contribute to the challenges in schizophrenia, including suicidal behaviour and suicide.

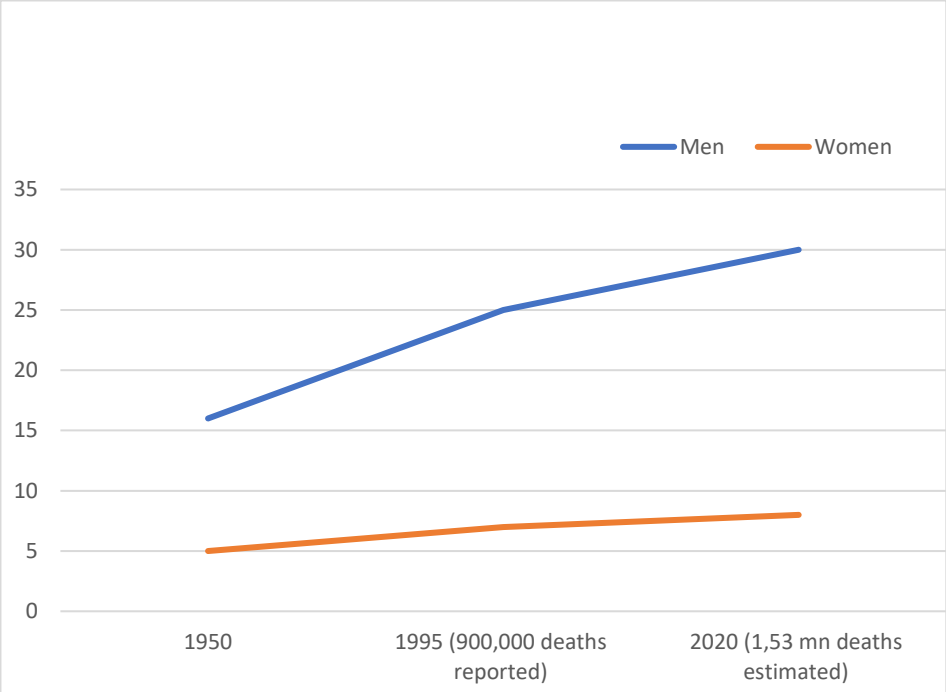
1.6 Suicide

Suicide is a leading public health concern worldwide and just over the last decades it has started receiving adequate scientific attention compared to other challenges such as heart disease or cancer. This is because of the highly increasing numbers over the last years and to the research on prevention and stigma. According to the World Health Organization (WHO) an individual will die by suicide somewhere in the world every 20 seconds (64) and approximately 1.53 million people will die by suicide in 2020 (see Figure 1.5).

Suicide is defined as death caused by self-directed injurious behaviour with intent to die because of this behaviour. However, suicide differs from the term *suicide behaviour* which, is broader. Non-fatal suicidal thoughts/ideation (thinking about, considering, or planning suicide) and suicidal attempts (engagement in potentially self-injurious behaviour in which there is at least some intent to die) are classified under the category of *suicidal behaviour*. Suicidal behaviour also differs from *self-harm* which refers to intentional self – injury, irrespective of type of motive or the extent of suicidal intent (65). The categorization of these conditions and their

reliability have been followed in clinical practice and research, contributing to better clarity and replicability in studies (66).

Figure 1.5 Estimation of global rates of suicides until 2020



(This is a modified figure from Bertolote and Fleischmann, 2002. Original Source: (67)*)*

The National Health System (NHS) in the UK estimates that 17 people die by suicide every day in the UK (68) occurring approximately 6,500 suicides per year. The Office of National Statistics in the UK, defined suicide as the first cause of death in young people in the UK (69). Research on suicide requires an adoption of a multifactorial investigation. The field expands on many areas such as suicide mortality, patterns in suicide methods, access to lethal means related to suicide, suicide rates based on indices of economic quality and inequality, suicide rates in different nations. Such attempts to understand suicide, reveal that suicide is a not a solely medical outcome, neither an outcome which affects certain age groups or countries only. Instead, it is a

complex outcome affecting all the age groups and people in the world regardless financial situation, social status, nationality, religious beliefs, or health conditions.

1.6.1 Risk factors for completed suicide

Suicide is rarely caused by one thing, most of the time it is an outcome followed by a combination of factors reflecting struggles the individual faces in different aspects of life. Research on suicide risk factors report the following as the main risk factors: financial crises/ unemployment, depressive feelings or symptoms, self-harm, gun ownership, family violence, impulsivity, history of suicide attempts, single marital status, lower social class, substance abuse, physical illness and psychiatric disorders (70–72). However, suicide in young people might be an outcome due to adverse childhood experiences and/or stressors in early life and recent events such as neglect and abuse, academic pressure, bullying or emotional distress occurred by social media (73,74). According to suicidal autopsies and assessments, almost 1 million suicides are reported in the western world each year, of which approximately 90% had a diagnosis of a mental disorder at the time of death and 12% of those suicides is attributable to schizophrenia (64,75,76).

1.7 Suicide in schizophrenia

One of the biggest challenges in schizophrenia is the high rate of completed suicide. Approximately 40% of premature and unnatural deaths in schizophrenia have been attributed to suicide (77) and around 12% of suicides worldwide is attributable to schizophrenia (75,76). Despite progress in treatment and mental health policies, the number of people who complete suicide per year is enormous and that makes

suicide one of the 10 leading causes of premature death globally (78). Existing literature gives an insight into the suicide risk factors and reports several factors that lead to suicidal behaviour (including suicide ideation and suicide attempt). The main factors that have been consistently reported in existing research are hopelessness, depression, positive symptoms and/or substance misuse (79). However, not all features of schizophrenia have been systematically examined in relation to risk of suicide. Although, negative symptoms may precede the emergence of positive symptoms, they attract less attention in risk assessment due to the diminished clinical presentation as these symptoms tend to persist as residual symptoms (80). Therefore, they might play a role in the development of suicidal behaviour in a non-obvious way.

1.7.1 Risk factors for completed suicide in schizophrenia

Several factors have been introduced as suicide risk factors in schizophrenia including the period of illness, psychotic symptoms, history of suicide attempts, male gender, substance abuse such as cannabis or alcohol, hopelessness, and hospitalization (75,81). Most reported suicide risk factors include depression, hopelessness and positive symptoms (82). While depression and hopelessness are not negative symptoms, they significantly affect the development and presentation of secondary negative symptoms. On the other hand, positive symptoms have been traditionally one of the main risk factors particularly in subjects at the early phases of schizophrenia or first-episode psychosis (FEP) (83).

As I reported above, negative symptoms have been poorly examined regarding their relationship with suicide. However, retrospective, and prospective cohort studies on completed suicide have highlighted the substantial prevalence of negative and depressive symptoms in schizophrenia with a score of 40% and 30%, respectively. In other words, that 40% of patients with schizophrenia experience negative symptoms while 30% of patients experience depressive symptoms (84,85). Certain negative symptoms such as diminished social functioning, social isolation and lack of motivation have been suggested to have a significant impact on suicide in schizophrenia as the sense of social isolation and inability to find a drive for something, seems to diminishes self-esteem, increases individual's social anxiety and intensifies the sense of worthlessness (86). Such conditions interact significantly with depression and hopelessness and therefore position the risk for a suicide attempt at a high level (87,88).

Research on negative symptoms is necessary to aid our understanding of schizophrenia and to the identification of treatments for schizophrenia. Negative symptoms can determine an individual's quality of life, ability to work and to live independently. Consequently, huge economic and social problems arise every year due to the prevalence of negative symptoms (30,89). Secondly, current pharmacological treatments are limited or in some cases they have no impact on negative symptoms; which leads to the need for further examination of those symptoms (38). The current gaps, therefore, regarding the link between negative symptoms and suicide make the aim of this thesis vital and significant.

Lastly, although this thesis focuses on clinical population only, it is important to report that the act of suicide does not affect clinical populations only. Suicide is a

multifactorial phenomenon and can affect people who do not experience any mental disorder (64). In fact, some of the risk factors are common in both populations. Brent et al., (90) in their study on suicide in adolescents reported that availability of firearms, family history of suicide or alcohol misuse are considered as suicide high risks independently of any psychiatric problem. In a later study, Conwell et al., (91) indicated that physical illness and functioning impairments are potential suicide risk factors and can be meditated by depression (particularly in elderly).

1.7.2 Suicide as a rational choice

Research on suicide motives and drives has contributed to our understanding of why these people choose to complete suicide. However, little has been done on whether these reasons (i.e motives, drives, intentions) can be considered as rational reasons or not, particularly in multifactorial conditions such as schizophrenia. The role of rationality in suicide research in schizophrenia should be taken into account as it provides an understanding on how patients interpret the option of suicide during their symptoms and why suicide has been reasonably seen as the only option left to reduce their suffering.

Theoretical accounts suggest that suicidal behaviour should be seen as an outcome related to emotional disturbances or mental illness the individual goes through in their life (92). Such conditions are not easy to cope with and therefore the action of suicide can be considered as a rational action in mental disorders. Oliffe et al. (93), reported that although the patients presented lower productivity and functionality, the way they were thinking about ending their life was quite rational. For example, a 43-year-old patient reported that: ‘‘As soon as you see some problems come up, you

worry and then it makes you depressed and you say ‘gosh’, you know, ‘how am I going to solve all those problems’ and then you feel like. You just want to die. You know, you, feel like you cannot live anymore’’.

However, in schizophrenia, even today, the possibility of rational suicide is not broadly accepted as psychotic symptoms have been seen to equate with a lack of mental capacity (94). Additionally, depressive or emotion related symptoms are considered as factors that prevent the function of decision making which is directly involved in suicide. An attempt, to examine further the action of suicide as a rational action in schizophrenia population could shed light on potential misunderstandings and misjudgements that are made about people with schizophrenia. It seems that a patient can make a sufficient comparison and eventually makes a rational decision between their two possible options that are presented with – the first option is to carry on living in their present or worse circumstances, and the second one is to end their life. The idea of rationality suggests that suicide can be explained under different perspectives which are not necessarily clinical, as some of the facilitating factors for suicide are part of a long-lasting vulnerability (95) and associate with several aspects in an individual’s life. Consequently, an attempt to integrate findings from different fields such as philosophy, psychiatry, psychology, and neuroimaging might potentially provide a multidimensional account of suicide in schizophrenia and give primary evidence as to whether this can be considered a rational act.

1.8 Neuroimaging in Schizophrenia

Over the last decades, research has shifted from traditional ways of understanding schizophrenia symptoms and outcomes to more complex and advance techniques that include the use of neuroimaging. The application of developing technologies to heterogenous and complex disorders like schizophrenia, has contributed to the advancement of hypotheses about functional and structural changes, symptom clusters and outcomes (96). As schizophrenia is disorder that affects the entirety of the brain rather than focussed on one key brain area. Hence, neuroimaging in schizophrenia has allowed detailed examination of the brain in different aspects such as: executive function, reward and salience, emotion processing and social cognition. Moreover, the field of brain imaging has been useful in defining abnormal circuits, namely potential disturbances of integrated activity in the brain which seems to play a crucial role in schizophrenia outcomes such as suicide (97). Therefore, including neuroimaging data in this thesis might also contribute to better understanding of underexamined symptoms and their associations to suicidal behavior.

Evidence on structural MRI in schizophrenia report correlations between certain symptoms and morphometric alterations in the Orbitofrontal Cortex (OFC), the insula and the superior temporal gyrus using region-of- interest (ROI) analysis (98–100). In their study, Meisenzahl et al., (101) found significant reductions in grey matter within the frontal, temporal and limbic lobes in people with schizophrenia. Other studies have suggested that patients with schizophrenia show volume reductions in other areas such as the amygdala and hippocampus (102,103). Further research has consistently reported the amygdala to play a significant role in schizophrenia,

suggesting that the amygdala is important not only for directing us to who we should trust (104,105) but also for the size and the complexity of our social network (106). Following this evidence, studies in schizophrenia suggest that poor functioning, poor social cognition and emotional disturbances might be significantly associated with the amygdala's processing capacity and size (107,108).

Other studies focusing on neural functioning in schizophrenia, observed differences in interregional functional connectivity during resting state mode (109,110). Resting-state fMRI has been increasingly used over the last years to examine functional networks in the entire brain in different populations without interference of tasks or stimulation (111). Studies examining the functionality in complex brain networks have found that such networks are less hierarchical, less clustered, and less efficiently wired in people with schizophrenia compared to those without (110,112). In their study, Lynall et al., (112), suggested that people with schizophrenia show less strongly connected, less globally integrated and less clustered brain functional activity and this might lead to impaired verbal fluency and slower processing speed.

Overall, and following existing evidence, it is clear that there is a significant contribution of neuroimaging in schizophrenia research. In the same way, the advances of neuroimaging might potentially contribute to understanding further challenges in schizophrenia, such as suicide.

1.8.1 Neuroimaging in Suicide

A better understanding of the pathological mechanisms leading to suicide is an urgent challenge in public health as prediction and prevention remains weak (113).

The individual's vulnerability to suicidal behaviour might lead to a completed suicide and therefore such vulnerability might reflect potential outcomes which affect many aspects of their life (95).

Studies on neuroimaging have strongly supported the idea of a vulnerability to (114) suicidal behaviour by providing evidence of specific brain regions which show reduced or impaired activity and therefore influence a greater risk to develop suicidal thoughts that carry on to a suicidal behaviour. Existing brain-imaging findings have been extracted by structural magnetic resonance imaging diffusion tensor imaging, positron-emission tomography, single-photon emission computed tomography, resting-state and task based functional magnetic resonance imaging. Although, the imaging methods vary across suicide studies, findings seem to be consistent about the importance of structure and function of the frontostriatal network and fronto-limbic structures, and the serotonergic system. Therefore, structural, and functional evidence has been reported as the source of crucial information about the brain structures and neural activity and circuitry associated with suicide risk.

Existing functional neuroimaging findings consistently report the role of ventrolateral and dorsomedial prefrontal cortex, the anterior cingulate gyrus, the amygdala, and medial temporal cortex in people who experience high levels of suicidal behaviour or attempted suicide (104). Those areas have been suggested to influence attention, problem-solving skills, verbal fluency, emotional distress, negative feelings and sensitivity to psychological pain which have been reported to be present in suicidal behaviour (115–117).

Research on connectivity and functional imaging suggest dysfunctions in certain brain regions and brain circuity. In their study, Vanyukov et al., (118) examined neural responses to emotional faces and their relationship to impulsivity in suicide attempters. They concluded that the participants who reported exaggerated responses to angry faces in fronto-opercular and dorsomedial prefrontal cortex, reported higher impulsivity, a main component of suicidal behaviour in schizophrenia and depression. Spoletini et al.,(119) showed abnormal brain structure and connectivity in frontal-temporo-limbic regions and suggested that OFC is another region associated with suicidality in people who experience schizophrenia as it concerns decision-making and though processing. They found evidence that points out the role of the frontal cortices and their connections to the suicidal behaviour. For example, in one study OFC dysfunction is considered as a potential biomarker for suicide behaviour in people with mood disorders (120). A different study reported that the OFC plays a significant role in human decision making particularly under uncertainty, a situation that many people with suicidal behaviour experience (121). Another study found that disturbance on closely-linked frontal cortical regions (including Prefrontal Cortex - PFC),which represent information about goals and decision making, might manifest disturbances on thought processing and behaviour control which might lead to suicidal ideation and behaviour in schizophrenia (122).

On the other hand, studies on structural MRI have reported that people with schizophrenia who have attempted suicide in the past, also have increased volumes of inferior PFC white matter (123). Giakoumatos et al., (124) compared patients with and without a history of suicide attempt. They also reported that attempters had significantly less grey matter volume in certain areas, such as bilateral inferior

temporal and superior temporal cortices. They also reported that suicide attempt was associated with significantly smaller volumes in the left lingual gyrus and right cuneus. Post-mortem studies found that differences in thalamus size and reduced number of axon terminals or dendritic spines (that represent the principal components of cortical synapses and transfer information) which might associate to poor functioning and suicidal behaviour (31,125,126).

Neuroimaging modalities provide a unique ability to shed light on current understanding of multifactorial and complex nature of suicidal behaviour. Such modalities give the opportunity to scientific community to explore in detail the relationships between cognitive, emotional, and behavioural components of suicide and the impaired neural function during the development of these thoughts and behaviours.

1.9 Summary and conclusion

Current research on schizophrenia includes the conceptualization and definition of symptoms, underlying mechanisms, and outcomes. The remarkable advances that have developed reveal the complexity of schizophrenia, which cannot be analyzed fully by following a single pathway. Therefore, the idea is that complexities in schizophrenia, such as suicide, should be understood by exploring multiple factors that potentially contribute. This requires the integration of different fields and perspectives. Thus, this thesis presents a review of existing evidence and new data investigating the association of under researched clinical factors, such as blunted affect and diminished social functioning, that might potentially contribute to suicidal

behavior. Furthermore, it examines functional brain changes that might be related to suicidal behavior and lastly, argues that all these factors should be considered in a framework against invariably, considering irrationality as an explanation for suicide in schizophrenia.

CHAPTER 2: AIMS AND HYPOTHESES

2.1 Aims

Conducting multidisciplinary research is a way to approach and understand a problem from many different perspectives. It is generally accepted that when examining complex issues, a holistic approach, which attempts to deal with the whole system will provide better potential for advancing understanding (127). Following the idea of multidisciplinary research, this thesis examines the issue of suicide in schizophrenia from three different perspectives that complement each other and offer novel findings.

The overall aim of this thesis is to examine suicidal behaviour in schizophrenia from multiple perspectives, with focus on the under-examined symptoms of blunted affect and social withdrawal. Furthermore, extending the examination to include brain function may further elucidate aetiological processes behind reasoned actions and contribution to suicidal behaviour. The multidisciplinary character of this project aims to present a deeper and more multidimensional understanding on the context of suicide; and how unmet social and emotional needs for connections and belongingness can make the action of suicide as an action based on rational reasons.

In chapter 3, I begin by approaching the problem of suicide in schizophrenia from a philosophical perspective. Exploring the underlying mechanisms of suicidal behaviour, and people's motives to complete suicide under the light of philosophy, will bring the opportunity to engage different interpretations of this human action. As Hume wrote, ''…it will here be superfluous to magnify the merits of philosophy'' since philosophy ''cures the human mind'' (128). Therefore, I find this reason adequate to

use the principles of philosophy as the first foundation to examine and understand a problem. Hence, chapter 3 aims to explore arguments of rational suicide and explain why suicide can be a rational action in general populations, but also that it can be a rational action in patients with schizophrenia. The significance of this chapter lies in the knowledge it will bring in terms of how certain symptoms, such as blunted affect and social isolation, are considered in the context of rational suicide. Overall, Chapter 3 is the starting point of this thesis, by which I present the theoretical background behind clinical concepts and a new attitude that we should adopt towards the people who experience suffering. Therefore, the objective in chapter 3 is to argue that people with schizophrenia may take their own lives based on rational decisions.

In chapter 4, I conduct a systematic review reporting existing evidence of the association between blunted affect and suicide in schizophrenia. As outlined in the introduction (See chapter 1, page 35), negative symptoms such as blunted affect, may lead to social isolation and thus contribute to a rational choice of suicide. This contrasts with actions in response to positive symptoms such as command hallucinations or delusional beliefs, which have been the predominant focus of past research. Chapter 4 aims to highlight the potential gaps in the literature regarding the association between blunted affect and suicide in schizophrenia, on the basis of current evidence.

Chapter 5 examines the problem of suicide in schizophrenia by adopting an empirical approach and explores whether symptoms of blunted affect and social withdrawal may be related to suicide. I aimed to address the evidence gaps highlighted in the systematic review (described in chapter 4) and explore potential

associations between blunted affect, social withdrawal, and suicidal behaviour in people with schizophrenia, by using quantitative research methods. The focus is on “first-episode psychosis” (FEP), given that in the earliest phases of schizophrenia, where negative symptoms first emerge, individuals have the highest risk for completed suicide. Quantitative research methods are deemed necessary in order to examine the specific development and impact of symptoms on patients’ life and function. This approach also allows us to conduct evidence-based research, which contributes to higher validity and reliability of outcomes. The objective in Chapter 5 is to examine suicidal behaviour in people with FEP and report the association of suicidal behaviour with blunted affect and social withdrawal by using validated and standardised measures.

As chapters 4 and 5 examine potential associations between specific negative symptoms and suicidal behaviour, an attempt to examine potential biomarkers of suicidal behaviour in schizophrenia would add on to the multidisciplinary approach. Such attempt will be relevant in understanding how changes in brain function might associate to suicidal behaviour. If suicidal behaviour in people with schizophrenia, who may have high levels of blunted affect and social isolation, is indeed related to clear underlying neurobiology, this may in turn question whether the choice to act this way (suicidal behaviour) can be rational. For example, if the choice is driven by a ‘disordered’ function of the brain, can this choice be rational? Therefore, Chapter 6 aims to explore whether people with FEP and high levels of suicidal behaviour show different brain activation during an emotionally relevant faces task, compared to those with low levels of suicidal behaviour. Examining whole brain activation and comparing people with schizophrenia who have high vs low levels of suicidality may

help to understand changes in brain function that may underlie these and shed light on the potential pathways that may lead to suicidal behaviour. Brain imaging methods can be an important tool which can show that human beings are not just behavioural beings, but these behaviours are driven by direct neuronal changes that significantly impact their overall function, behaviour, and cognition. Moreover, neuroimaging data may indicate potential relationships between cognitive- and emotional processing critical to developing the antecedents to completed suicide.

2.2 Hypotheses

The overarching hypothesis of this thesis is that suicidal behaviour in schizophrenia may be the rational act resulting from unending suffering and isolation. I hypothesize that lack of emotional expression and low social functioning may be significant risk factors for (rational) suicidal behaviour in schizophrenia. The inability to express one's emotional state leads to the inability to connect and interact, both socially and emotionally, with other people. Such associations might contribute to and predict potential risk for suicidal behaviour, which is one of the main challenges in schizophrenia research. Furthermore, emotional dysfunction in people with schizophrenia with and without suicidal behaviour may be related to how the brain responds to emotion-related tasks, further compounding risk of social isolation from a biological perspective.

Based on whether suicidal behaviour in schizophrenia is related to functional changes in emotionally relevant areas of brain activity, I further hypothesise that although the patient might experience a disordered brain function (particularly in

emotionally relevant brain areas), they are still able to see suicide as a rational option, since these factors potentially contribute to isolation and suffering.

CHAPTER 3: RATIONALITY AND SUICIDE IN SCHIZOPHRENIA: A PHILOSOPHICAL APPROACH

Part of the chapter (p.81 – p.985 follows Journal of Medical Ethics guidelines (published on 19th August 2019)

3.1 Introduction

Traditionally, rationality has been concerned with two specific aspects: firstly, the development of the norms of rational thinking and behaviour and, secondly, the reasoning procedures that satisfy them (129). The investigation of rationality, thus, can be pursued under different perspectives depending on the notion of rationality we adopt. In this chapter I focus mainly on instrumental rationality, although I will present another account of rationality (epistemic rationality) and show how each one relates firstly to schizophrenia and secondly to suicide in schizophrenia. I will first discuss epistemic rationality because it provides insight regarding certain aspects of the formation of some positive symptoms such as delusions and thought insertion. I consider epistemic rationality as the capacity to support belief-like states with evidence (130). Secondly, I will expand the topic of instrumental rationality and argue that instrumental rationality is particularly important as it relates to the justification of action and therefore will be examined regarding suicide. Instrumental rationality concerns the agents' intentions and the means they take to their ends. This is the focus of this chapter because it applies to suicide driven by negative symptoms as suicide is a form of action and the primary focus of this thesis. Since, historically, rationality has been considered as a determinant factor in suicide cases (131), it is crucial to examine how rationality relates to suicide in schizophrenia today, and how society, clinical practice, and research have shown significant progress.

Currently, it is estimated that up to 7500 people develop schizophrenia each year in UK. Schizophrenia has significant consequences, with 28% of the excess mortality in schizophrenia being attributed to suicide. Previous research suggests that suicide in

schizophrenia may be more related to affective factors such as depression and hopelessness, rather than psychotic symptoms themselves. Considering suicide in schizophrenia within this framework enables us to develop a novel philosophical approach, in which suicide may not be related to loss of self-consciousness, thought processing dysfunctions or perception disturbances. Rather than action of suicide being attributed to persistent hallucinations or other psychotic symptoms, such as delusional beliefs, it may be due to other underexamined, perhaps more rational reasons, such as extreme social isolation, severe depression, or emotional withdrawal or even awareness of the existence of these symptoms.

In this chapter, I aim to present the two different accounts of rationality and how they relate to schizophrenia and suicide. This chapter does not examine the moral character of suicide. Instead, it argues that we should conceive the action of suicide in schizophrenia as an act that is not necessarily irrational. People with schizophrenia might end their life based on reasons if suicide is the best means to achieve their ends. The chapter's objective is to present the two different accounts of rationality, provide a better understanding of the reasons people take their own lives and why we should see suicide in schizophrenia as a rational action. This work is based on the idea that a better examination of this topic will lead to understand better why people with schizophrenia attempt or complete suicide and will serve to build up effective interventions to reduce high rates of suicide.

3.2 Accounts of rationality

3.2.1 What rationality is and how it differs from intelligence?

Before any attempt to elaborate my argument on rationality and suicide, I need to define rationality and distinguish it from intelligence since in psychological literature rationality differs from cognition, wisdom, and intelligence. As my primary question in this chapter is to examine why people do what they do, I will use a definition of rationality that applies effectively to my interests. Therefore, I will examine rationality as the process in which one's actions or thoughts are based on reasons, and these actions or thoughts are irrespective of what these reasons are (132).

It would be incorrect to assume that rationality relates to high IQ or that rational actions are the socially acceptable ones. This is because IQ is just one cognitive domain, we can measure using intelligence tests and provides specific scores about specific skills. Furthermore, other domains, such as Emotional Intelligence and Social Cognition, seem to be more important in assessing people's judgment process, decision making and thought process (133). Rationality differs from intelligence as it refers to which means we select for our goals (instrumental) or how we represent the world via our beliefs (epistemic). Rationality is not a specific skill or a single cognitive domain such as intelligence. It affects several other skills, processes, functions and mainly actions.

3.2.2 Cognition and Social Cognition

Although, rationality is not the same with intelligence, it can be relevant to cognition and its functions. It is important to point out that cognition is as important as

rationality is, since symptoms in schizophrenia not only include irrational beliefs, distorted thoughts, or detachment from reality but also cognitive deficits and dysfunctions. Cognition mainly refers to mental abilities such as problem solving, remembering, learning, thinking, ability to succeed in reasoning tests and to achieve high IQ scores (134). The National Institute of Mental Health in Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (135), recently standardized the seven cognitive dimensions that people have. The six out of seven domains fall under the heading of neurocognition, while the function of these domains associate with specific brain areas. Six out of the seven domains of neurocognition are: 1) Processing speed, 2) Attention, 3) Working memory, 4) Verbal Learning, 5) Visual Learning, 6) Reasoning (136). The last cognitive domain relates to social cognition (perceptual and social skills) which is essential for the relations people build with the world and other people.

The National Institute of Mental Health (NIMH) consensus identified five relevant domains of social cognition: 1) Emotion Perception and Processing, 2) Social Perception and Social Knowledge, 3) Attributional Bias, 4) Theory of the Mind, and 5) The ability to make inferences about beliefs and intentions of others (136,137). Although research characterizes cognitive deficits in schizophrenia as neurological changes (136), there is much more work needed on cognitive deficits and social cognition which is a very recent challenge in the scientific field. Social cognition relates to emotion perception and understanding, a condition with significant implications as people with schizophrenia often present dysfunctions on emotion processing or salience of emotion (138). The reference of certain domains of social cognition aims to show that the concept of cognition is a multi-dimensional concept

and so it cannot be measured and interpreted by IQ only (139). Lastly, IQ measures or cognitive skills fail to explain the way we act the way we act or think the way we think and therefore approaches on social cognition and intelligence do not tend to measure rational thinking and action (133). Namely, they fail to provide explanations regarding my primary question: What leads people to act the way they act?

3.3 Schizophrenia symptoms and rationality

Schizophrenia is a condition characterised by a multiplicity of symptoms. According to the recent literature, there is no a single cause of schizophrenia (140,141) and the symptoms are characterised as complex and diverse because they affect fundamental mental activities (20). Although in the literature we can find many attempts to define these features appropriately and correctly, the most accepted classification of those is the one which divides the symptoms into positive and negative ones. The term positive refers to the fact they reflect an excess or distortion of the normal function (22). This is a distinction derived from the physicians John Russell Reynolds and Hughlings Jackson who defined positive symptoms as the result of a pathological insult to a higher level of brain functioning. They referred to the positive mental symptoms such as illusions (incorrectly perceived and misinterpreted sensory stimulus), hallucinations (hearing or seeing things that do not exist), delusions (unusual beliefs which are not based on reality) and perceptual disorders (confused thoughts) as the outcome of hyperactivity of nervous elements. In contrast, negative symptoms such as avolition, blunted affect, poor speech and thought process or impaired attention reflect the diminution or in most of the cases

the loss of normal function (20). The differentiation of positive and negative symptoms has become a key factor for understanding and treating schizophrenia is relevant to both clinical practice and research.

According to Andreasen, (20) positive symptoms are those which first call for clinical attention because they indicate the existence or the development of a psychotic disorder. On the other hand, negative symptoms seem to become more notable in the later stage of schizophrenia, (although these may be present during the early phase for some individuals). However, autobiographical reports from patients with schizophrenia demonstrate that often negative symptoms are not easily separated from positive; instead, they involve positive aberrations. In their research Huber, Klosterkotter and colleagues, found that even the most clearly negative symptoms are associated with disturbances which relate to positive symptoms such as disturbances in perception (hallucinations or delusions), impaired cognition and impaired bodily experience (142).

The categorisation and interconnection between symptoms are new developments in psychiatry which have been based on evidence and applications of certain methodology. Historically and even philosophically, this was not the case. Literature provides us with theoretical accounts written many years ago, characterised schizophrenia as a sole indicator or sign of irrationality. Such accounts can be found in ancient Greek literature, Roman years or middle age (143). However, today we face the same problem in a contrary way. We do not interpret schizophrenia as a sign of irrationality, but we tend to introduce irrationality as a mark of schizophrenia. We can improve our understanding around the relationship between schizophrenia and rationality by going back to the function and interconnection between the

symptoms and patients' presentation. For example, negative symptoms such as blunted affect, or poor speech do not seem to involve breakdowns in evaluation and judgment of events that are typical of irrationality whereas positive symptoms such as delusions and thought insertion are linked significantly to executive function.

This chapter aims to present that people with schizophrenia should not be characterised as irrational, since they are not necessarily irrational. Positive and negative symptoms people with schizophrenia experience are not forms of irrationality (not even forms of limited intelligence), even though the behaviour of people with schizophrenia might appear as violating norms of acceptability or rationality (144). From what has been observed, there appear to be cognitive and neurological dysfunctions, self-disturbances, perceptual misunderstandings, and consciousness's difficulty to process information which should not be considered as forms of irrationality.

Rationality and irrationality impact the thought processing, belief formation, intention, and action among clinical and non-clinical populations. Namely it plays a significant role when it comes down to reasons people have to act in a certain way. But this is not the only reason rationality examination is worthy. Such exploration will improve our understanding of emerging issues such as suicide which is the ultimate aim of this thesis. To better understand what rationality consists and when people act based on rational reasons, I will present the two types of rationality in relation to schizophrenia (epistemic and instrumental rationality). I will focus on instrumental rationality and the link between rationality and suicide in schizophrenia.

3.3.1 Theoretical Rationality and Positive Symptoms

In this section I will focus on epistemic or procedural rationality in relation to a) to reasoning tests and syllogisms and b) to beliefs. The first part relates more to cognitive functions and presents a neuropsychological perspective on how rationality works in schizophrenia. The second part concerns the relationship between subjects' beliefs of the world and whether these beliefs are responsive to the available evidence (130). The idea here is that epistemic or procedural rationality could be a matter of degree when is examined in reference to cognitive functions and abilities like IQ but also it concerns the way a person formulates a belief or a thought. For better coherence I will use the following definition: Epistemic rationality is the form of rationality which one displays when one believes propositions that are supported by evidence. In other words, ones' evidence must be undefeated and their beliefs must be supported by such evidence (145).

3.3.2 Procedural Rationality and Reasoning tests

Schizophrenia symptoms seems to affect patient's ability to be epistemically rational. Literature demonstrates a novel relationship between schizophrenia and epistemic rationality, reasoning tests and syllogisms which is explained by thought processing and how thoughts are formed in accordance with logical rules (146). Minkowski explains this by suggesting that people with schizophrenia are more likely to lack what is contextually adapted due to hyper-logic they have by saying that they are governed more by the logic of the world rather than the logic of logicians (146,147). Minkowski here means that people with schizophrenia form their beliefs and

thoughts based on their own perception of how the world exists even if this perception is disturbed or does not justify reality. They do not bother about the social norms or physical laws. Minkowski's idea can be justified and explained by the perceptual disturbances and cognitive deficits people with schizophrenia experience indeed. People with schizophrenia perceive reality in a different way than people without schizophrenia do. They possibly, thus, seem to construct their reality on different foundations (i.e people who experience delusions they perceive the world and others' behaviours in a much different or even bizarre way than non-clinical population do).

In their study, Owen et al., (148) measured rationality in people with schizophrenia using syllogisms and reported that patients with schizophrenia perform better in reasoning tasks than is usually assumed as they do not differ qualitatively from non-clinical population. The measures of rationality that were used by Owen and his colleagues showed that the same people are more rational in some tasks than controls (136). According to the same study, under conditions where reason and action conflict, people with schizophrenia seem to be more rational than healthy controls. In other words, they seem to perform better in generating reasons.

In contrast, Mirian et al. (149) in their study found that people with schizophrenia perform at low levels in reasoning tests. They attributed this to cognitive and neuropsychological dysfunctions. It seems that epistemic rationality is a matter of degree because solving a syllogism test is associated with intelligence which is a factor which varies from person to person (146,148,149). This is justified when we think that not everyone is efficient in solving test items, nor reflects high levels of IQ,

nor understands the content of certain arguments, neither our perceptual abilities such as perception is fixed and same in everybody.

Another study reported that people with schizophrenia possibly have a performance impairment in the syllogistic reasoning test (137), because of cognitive deficits which might impact the way they form arguments. Between 75% and 85% of the patients with schizophrenia exhibit mildly abnormal intellectual functioning, including below normal IQ, poor speech, abnormal declarative memory, working memory, attention and executive functioning (139,150). However, it is unfair to claim that a person is irrational based on his inefficiency to solve a syllogism tests or a lower IQ, nor would be accurate to name a person as irrational due to other cognitive deficits such as deficits on working memory or emotion perception. Although, some people with schizophrenia fail to deliver a good performance in reasoning tests and syllogisms and fail to perform cognitive functions (137), this should not lead to the conclusion that these people lack rationality, but rather, they experience clinical symptoms which affect their overall performance and sometimes determine it.

3.4 Epistemic Rationality, Beliefs and Thoughts

Rationality is associated with beliefs. As I presented above, people with schizophrenia perceive and understand the experiences under different terms. However, we do not know whether their beliefs and thoughts are totally unconnected with real aspects of a patient's life nor do we know how they formed these beliefs and thoughts. Thus, the different approaches of rationality are of great interest in scientific research since they explain certain features of the thinking process in

patients' performance such as delusions, hallucinations and inserted thoughts which can be rationally assessed.

For example, positive symptoms impair the thought processing, beliefs' formation, perception of reality and cognitive processes which are the main components of epistemic rationality. On the other hand, negative symptoms such as poverty of affect or flat affect, social withdrawal or poor speech do not seem to involve breakdowns in thought processing or belief formation which relate to epistemic rationality. Negative symptoms seem to affect the willingness to carry on out an action, the development of motivation and the intentions, which are very important conditions of instrumental rationality (151). It is therefore important, to explain the relation between positive symptoms and epistemic rationality and mainly the role of delusions in epistemic rationality. Delusions can be explained under different perspectives such as false beliefs or even cognitive mistakes (152) and therefore a presentation of these accounts would be beneficial in terms of understanding how epistemic rationality works in people with schizophrenia.

3.4.1 Delusions as false beliefs

The *Diagnostic and Statistical Manual of Mental Disorders, fifth* edition (DSM-V), defines *delusion* as: ''Fixed beliefs that are not amenable to change in light of conflicting evidence. Their content may include a variety of themes (e.g. persecutory, referential, somatic, religious, grandiose). […] Delusions are deemed bizarre if they are clearly implausible and not understandable to same-culture peers and do not derive from ordinary life experiences. […] The distinction between a delusion and a

strongly held idea is sometimes difficult to make and depends in part on the degree of conviction with which the belief is held despite clear or reasonable contradictory evidence regarding its veracity'' (153).

It follows that delusions are formed beliefs that lack evidence of justification. Namely there is no connection between a belief or thought and the available evidence of this belief or thought but our beliefs should relate and respond to the available evidence (154). Particularly, beliefs need to be supported by and responsive to the evidence. What we call delusions reveals a kind of misconnection between the belief or thought itself and the reason this belief or thought developed. Moreover, there is a vital difference between the development of the positive symptom of delusions and the maintenance of this symptom. It seems possible that the formation of the delusions, which an individual holds, can be rational (151) whereas the maintenance of the delusions might be due to other mechanisms.

In his paper, Bentall (155) explained the formation of false beliefs or delusions and argue that they might emerge due to the misinterpretation of social interactions and events rather than interpersonal disturbances. For example, a person experiencing delusions is preoccupied with others' intentions and they might have reasons for this. In other words, they are preoccupied with a belief which relates to their social interactions with others and inferential processing. Following this, the maintenance of delusions might depend on the struggle people experiencing delusions face to build social relationships. There is no doubt the mechanisms underneath delusion formation and maintenance are much more complicated and involve cognitive and neural function as well. However, what Bentall argues is that we might find an answer if we look at social functioning and other psychosocial areas without avoiding

the fact that social functioning and inferential processing are brain processes. By suggesting this, Bentall avoids classifying delusions or other positive symptoms as irrational marks but rather suggests having a deep look on how these people shape relationships and perceive reality.

Literature on delusions provides several ways we could examine the topic. The presented concept explains delusion as a false belief due to the gap between this belief and the justification of this belief. However, there are two more accounts of delusions which attempt to explain delusion formation. The first one is the empiricist approach and provides explanations based on functional and neurocognitive processes. The second one is a phenomenological approach which refers to patients' insight disturbances.

3.4.2 The Empiricist Approach to Delusions

Brendan Maher argues that delusional beliefs are attempts by the deluded person to explain something the person, otherwise is unable to explain. He also suggests these delusions are due to neuropathologic factors (152) or a brain damage. The empirical concept of delusions argues that people with delusions are not irrational but are the result of cognitive dysfunction. This account adopts a neurocognitive and neuropathological perspective and according to it, a brain dysfunction is responsible for the occurrence of certain positive symptoms people with schizophrenia experience such as delusions and thought insertion (140).

This cognitive model of delusion has been explained in detail by Chris Frith (155) in order to provide an understanding of the thought insertion occurs in patients.

According to Frith, delusions are held to be a result of a dysfunction in normal cognitive self-monitoring. The main idea is that there is a misconnection between the intentions and the actions of a person. The person fails to recognize that an action or a thought developed due to his own willingness to develop this thought or to do that action. The result, thus, of this cognitive dysfunction is that the person misrepresents the intention as not originating in the self and therefore they get confused about why they acts in that way or why they have this belief (152,155). The person then is looking to justify this thought or intention for an action but they fail to recognise their own intention and so they attribute responsibility to external sources which, according to the patients, have generated these thoughts, intentions and actions (152,155). Consequently, the person seeks to explain these experiences as external experiences which have developed due to some other agent and therefore, delusions result.

Frith's model interprets an account of delusions' formulation based on how cognition functions; it is true that there are cognitive disturbances in schizophrenia and existing findings insist that positive symptoms possibly relate highly to these cognitive disturbances (136). For example, Firth suggested that delusions occurred due to individual's inability to represent others' beliefs and thoughts; a cognitive ability and broadly recognised named as Theory of Mind. Furthermore, he explained that these psychotic symptoms arise as a result of a cognitive deficit to infer what is on other's mind (155). Even if we are not confident to support the cognitive approach there promising evidence supporting delusions may be a result of a brain dysfunction or due to changes resulting from neuropathology of the brain (156). However, objections to this account exist as well. The main objection the neurocognitive and

biological accounts faced is that such accounts provide no explanation of the content these delusions occupied. Even more, if we accept that the formulation of delusions can be explained by cognitive theories and relates to cognitive dysfunctions, the main problem remains. The current approach fails to explain the delusional content itself. Too often, the deluded person acts rationally in accordance with his apparent delusion content, and as Klee mentions this makes up an irony: We render the sufferer's behaviour rational by attributing to him or her a belief that is itself irrational (141).

3.4.3 The Phenomenological Account of Delusions

The use of neuroimaging is a new era on delusions examination and even so is a well-formed account which provides significant evidence on how brain works in relation to thought processing and cognition. However, it cannot provide us information about the content of these delusions, whereas theoretical accounts seem to interest in examining the deep nature of these strange beliefs.

Sass attempts to solve the problem of delusions content by developing a conceptual analysis on the hyper-reflexivity of consciousness people with schizophrenia experience. He suggests that, the exaggerated process of self-consciousness is the reason people with schizophrenia experience positive symptoms, mainly delusional thoughts or auditory hallucinations (142,157). Sass explains consciousness' hyperactivity using phenomenological terms, which is in contrast to Gerrans who suggests a neurocognitive model of delusions (156). Sass suggests that schizophrenia is a self-disturbance and therefore the insight of the person is

impaired (158). Sass's definition of schizophrenia suggests that fundamental abilities such as agency, intentionality, motivation, affect, awareness, and first-person perspective of the world are not impaired due to neurological dysfunctions but rather due to a hyperactivity of the consciousness which produces a failure of self-awareness (145). Namely, the individual lacks the insight that she is the subject of her own experience. There is a diminished vitality of person's self-presence.

Nelson et al. in their study argued in favour of what Sass proposed and they suggested that the phenomenological model of the disturbance of the self might be the core marker of schizophrenia spectrum disorders (159). They found considerable clinical evidence which links the phenomenological concept of self-disturbance with the fundamental feature of schizophrenic prodromal. Their findings insist the experience of schizophrenia represents the distorted perspective of the self, a loss of the sense of ‘‘mineness’’ on the one hand, and a heightened awareness of an experience, on the other hand (146). They also referred to qualitative studies suggesting that a disturbance in self-awareness is the earliest and fundamental feature of the prodromal of schizophrenia.

In agreement with this perspective, Gold and Hohwy, (129) suggest that delusions and hallucinations are due to a failure of the egocentricity of the patient. They define egocentricity as the property of a thought which allows the thinker to recognise this thought as having originated in his own mind. They carry on that the subject is not aware that a thought or a hallucination is originated in his mind. The central aspect of this egocentricity model is the link between the awareness that someone creates a thought or a belief and the awareness that I am this person. Therefore, the lack of transition or the gap between these two kinds of awareness is what leads to

delusions. Gold and Hohwy interpret egocentricity as rationality since according to them egocentricity without disruption is a condition of rationality and therefore, the impaired egocentricity is a form or irrationality (119).

3.5 How does theoretical rationality relate to schizophrenia?

In previous sections I have presented the account of epistemic rationality and the two different approaches to whether delusions are failures of epistemic rationality. However, the reason it is difficult to explain whether people with schizophrenia are rational (based on their positive symptoms such as delusions or hallucinations), it is because there are different types and degrees of rationality. What happens in schizophrenia is that some parts of rationality are impaired (144,152) but rationality is not globally impaired. Gold and Hohwy support the idea that irrationality is not a unitary concept (129), an idea which Garety and Hemsley explain by saying there are some notions of rationality that have a constitutive role and that delusion may fall outside the scope of the notion of rationality we adopt (160).

However, Klee's argument about the formation of delusion states that the person accepts these false beliefs because their cognition falls below the normal standard of rational coherence that is otherwise necessary for healthy cognitive operations and not because of lack of rationality (152). Klee's argument is supported by studies on cognitive function showing that people with schizophrenia are more likely to display low levels of cognitive processing (161,162) and should not be characterised as irrational. Instead, some aspects of their rational thinking and cognitive processing fail to get completed. Broome seems to corroborate this concept suggesting that

although beliefs such as delusions may prejudice reasoning, patients are keen to point out why other deluded patients are mistaken about their beliefs (144). Another study on social knowledge and insight demonstrated that patients with schizophrenia were able to make sensible and reasoned judgments of social situations outside of their own personal experience or relation to illness (163). Consequently, their inferential ability might not be impaired and therefore it should not be ruled out that they can appreciate at some stage that their delusion is a false belief.

What follows here is that people with schizophrenia are not necessarily epistemically irrational. The fact these delusions are not in agreement with what we perceive as real does not necessarily mean that the people who experience these delusions are irrational. Our ability to evaluate others' beliefs is limited because we often ignore or do not have sufficient information about the content and causes of these beliefs. This happens because we are unable to have a first-person perspective on the person's beliefs.

People with schizophrenia can adopt false beliefs, and I have given two explanations of these in relation to judgements of rationality. The first one is the empirical approach/neurocognitive of delusions and the second one is the phenomenological one. People with schizophrenia experience delusions either due to a biological impairment or due to a disturbance of consciousness and their inner world. If we accept the first account, we must explain what the content of delusions is and how this content is been formulated. If we accept the second approach, we must argue in favour of the idea that consciousness can be disturbed. This chapter, though, is not about adjudicating between these approaches or proposing a hybrid theory incorporating aspects from both approaches. Rather, the chapter focuses on

rationality with respect to the action of suicide in schizophrenia. That is why we are going to leave behind the question whether people with schizophrenia are epistemically irrational and to ask instead whether they are instrumentally irrational, as this will help us establish how they make decisions. Can suicide in schizophrenia be a rational action?

3.6 Theoretical Rationality and Suicide in Schizophrenia

Although, this chapter focuses on instrumental rationality and negative symptoms (see below), it is important to at least report briefly whether a suicide driven by positive symptoms can be a rational suicide as well. It is very important to distinguish between an instrumentally rational suicide and epistemically rational suicide, as each type of suicide is defined differently. In the case of a suicide driven by positive symptoms (which is not uncommon in schizophrenia), we can say that this suicide is rational as long as it is examined under the light of epistemic rationality. An epistemically rational suicide is the suicide that is adequately grounded or mandated by the situational evidence (164). In this case such evidence are the main positive symptoms of command hallucinations, delusions and thought insertion which have been consistently reported to play a significant role in suicide in schizophrenia (91).

The reason we face this challenge here is that if we try to argue that a suicide driven by positive symptoms is an instrumentally rational suicide, we are at serious risk to fail arguing in favour of this statement, because the nature and clinical characteristics of positive symptoms do not meet the requirements for an action to be instrumentally rational (compared to negative symptoms which meet the

requirements). Positive symptoms tend to distort reality and the perception about the current situation (165), which is likely to lead to inconsistencies between the means and the ends (which is the main criterion for an action to be instrumentally rational – see later in this chapter). Studies on positive symptoms and cognition indicate that such reality distortions relate to misattributions and altered perceptions of environmental cues, such as situational context (155,160). Delusions are one of the main suicide risk factors, associated with attentional bias toward threatening information received from the environment and with a tendency to misattribute meaning which leads to wrong expectations (160).

The nature of positive symptoms, thus, incommode us to argue that positive symptoms should be examined under the light of instrumental rationality, since a suicide driven by positive symptoms, is an outcome followed by a command that the person somehow receives (and cannot ignore–such as a voice or a thought to kill themselves) rather than by their genuine will or intention that aims to an outcome (instrumental rationality). As Frith mentioned in his study in 1987, ‘‘positive symptoms involve a dissociation between will and action such that the patient fails to perceive his actions as a consequence of his own will’’ (166). This leads to argue that a suicide driven by positive symptoms should be examined under the terms of epistemic rationality which refers to the content of the beliefs the patient holds and how these beliefs impact patients’ actions.

The paradox, therefore, on whether people with schizophrenia can be rational in the case of suicide, can be solved only if we examine each case of suicide based on the type of symptoms that lead to the suicide. Namely, to see each suicide as a unique case. The implication of examining each case individually has significant implications

for research and clinical practice. Firstly, is prevents us from generalisations that are likely to lead to bias in research and secondly, and most importantly for this chapter, it allows us to be fair with everyone who is dealing with suicidal thoughts, as rationality has not been seen as a privilege for a group of people (as it happens currently whereas we regard suicides in non-clinical people as rational and suicides in clinical population as irrational) but rather as a quality that everyone shares. The point where epistemic rationality differs from instrumental rationality is in the object each account has. Instrumental rationality concerns the planning and execution of action while epistemic rationality concerns the formulation of a belief or a thought (167). The principles of instrumental rationality are constitutive principles of rational agency and volitional activity whereas this is not the case in epistemic rationality. As this thesis focuses on the action of suicide, in the following section, I will present instrumental rationality and the link to suicide in schizophrenia.

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Instrumental Rationality and Suicide in Schizophrenia: A Case for Rational Suicide?

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3.7 Abstract

It is estimated that up to 7500 people develop schizophrenia each year in the UK. Schizophrenia has significant consequences, with 28% of the excess mortality in schizophrenia being attributed to suicide. Previous research suggests that suicide in schizophrenia may be more related to affective factors such as depression and hopelessness, rather than psychotic symptoms themselves. Considering suicide in schizophrenia within this framework enables us to develop a novel philosophical approach, in which suicide may not be related to loss of self-consciousness, thought processing dysfunctions or perception disturbances. The action of suicide may be due neither to persistent hallucinations nor other psychotic symptoms, such as delusional beliefs, but to other underexamined, perhaps rational reasons, such as extreme social isolation, severe depression, or emotional withdrawal. This paper does not examine the moral character of suicide. Instead, it argues that we should conceive the action of suicide in schizophrenia as an act that is not necessarily irrational. People with schizophrenia might end their life based on reasons if suicide is the best means to achieve their ends. However, the paper does not support assisted suicide. It aims to provide a better understanding of the reasons why people take their own lives and suggests that understanding can inform effective interventions to reduce high rates of suicide.

3.8 Instrumental Rationality in schizophrenia

There is also a reason why examining suicide is important. It is the most inconceivable of human acts that has been examined by multiple perspectives, yet remains unexplained with, and is an inconsistent concept in, modern societies. However, philosophers and physicians have been interested in suicide since Plato's time (1). One of the reasons why suicide has attracted greater attention recently is that there is an increased awareness of mental health challenges in our society and particularly there has been progress in the research surrounding mental disorders which might lead to suicide or might manifest in self-harming behaviour. We now believe that several mental disorders are strongly related to suicide or suicidal behaviour and they have been indicated as suicide risk factors.

Going back to ancient times, in his book ‘‘The Holy Disease’’ Hippocrates first examined empirically the conditions of epilepsy, madness and confusion. Although Ancient Greeks considered these conditions as possession, or the effect of a supernatural power, (143), Hippocrates suggested that these conditions stem from brain activity. He introduced the idea that happiness, laughter, neurosis, madness and confusion are outcomes of how our brain works: ‘‘The same organ makes us mad or confused, inspires us with fear or anxiety”,(169). The concept of madness in Greek and Roman times inspired people from different fields to focus on empirical examinations. Ancient physicians reported several expressions of madness or insanity (schizophrenia is a later term for this). Examples of such expressions are Achilles and Ajax who displayed a madness of the warrior because of the events that occurred during or after a battle; Dionysus who expressed a madness that unlocks destructiveness, by distorting his identity for revenge; and even Nero who

experienced a madness of the emperor due to his increased need to fulfil his desire for lust and power. Such expressions had been linked with bizarre behaviour and excessive imagination (ancestors of today's hallucinations and delusions) or with melancholy and sadness (similar to today's depressive signs in schizophrenia).

In the ancient times, insanity was recognised as one of the reasons why people completed suicide. In his writings, Herodotus reported how the king of Sparta Cleomenes became mad and completed suicide due to the loss of the reputation he experienced as a king. Writers mentioned Cleomenes forced a guard to hand him a knife with which he ''sliced his flesh into strips'' and died,(143). Although this is not the only case in the literature, it is a starting point for introducing the idea of this paper. The case of Cleomenes demonstrates the idea that suicide can be rational even when the person completing suicide is not mentally stable. People linked the bizarre behaviour of Cleomenes to his unstable mental condition after he was defeated. His choice to complete suicide was motivated by reasons and was not necessarily to be viewed as irrational. He was a king and he faced absolute failure. He had been admired by the Greeks and later he lost their devotion. This was a situation Cleomenes could not afford due to the value of being a king in those times.

Thousands of years later, the symptoms and other aspects of schizophrenia make people struggle with their day to day life. Schizophrenia is a condition affecting approximately 1% of general population,(78), whereas 5.6% of those complete suicide per year,(5,6). Examples of completed suicide in schizophrenia underpin our explanation of relevant causes. A study examining depression and suicidality in people with first episode psychosis reported that 63% of patients expressed suicidal intent or worse during the first 18 months of their interview,(172). In his review Siris,

assessed the features that might be indicators of suicide in schizophrenia and reported factors such as being unemployed or unmarried, having a negative attitude towards life, living alone, homelessness, having recent traumatic events or being aware that life expectations are unlikely to be met, were major factors associated with suicide or suicide attempts,(173). Another study considered suicidal ideation in schizophrenia as a rational response to unendurable suffering due to reduced quality of living and the patients' high awareness of their condition,(94). We could say that research suggests that suicide in schizophrenia is not an irrational act, as it is not based on people's psychotic symptoms but on their assessment of how their lives are going. However, we first need to examine what it means to say that suicide is not irrational as a response to life events.

Traditionally, rationality has been concerned with two specific aspects: firstly, the development of the norms of rational thinking and behaviour (*substantive rationality*) and, secondly, the reasoning processes that satisfy them (*instrumental rationality*),(129). The investigation of rationality, thus, can be pursued under different perspectives depending on the notion of rationality we adopt. It is interesting to consider the rationality of completing suicide in general, and especially in people who experience a psychiatric condition. Actions such as completing suicide in the clinical and non-clinical population can be considered in the light of instrumental rationality. Instrumental rationality concerns the means one takes to achieve one's ends. Instrumental rationality has been defined in a variety of ways, but we will use the following definition: Instrumental rationality concerns the planning and execution of action,(167). Can we talk about instrumentally rational suicide in a clinical

population experiencing schizophrenia? Do patients simply decide to take the best means to achieve their own death and succeed?

Instrumental rationality refers to which decisions and actions approximate the best ways to achieve one's goals. A person is regarded as instrumentally irrational, if they display behaviours, thoughts, beliefs, actions, desires and intentions which do not further the fulfilment of their goals,(146). The coherence of this kind of rationality depends on the relation between the means (a person's behaviours, thoughts, beliefs, actions, desires, and intentions) and the ends (the person's actions). Thus, means and ends, intentions and actions, motivations and attitudes must be a coherent fit with the person's goals,(167) for instrumental rationality to be achieved.

However, to apply the concept of rationality to people with schizophrenia seems complicated for two reasons.

Firstly, schizophrenia is a condition with diverse types of symptoms which affect patients' beliefs and actions. For example, common symptoms include holding false beliefs, hearing command voices or display a blunted affect, which impact on people's actions. However, instrumental rationality concerns the relation between beliefs or intentions and actions and not how the beliefs or intentions have been formed. Therefore, if the belief or the intention is delusional it does not necessarily mean that the person is instrumentally irrational. Thus, questions concerning how perceptual disturbances (such as auditory hallucinations) or inserted thoughts occurred and why these symptoms might lead to false beliefs are not relevant to an assessment of instrumental rationality. The primary aim of instrumental rationality is to examine whether a person's behaviour is conducive to the 'desired' ends.

Secondly, there is an old idea that rationality is a mark of sanity while irrationality is a mark of insanity. This idea has recently been challenged based on (a) the psychological support for the view that non-clinical populations think and act irrationally most of the time; and (b) the recognition that in some situations and context the presence of a psychiatric diagnosis increases rather than reduces the chances that a person thinks or acts rationally,(13,14).

Based on the general opinion, people with schizophrenia cannot be rational, and will act on bizarre ideas. This is explained by reference to a patients' lack of awareness that their own experiences and beliefs do not track reality. Such a pattern of behaviour would attract a negative assessment in terms of substantive rationality, but we are focusing on instrumental rationality here. So, there are times when people with schizophrenia are aware of the existence and the content of their delusions, hallucinations, thoughts, and their own condition generally. In psychiatric terminology this awareness of their condition is termed *insight*. Studies indicate a link between insight and behaviour,(15,16) and suggest that patients with high insight exhibit higher scores on social functioning and cognitive function,(175) which relates to decision making. Consequently, people who experience schizophrenia and have insight can be aware of their goals, and of the means they need to take to pursue their goals, including in the context in which they decide to complete suicide.

What about people with schizophrenia who do not have insight? As it has been mentioned above, instrumental rationality is not about the content of one's ends but refers to whether one takes the best means to fulfil those ends,(167). Having beliefs that are false does not in itself make the person irrational. If a person intends to satisfy their desires and they take the best means to achieve their goals, there is

nothing wrong with what they do from an instrumental rationality perspective. Applying this claim to the most common symptoms of schizophrenia such as delusions and hearing voices, we observe that delusions and hallucinations seem irrational and unreasonable from a third-person perspective, but this happens only regarding their content, and often when their content is taken out of contexts. Patients often tell a coherent story or a story that makes sense to them given their experiences—maybe Klee is right when he suggests that we cannot have a complete understanding about others' symptoms,(156). It would seem, thus, that the content of psychotic symptoms (hallucinations, delusions, inserted thoughts) does not compromise instrumental rationality even when insight is lacking, though the question about insight might have implications for an examination of executive function and its role in decision making,(176).

The aspects of rationality we have discussed above also are relevant to whether agents are autonomous. The concept of autonomy as a core concept in practical and applied ethics is especially important in the context of how and when agents choose to die. In case of suicide, autonomy should be understood as self-rule: the agent acts based on their own beliefs and desires concerning death (177). The way an agent exercises self-rule may differ depending on many factors including personality traits, social attributions, and symptomatology (when self-rule applies to a clinical population). There is much that can be said about whether agents who take their own lives are autonomous. What we suggest is that, if the agents' instrumental rationality is not compromised, then there is no reason to believe that they are unable to exercise self-rule, and thus we should assume that they can act based on their own beliefs and desires concerning death.

My argument here is neither a defence of the action of suicide in schizophrenia nor a defence of assisted suicide in this context. Rather, our argument should be interpreted as an attempt to enhance our understanding of the reasons why people with schizophrenia are vulnerable to suicide and a rejection of the assumption that attempting or completing suicide in this population is a result of having schizophrenia.

3.8.1 The concept of Rational suicide

One important point is that the commitment to the ends must be established before the means are selected. Bernard Williams claimed that there is rational coherence between the reason and the action if, and only if, the motivation or intention to do that action is prior to the occurrence of the action,(178). What Williams means here is that, if there are reasons for an action, then people must act for these reasons and must want to act for these reasons. When they do so, these reasons must figure in some correct explanation of their action,(179). So, the intentions and motivational set that people have exist before their actions and constrain their actions,(180).

While examining the literature on suicide it is interesting that most of the accounts of suicide include an analysis of intention and motivation. Studies on communication and suicidal notes indicate a mixture of motivations and intentions people have to end their lives,(181). Namely, the action of suicide requires an opportunity or broadly speaking a motive that will make people consider suicide as an option. Could these motives affect the rationality of the choice to complete suicide? To answer this, we will examine in which cases an action can be regarded as irrational. Using the notion

of instrumental rationality mentioned above, an action is instrumentally irrational when it is not suitably connected with the person's motivations and intentions.

Existing findings suggest that some of the main suicide risk factors in schizophrenia are depression, compulsive voices and hallucinations, hopelessness or affective disturbances,(22,17,23). Also, further factors such as extreme, alienation, anxiety, social avoidance and inactivity, lack of a social network and interaction with peers and poverty are common in schizophrenia and certainly affect not only people with schizophrenia but the non-clinical population too. However, people with schizophrenia perceive these factors as a big challenge in their lives and it is very possible that such challenges will make them seek escape—of which suicide is sadly a potential one.

Suicidal behaviour also appears when patients recognise that they feel disappointed or they feel like a failure instead of being in a state they desire. The salience between their current situation and the desired situation generates negative emotions and feelings about the self and the future. People then tend to blame themselves about their situation and progressively reach a state of cognitive deconstruction which leads to solutions such as suicide appearing as appropriate and effective (26).

Another study suggests that a suicide attempt becomes significantly accessible to the person when a motivation to escape is activated by a failure in the person's life,(184). Furthermore, a study showed that the process of activating a goal increases the ability to take the most efficient means for achieving that goal,(185). A person's failure then to meet her standards increases the desire to escape the conscious state of this failure. Thus, the evidence suggests the existence of a causal

link between self-awareness and suicidal behaviour, particularly in people who experience depression, other mental disorders and negative feelings,(186). Caldwell and Gottesman, in their review on suicide and schizophrenia demonstrated evidence in favour of the results of the above studies. Specifically, they found that the main reasons leading people to end their lives relate to their awareness of pathology (insight), high self–expectations, feelings of inadequacy, hopelessness and depression,(182). However, the interesting detail in this review is the timing people choose to end their lives. Most of the evidence report that patients attempted suicide in their early course of illness (onset) or during hospitalization rather than in the late phase of the illness,(171).

A different approach regarding reasons to attempt suicide comes from suicidologist Thomas Joiner who reported that suicide is the outcome that occurs when people perceive that they are a burden or fail to feel they belong. The failure of belongingness is the disconnection from other people and the inability to feel intimacy with others,(187). Indeed, the sense of belongingness is a concept that receives much attention nowadays due to the evidence on how being part of a social network can be a protective factor for suicide and how loneliness can lead to devastated feelings.

Regarding rationality now, the findings suggests that there are two issues for consideration. Firstly, people with schizophrenia can be instrumentally rational and conscious of what they are willing to achieve when they decide to complete suicide, whether they have insight. Secondly, many patients who attempt suicide have insight and therefore a reason to end their lives. Consistent with the studies we mentioned at the beginning of the paper, in their systematic review on rates and risk factors on

schizophrenia and suicide, Hor and Taylor identified the major suicide risk factors as insight, hopelessness, depression and negative symptoms whereas symptoms such as hallucinations, paranoid symptoms or delusions demonstrated having with less impact,(188). Thus, the current evidence supports the view that for people who experience schizophrenia death can be chosen for reasons that are understandable and the choice need not be instrumentally irrational.

The legitimate question is why death is seen as the only option to terminate the suffering and the feeling of failure a person with schizophrenia may experience. One idea is that some people with schizophrenia have an exaggeration of consciousness,(157) and a high self-awareness (insight) which makes a suicide attempt the only solution to overcome their suffering and obtain a state without pain. So, if people with schizophrenia can determine their ends and produce motivations and intentions that are consistent with their ends, why don't they find alternative means to change their current condition but instead choose to attempt suicide? In other words, how can people find it easier to complete suicide rather than try to change the situation that leads them to end up their lives? We can think only of two answers to these questions: either they do not have a clear understanding of what suicide will bring (that death is a permanent and unchangeable condition), or they have a very clear understanding of their illness which leads them to a deep insight that the current condition is so ruinous that death seems less painful compared to it.

3.9 Conclusion

Rationality is a network of principles governing decision making, reasoning and inference, and agency. Reasoners are rational to the extent that they work within the framework set by those principles and recognise themselves as subject to those principles (151). What I argue, thus, is that rationality should be a concept of necessary links or interconnections between our desires, beliefs, intentions, perceptions, decisions and our actions, ends and goals (94).

Although people with schizophrenia are seen as people who may not act 'normally', their behaviours and actions are often intentional and interpret their own reasons and intentions. Both negative and positive symptoms, are more like marks and indicators which on the one hand reflect fundamental impairments in basic brain mechanisms like cognitive coherence (189) and on the other hand reflect a reduced quality of life, poor social functioning and an unendurable suffering, which the person believes will continue indefinitely (84). However, this does not disable them from evaluating and judging their life events and whether is worthy to stay alive (139).

This chapter suggests that a person is instrumentally rational as long as he chooses the means he ought to take for achieving his ends (190). Although, other accounts of rationality posit a link between the content and the intention of an action, my suggestion is in favour of Finaly's and Hewitt approaches and what the field of phenomenology presents as self-disturbances. According to these approaches, I would not characterise people with schizophrenia as irrational. However, it is very possible for individuals with schizophrenia to reflect a false application of logic or have impaired cognitive processes or neurological dysfunctions or consciousness's misunderstandings or brain injury as findings insist. Nonetheless, even if all these

impairments affect the person as unity, it does not mean this person is irrational at all. I argue that there are multiple functions of rationality and therefore a person could have impaired processes of rationality rather than being completely irrational. Our lack of understanding on reasons to attempt suicide should not define individuals as irrational. It looks like they express something we do not experience and thus any attempt we make to explain it, involves misconceptions and misunderstandings.

Starhan, distinguished the rational from irrational suicide by explaining that in the former situation the person seeks death for death itself (191). They are impelled by a conscious impulse which finds irresistible at that time. This conscious impulse might have developed due to social circumstances, mental health problems including symptoms' impact on individuals' quality of life, poverty, financial struggles, or other factors relate to suicide behaviour such as substance misuse. In the case of irrational suicide, though, individuals destroy end their life by an innate craving or instinct or by an unhealthy reasoning or a disordered intellect (177). The main difference between the two different subtypes of suicide Strahan suggested, is the lack of consciousness in the case of irrational suicide. The individual who fits into rational suicide category is aware about the reasons they hold to end up their life. Even if they experience severe symptoms they are aware of the fact that these symptoms are intolerable struggles and they cannot cope with. It seems that rational suicide in schizophrenia has little to do with the severity of symptomatology but rather it is more about the awareness that these symptoms are unbearable (although severity of the symptoms can impact on patients' insight). The difference thus stands on the insight and realization.

Philosophers are still seeking the “why” when they examine suicide. Clinicians and researchers are still trying to measure how big, how significant this “why” is, and develop interventions to prevent suicide. Every reason people have to end their lives is worth examining, and especially the connection of these reasons with social intimacy, quality of life, employment, and education, which are factors on which society can intervene. A better understanding of the reasons for suicide may not lie only in people’s awareness and in their willingness to stop their present condition, but also in the fact that suicide is a solitary act that leads to an unchangeable condition. Therefore, it is of great importance to examine and understand the act of suicide in schizophrenia as a whole, whether rational or irrational, in order to then develop interventions that allow people to contemplate the existence of a different option from choosing an unlived life. In conclusion, this chapter is in favour of a deeper understanding of the motives leading people with schizophrenia to attempt suicide in order make clear why the implementation of a well-established suicide prevention plan is needed.

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CHAPTER 4: BLUNTED AFFECT AND SUICIDE IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW

Blunted Affect and Suicide in Schizophrenia: A Systematic Review

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Summary of revision:

Reviewers have submitted their comments on the content and structure of the paper. Main comments referred to the terms used in the paper, mentioning the need to explain terms clearer (e.g. the difference between blunted affect and emotional withdrawal). Further comments were on the associations that should be expanded (e.g. relationship between blunted affect and depression vs schizophrenia). Other comments suggested a slightly different structure of the data presentation. Paper resubmitted and is now published. The text follows is the revision of the review.

4.1 Abstract

Individual negative symptoms have rarely been examined with regard to their relationship with suicide in schizophrenia, which continues to effect up to 13% of people with the disorder. Symptoms such as blunted affect, which can be an enduring hallmark of schizophrenia, may have an impact on suicide through increasing isolation, leading to poor functional recovery and diminished quality of life. A systematic review following PRISMA guidelines and pre-registered on PROSPERO (CRD4219143373) was conducted, using EMBASE, PsychInfo and MedLine searched until January 2020. 856 articles were identified from the databases and 2 papers were identified from other resources. 12 papers met inclusion criteria for the review. 9 out of 12 papers report a positive direct or indirect association between blunted affect and suicide in schizophrenia and 3 papers showed no association. The majority of included studies suggest that blunted affect may be indirectly related to suicide through risk factors such as emotional withdrawal, depressive symptoms, hopelessness, low self-esteem, and negative evaluation. Future studies should include assessment of blunted affect as a potential mediator in the generation of suicidal behaviour in patients with such factors.

Keywords

Suicide, Negative Symptoms, Blunted Affect, Schizophrenia

4.2 Introduction

Schizophrenia is among the top 10 disabling conditions worldwide, with serious and life-impacting consequences (192). One of the biggest challenges of schizophrenia is completed suicide. Approximately 40% of premature and unnatural deaths in schizophrenia have been attributed to suicide (77) and around 12% of deaths by suicide worldwide are attributable to schizophrenia (75,193). Despite progress in treatment and mental health policies, the number of people who die by suicide per year remains enormous and makes suicide one of the 10 leading causes of premature death in the world (64).

Schizophrenia is characterised by a multiplicity of symptoms that are complex and diverse (20). Although multiple factors have been investigated in relation to suicide in schizophrenia, such as positive symptoms, hopelessness and depression (79), there are symptoms have not been examined systematically and might play a role. Negative symptoms are some of these underexamined factors. Negative symptoms can be defined as those ‘‘involving primarily an absence of normal functions’’ (194). Blunted affect, loss of motivation, alogia (poverty of speech and content), apathy and avolition (lack of motivation, physical anergia, poor hygiene), anhedonia (diminished ability to experience positive emotions from pleasant events) (23), social withdrawal and poor psychomotor movement are the main negative symptoms in schizophrenia (195).

Carpenter et al., (28) suggested a division of negative symptoms into primary and secondary. Primary (deficit or enduring) negative symptoms refer to symptoms that are intrinsic to schizophrenia, namely they relate to illness (29,30). In this case,

primary symptoms are part of the disorder itself. In contrast, secondary symptoms refer to negative symptoms that occur in association with, or caused by, positive symptoms, neuroleptic – drug effects, depression, psychotic symptoms, social/environmental deprivation, or chronicity (26,27). Primary symptoms are present during or between positive symptoms performance while secondary symptoms may not be persistent. Secondary negative symptoms can occur due to antipsychotic medication or depression (27).

Research shows that negative symptoms are associated with a variety of poor functional outcomes including social functioning, rehabilitation, productivity, and living skills (196). However, examining and targeting individual negative symptoms, may have significant functional benefits for patients as we become more precise in terms of how these symptoms interact with other symptoms (mainly with positive and depressive symptoms) and treatment. Specific symptom approach has been successful in terms of improving the reliability of evaluation of examined symptoms and of understanding in multifactorial outcomes (such as suicide). Such approach also eliminates the risk of dismissing complicated mechanisms that might need a detailed examination.

Blunted affect has been reported as one of the core primary negative symptoms which is prevalent to approximately one-third of the patients with schizophrenia. It reflects a deficit of emotional and affective expression, a tendency to keep emotions hidden and unknown from others, together with a reduction in the intensity of an individual's displayed emotional response (11,197). However, studies which examined the affective experience in schizophrenia, have reported that there is not a lack of emotional and affective experience, instead, very strong emotions are

experienced in the presence of relative events or stimuli but they are not expressed facially (11,40,41). Blunted affect reflects a lack of emotion expression and relates to the facial display of the emotions rather than the personal dynamic experience and the content of these emotions. Blunted affect is one of the symptoms that needs to be examined separately not only due to its prognostically important role but also because of its significant associations with other functional processes such as vocal expression, emotion processing, social functioning and ability to perform daily tasks (198,199).

Although, some studies reported that negative symptoms may have a significant impact on the risk of suicide in schizophrenia (87,88), such symptoms generally have been poorly examined individually compared to positive symptoms. A symptom specific approach into blunted affect which relates strongly to suicide risk factors such as hopelessness, depression, and social withdrawal, may reveal detailed information about how each symptom impacts suicide in schizophrenia, and where interventions could be better focused. Treatment of negative symptoms has been identified as a vital unmet clinical need for many people experiencing schizophrenia (200), as negative symptoms tend to persist, and are difficult to treat (7). This review aims to provide a starting point of examining the gap between blunted affect and suicide and summarize existing evidence as a foundation for future research and effective, much needed, interventions.

4.3 Methods

4.3.1 Study Selection

A literature search was conducted by following the PRISMA guidelines (201) using the following databases: MEDLINE (R) from 1946 to January 2020, EMBASE from 1973 to January 2020 and PsycINFO from 1806 to January 2020 (using OVID interface). The search included papers by web based electronic databases named above published up to January 2020. The review protocol was registered in advance with the International Prospective Register of Systematic Reviews (PROSPERO), protocol CRD42019143373.

Search terms included: schizophreni* AND suicid* AND negative symptom* OR affective symptom* OR expressed emotion* OR emotional internal*. In title, abstract and original title fields, the terms were also included: primary symptoms, secondary symptoms, positive and negative symptoms, flat adj1 affect, flattening adj1 affect, blunted adg1 affect, blunt adg1 affect, affective adg1 flattening, affective adg1 blunting, lack adg2 emotion, lack adg2 emotional and lack adg2 affect.

The reference list of included studies was searched manually for further relevant studies on negative symptoms (including measurements of blunted affect) and suicidal behaviour in people experiencing schizophrenia.

4.3.2 Selection of Papers

Studies were included if patients had a diagnosis of schizophrenia, schizoaffective disorder, or psychosis, according to diagnostic criteria. Included studies should also report negative symptoms measures including the symptom of

blunted affect. Selected studies should include patients who have experienced suicidal behaviour, attempted suicide, or died by suicide.

Excluded studies were concerning studies on organic mental disorders, studies of substance misuse and trials, non – English papers, review papers, conference abstracts and book chapters.

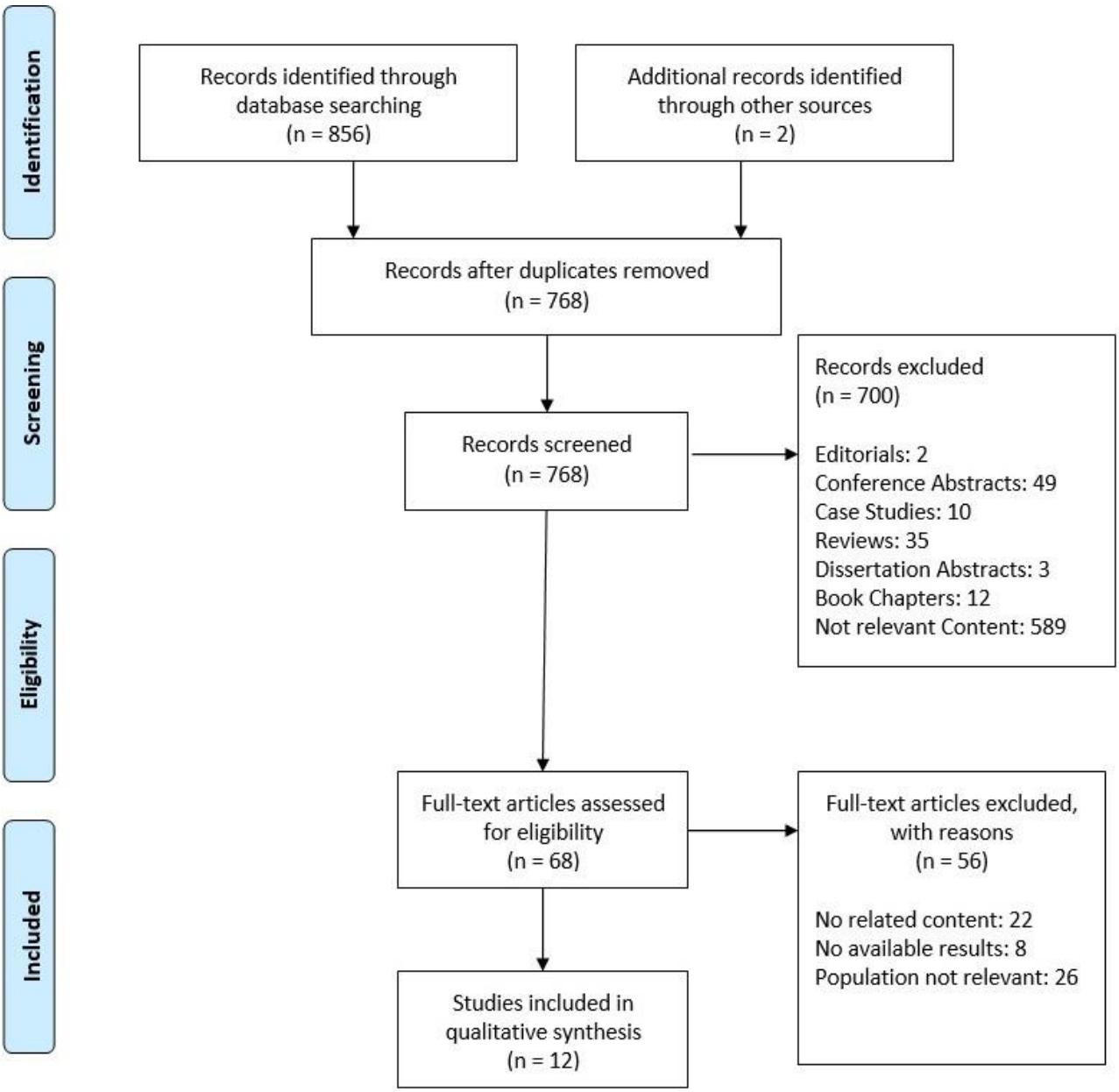
4.3.3 Outcome measures

The main outcome measures focused on the relationship between blunted affect and suicidal behaviour in schizophrenia spectrum disorders. However, since blunted affect is located under the umbrella of affective impairments in schizophrenia and is likely to relate to other impairments such as emotion withdrawal or low mood symptoms, the investigation of the association between blunted affect and relevant symptoms is important. Results were summarised in a narrative synthesis.

4.4 Results

A total of 858 articles were identified including 2 further papers identified through references hand search. Following the removal of all duplicates, 768 papers were screened manually (title and abstract). Of those 68 papers, read in full and 12 papers fulfilled the inclusion criteria (see Figure 4.1)

Figure 4.1 Search strategy and Results



As a summary, nine papers reported a positive and direct (202–205) or positive and indirect (206–210) association between blunted affect and suicide in schizophrenia spectrum disorders. Three papers reported no association between blunted affect and suicide(211–213). Six papers reported a measure of blunted affect (203–208) and demonstrated a positive relationship between diminished emotion expression and suicidal behaviour mediated by emotional dysregulation (208), affective isolation (202), diminished capacity to experience affect (203), emotional withdrawal (203,211), inability to feel and inability to affective expression (209). Further details are given below.

4.4.1 Sampling

Six studies examined inpatients (202,205,209,211–213), three studies examined both inpatients and outpatients (207,208,210), one study examined discharged patients (204) and two studies did not provide information of where the sample was taken from (203,206). The total number of participants in this review is 1651.

4.4.2 Diagnosis

Six studies looked at a schizophrenia sample alone (202,205,206,209,212). Two studies compared schizophrenia, schizoaffective disorder, and schizophreniform (194,196), one study assessed schizophrenia and schizoaffective disorder (207), one study examined deteriorated schizophrenia and schizoaffective disorder (204), one study looked at first episode psychosis including schizophrenia (213) and one study examined schizophrenia, schizoaffective disorder, schizophreniform and schizotypal personality disorder (203).

4.4.3 Scales used

4.4.3.1 Clinical symptoms Scales

Five studies employed the Positive and Negative Syndrome Scale (PANSS) for assessing the blunted affect using Item N1 – Blunted Affect (202,203,208,210,213). Two studies used the Brief Psychiatric Rating Scale BPRS using Item 16 – Blunted Affect and Item 17 – Emotion Withdrawal (206,211), one study combined The Clinical Assessment Interview for Negative Symptoms (CAINS) using Section 2 - Expression Scale (including facial and tone expression) and BPRS Items 16 and 17 (207), one study used Scale for the Assessment of Negative Symptoms (SANS) alone using Item 1 – Blunted Affect (204), one study combined SANS Item 1 – Blunted Affect with BPRS Item 16 and 17 (206), one study employed Strauss and Carpenter's Psychiatric Assessment Interview (PAI) to report any facial expression when emotional material discussed and by avoidance in looking at the interviewer (205), and the last one employed data on personality traits, previous adaptive type on onset and symptomatology for assessing negative symptoms including (blunted affect, anhedonia, social withdrawal) using clinical data available at first admission (209).

4.4.3.2 Suicidal behaviour Scale

Two studies used questions of the Schedule for Affective Disorder and Schizophrenia (SADS) (205,206), two studies employed BPRS (207,213), one study employed the Reasons of Living Inventory (RLI), a scale with 70 items which determine the reasons for committing suicide (203), one study estimated suicidal and self-harm risk conducting interviews with family, patients and available medical

records (211), one study compared Suicide Risk Scale (SRS) with Child Suicide potential Scale (SAUMD) to estimate the risk of suicide (212). One study employed Beck Suicidal Ideation (BSI) (210), one study used Global Impression for Severity of Suicidality (CGI-SS) and Scale for Suicidal Ideation (SSI) (208), one study used semi-structure interviews for estimating variables related to suicide (204), one study used the 8th item of CDSS (Calgary Depression Scale for Schizophrenia) (202) and the last study employed a discriminant analytic method WHIDD combined with questionnaires and interviews with patients for predicting and assessing suicidal behaviour (209).

4.4.5 Blunted affect and Suicide

4.4.5.1 Positive and direct association between blunted affect and suicide

Only four out of twelve papers reported a positive and direct association between blunted affect and suicide in schizophrenia. Specifically, Hacaoglou and Babuc (202) suggested that blunted affect and hopelessness relate directly to suicidal ideation and suicide in depression-motivated suicides only, since psychosis-motivated suicide tend to associate with other symptoms (mainly anxiety and psychotic symptoms). Fenton et al., (203), demonstrated a positive association between three specific negative symptoms (blunted affect, poverty of speech and stereotyping thinking) and suicide attempt and ideation. However, no relationship was found between negative symptoms and completed suicide in this study. Vocisano et al., (204) provide similar outcomes by concluding that negative symptoms (including blunted affect) are highly related to suicide in schizoaffective disorder only. On the other hand, Kaplan and Harrow,(205), showed a strong

correlation between deficit negative symptoms (mainly blunted affect and emotional withdrawal) and suicide in schizophrenia.

4.4.5.2 Positive and indirect association between blunted affect and suicide

Five out of the twelve papers demonstrated a positive but not direct association between blunted affect and suicide since they suggested that other factors, such as mood symptoms, act as mediators between suicide and deficiencies in emotional expression. In their study, Jones et al., (206) reported that negative symptoms could be considered as suicide and self-harm risk factors in patients with schizophrenia and depression, by underlining the important role of depression in negative symptoms.

Jahn et al.,(207) examined the role of emotional blunting to social functioning in relation to suicide in schizophrenia. Although, they did not find any association between diminished expression and suicide, they found a potential interaction between blunted affect and social functioning in relation to suicidal behaviour. Furthermore, Mork et al., (208) suggested that symptoms related to emotional dysregulation such as blunted affect are associated with suicide in women only as no such association had been reported in men. Nyman and Jonsson, (209) provide consistent results as they suggested that blunted affect impacts the ability to feel and achieve feelings or the inability to express affection which have been reported as suicide risk factors.

Two papers reported that other factors (not schizophrenia symptoms) act as mediators between blunted affect and suicide. For example, Tarrier et al., (210) investigated the role of self-esteem and interpersonal environment in suicide and

although they found no association between blunted affect and suicide, they developed a model where negative symptoms (blunted affect and emotional withdrawal) increase the negative evaluation of the self which associates with failure to meet expectation and suicide risk.

4.4.5.3 No association between blunted affect and suicide

Three papers out of twelve reported no relationship between blunted affect and suicide. Schwartz-Stav, Apter and Zalsman, (186) suggested that suicide is related to post-psychotic depression and not to negative symptoms. However, they suggested that the similar clinical presentation between the depression and negative symptoms, is likely to be misinterpreted as blunted affect. Jarbin and Von Knorring, (213)found consistent results, reporting that suicide in schizophrenia relates to depression, anxiety, affective disorders and frequent re-admission and it is less likely to relate to blunted affect since this is less prominent during onset. These findings are also complemented to McNiel and Binder,(211) who examined the clinical and demographic variables related to short- and long-term risk of self-harm and suicide at the time of hospital admission and found that only emotional withdrawal can be regarded as a suicide risk factor and not blunted affect.

Table 4.1.
Detailed Analysis of Studies examining the relationship between blunted affect and suicide in schizophrenia.

Study Name	Participant Details	Aim and detail of the study	Negative Symptoms Scale	Suicidality Scale	Results	Other Information
1. Jahn et al., (2015)	162 patients Schizophrenia and schizoaffective disorder	To examine the moderated effects of social closeness and negative symptoms in patients with suicidal ideation and SCZ. A cross- sectional study	CAINS– Express item CAINS – MAP (Motivation and Pleasure) BPRS	BPRS- Suicidality item	Better social role functioning was associated with less suicide ideation only in those who had low motivation and pleasure-related negative symptoms. Prominent negative symptoms such as blunted affect may impact on the desire for social belonging and motivation to seek belonging.	SCID, SCS MPQ-SC, RFS
2. Mork et al., (2012)	388 patients (296 with schizophrenia, 23 with schizophreniform	Prevalence, clinical characteristics, and gender profile of self-	PANSS item G14	CGI SSI	Emotional deregulation was significant self-harm risk factor only in women	SCID, BIS), MARS, GAF.

	60 with schizoaffective disorder). Ages 18-62.	harm. Cross-sectional study using data from all hospitals in Oslo, Norway			(p<0.034) and was related to negative symptoms and current suicidality.	
3. Hacaoglu and Babuc, (2009)	120 in-patients with schizophrenia aged 18-65 (38 with suicidal ideation and 82 with not suicidal ideation).	To evaluate and compare the factors affecting suicidal ideas in SCZ. A cross-sectional study.	PANSS	8th item of CDSS	77.3 % of patients had taken medication and had applied for hospitalization one month before the attempt. 31.6% of patients had suicidal ideation and 18% had suicide attempt history. 1 committed suicide. Affective flattening was significant for suicide attempt only in suicidal ideation group with a p<0.000. 47.3% of patients with suicidal ideation had depression as well.	Socio-demographic data SCID-I, RLI

4. Schwartz-Stav, Apter and Zalsman, 2006 (2006)	48 in-patients with schizophrenia aged 13-19	To investigate the interrelationships between depressive symptoms, post-psychotic depression, negative signs, suicidal behaviour, and insights in SCZ. A correlative study	PANSS	SRS, CSPS	There is an inverse correlation between post-psychotic depression and blunted affect in schizophrenia. Patients without PPD had more blunted affect than patients with PPD. Suicidal risk is related to high PPD scores in SCZ.	BDI, CDSS, Self-reports, HS, SAUMD, Demographic details.
5. Tarrier et al., (2004)	59 patients with onset schizophrenia spectrum disorder (49 subjects with schizophrenia, 7 subjects with schizophreniform disorder and 3 subjects with schizoaffective disorder)	To investigate factors associated with suicidal ideation and previous suicide attempts in SZC. A path study-analysis.	PANSS	BSI	47% attempted suicide at least once. Isolation (social and emotional), hopelessness and high persistence of negative symptoms (p<0.018) increase suicidal ideation and behaviour. Negative	SESS-sv scales, CFI, EE, BHS,BDI, Multiple regression.

					symptoms are related more to the negative evaluation of the self (NES) which is one risk factor for suicide than suicide itself.	
6. Jarbin and Von Knorring, (2004)	45 in-patients with Psychotic Disorder at first episode.	To assess the risk of suicide and suicide attempts and determine factors associated with suicidal behaviour and adolescent-onset schizophrenia. A 10.6 years retrospective follow up study at the Department of Child and Adolescent Psychiatry, University of Lund, Sweden	PANSS	BPRS	26 patients attempted suicide (with a total of 95 suicide attempts) and 4 patients died. 10 of 45 patients attempted suicide during first episode while negative symptoms were less prominent. Suicide risk in early onset schizophrenia is related to low scores in negative symptoms.	Semi-structured interview, Child, and Adult Psychiatry Records.
7. Fenton et al., (1997)	322 patients (187 with	To examine the relationship	PANSS	RLI, Patient's self- reports.	19 patients committed	Interviews with parents, hospital

	schizophrenia, 87 with schizoaffective disorder, 15 with schizophreniform disorder and 33 with schizotypal personality disorder). The average age was 19 years old.	between positive and negative symptoms, illness subtype and suicidal behaviour among schizophrenia. A 25 years retrospective follow up cohort study in Chestnut Lodge Hospital in Rockville, Md.			suicide (10 with schizophrenia, 7 with schizoaffective disorder, 1 with schizophreniform disorder and 1 with schizotypal disorder). There was a significance between prominent negative symptoms and suicide (Blunted affect = p<0.02 and Emotional withdrawal = p<0.01). 30 patients with persistent negative symptoms attempted suicide.	data, Chi-square analysis
8. McNiel and Binder, (1997)	241 in-patients with schizophrenia spectrum disorders and risk	To estimate the risk of self-harm in schizophrenia at admission and discharge and to	BPRS 5th item	OAS, Patients' interview, Longitudinal Inventory of Function and	125 patients had history of suicidal behaviour and a high risk for self-harm in	Demographic assessments, Hospital-based Interventions conducted.

	of self-harm with age 16-87 years old.	document decision–making patters for self-harm. The short-term risk evaluation was up to 17 days and long-term risk evaluation was up to 1 year. The study was conducted in a locked university-based psychiatric unit.		Encounteur.	admission with p<0.001. BPRS-negative clusters (emotional withdrawal, blunted affect) are long-term risk factor for self-harm instead of short-term. Blunted affect as a significant risk factor only at admission with a *p*<0.05. Short-term risk was more likely to relate to acute symptoms of SCZ.	
9. Vocisano et al., (1997)	29 in-patients with deteriorated schizophrenia and schizoaffective disorder.	To examine the symptoms constellations of patients with schizophrenia and history of suicide attempts. A follow up study in a State Hospital in Long Island, New York	SANS	Semi-structured interview.	Patients with SCZ reported severe negative symptoms (in particular affecting flattening) than patients with schizoaffective disorder. 11 of 29 subjects	Personality Examination, SAPS, Qualitative analyses.

					attempted suicide. No one committed suicide.	
10. Kaplan and Harrow, (1996)	70 in-patients with schizophrenia.	To analyse whether positive and negative symptoms are diagnostic-general risk factors for later suicide in schizophrenia. A prospective 7.5 years follow up study examining the suicidal activity. The study of symptoms had finished up to 2 years follow up examination.	PAI, Behavioural rating scales.	Interview, Questionnaires, SADS	12 patients committed suicide, 6 patients attempted suicide and 9 patients showed serious suicidal ideation during study years. Some negative- deficit symptoms are predictors for later but not early suicide (p<0.01). 27% of the patients who committed suicide had high scores in flat affect. Depression, hospitalization, and high IQ seem to be major suicide risk factors.	Structured interviews, SSI, Proverbs Test, DSST, WAIS

11. Jones et al., (1994)	57 in-patients with schizophrenia	To determinate the value of positive negative and depressive symptoms and dexamethasone suppression test in patients with SCZ with and without history of suicide. All patients were approached with no knowledge whether they had a history of suicide attempt. They were in good physical health and free of antipsychotic medication for at least 14-day period preceding testing. A cross-sectional study	BPRS-Negative Symptoms, SANS	SADS, SSI	25 patients attempted suicide. BPRS-Negative symptoms and SANS scores were highly related to HRSD scores and both contributed to suicide attempt. Negative symptoms impact suicide behaviour in the depressed attempters only. Other risk factor was decreased serotonin function. Post-dexamethasone cortisol values differentiated suicide attempters from non- attempters.	HRSD, HRSA, BHS, Parametric comparison of cortisol concentrations in suicide attempters and non-attempters, DST
12. Nyman and Jonsson, (1986)	110 young in-patients with schizophrenia.	To elucidate the circumstances connected with suicide and suicide attempts.	Detailed anamnestic data on symptoms and traits	WHIDD	138 suicide attempts and 18 committed suicides. Inabilities to feel,	Relatives' interview, police and hospital records, socio-demographic

	A 14-17 years prospective follow up study from first admission up to death.		achieve feelings, data. express themselves and affective isolation and non-regressive symptoms were the main reasons for suicide. Suicidal thoughts and warnings from the patients are significant indicators for a later suicide.	

4.5 Discussion

This review examines the existing literature exploring an association between blunted affect, and suicide (including self-harm, suicidal ideation, suicidal attempt and completed suicide) in schizophrenia. Results of this review suggest that blunted affect may play a significant role on suicide mainly when interacting with other factors. Such factors include depressive symptoms, hopelessness, emotional withdrawal, low self-esteem, inability to express affection and negative evaluation of the self. Four papers suggested a positive and direct association between blunted affect and suicide, whereas five papers found that blunted affect associates significantly with suicide only through other symptoms or factors. Three out of twelve papers showed blunted affect cannot contribute to the development of suicidal behaviour in schizophrenia.

Blunted affect appears to be associated with diminished quality of life, depressive symptoms, poor social functioning, emotional withdrawal, and negative evaluation of the self. These have been consistently highlighted as high suicide risk factors in schizophrenia (176,214,215). The crucial role of blunted affect in suicide seems to depend on the factors which interact between blunted affect and suicide, rather than on the nature of the symptom itself. The current results indicate that blunted affect is not a strong component to influence suicidal behaviour significantly. However, this is not the case when blunted affect is accompanied by other factors related to diminished functions on emotion processing, mood, cognition and brain activity (120,216,217).

Following current findings, diminished function, and failure in emotional processing such as emotional dysregulation can influence suicidal behaviour in

patients. Such dysfunctions in emotion processing and regulation result the prominent emotional withdrawal, affective isolation and inability to feel and express emotions and counter the emergence of suicidality, particularly in the late phase of schizophrenia (203). At this point, is important to clarify the difference between negative emotions and negative symptoms that patients may experience. Few papers addressed how negative emotions may interact with negative symptoms although are not the same by definition. Tarrier et al., (210) suggested a model in which negative emotions such as lack of self-confidence and negative evaluation of the self can lead to hopelessness and then to suicide. Also, Pallanti et al., (218) reported that negative emotions in conditions such as social anxiety and dysphoria are highly disabling conditions and future indicators for a suicidal behaviour in schizophrenia.

Moreover, two papers in the review suggested that blunted affect can be a significant risk factor for suicide among patients with both schizophrenia and depression which underlies the significant role of depression in suicide (205,206). Two other papers reported that blunted affect can lead to reduced self-esteem, poor social function and the development of sense of worthlessness which are indicators of hopelessness and depression (207,210).

Drawing clear statements presently will be a challenge. The attempt to assess how diminished function-related symptoms interact to each other is a complicated task due to the overlap often these symptoms report. Another reason monitoring blunted affect can be difficult, is due to its clinical presentation. Blunted affect refers to patient's inability to express emotions and negative feelings they experience and therefore, clinicians might struggle to obtain an accurate picture of whether the patient is at risk or not. For example, a patient with a diminished facial expression

may not easily allow us to understand whether he or she is sad or scared or anxious or even hopeless, which may influence whether they fit into and interact in a group. It appears that blunted affect could be one of the fundamental conditions for developing suicidal behaviour, as a primary feature of negative symptoms, on which other factors are built on over time. At the same time, the very nature of blunted affect may hinder the recognition of this risk easily due to its neutral presentation in patients; we do not overtly see the distress or hopelessness. In contrast, positive symptoms (i.e. hallucinations, delusions, distorted thoughts) are more overt indicators for suicidal behaviour due to their acute clinical presentation and therefore it is more likely, clinicians to be accurate on whether a patient is at risk and more effective with treatment provided.

Acosta et al., (219) suggested that divergent findings and associations(220) between positive and negative symptoms in relation to suicide, are results of the thought we hold that there is only one ‘type of suicide’. Instead, they have categorised suicide into two groups; the depression-motivated suicide (occurred by negative symptoms, depression, and hopelessness) and the psychosis-motivated suicide (psychotic characteristics and anxiety) which are driven by different symptoms. This distinction may allow us to understand that different symptoms might lead to different aetiologies of suicidal behaviour, and therefore examining individual symptoms in detail, such as in this review, might help generate further advancements for clinical and research community.

4.5.1 Limitations

Although this review might provide an emergent insight to the problem of suicide in schizophrenia, there were few limitations including the heterogeneity of

subject samples, different measures and distinctive primary outcomes which did not allow a statistical synthesis of meta-analysis. Moreover, results have been heterogeneous regarding the association between negative symptoms and suicide due to different terminology studies use to describe blunted affect. Lastly, existing literature does not provide sufficient longitudinal studies on negative symptoms and suicide in schizophrenia, which remains an area that warrants further investigation. The search has been conducted in English language only.

4.5.2 Implications

Schizophrenia remains one of the most complex human experiences (212) with determinant outcomes such as suicide. This is the first attempt to review the current evidence on whether blunted affect should be considered as a suicide risk factor in schizophrenia. Despite the limitations, the results may indicate that the ability to display emotions contributes to sustainable and healthy social interactions, normal emotion processing and therefore might be a protective factor to suicidal behaviour in schizophrenia. Such a new pathway of research might lead to better understanding and introduce new avenues of developing tools for prevention and effective interventions for suicide in schizophrenia which remains unfortunately too frequent. Prevention tools refer to the early treatment and implementation of psychological therapies working on emotional behaviour, thoughts and coping with negative feelings, regular assessments of negative symptoms which impact recovery and rehabilitation, monitoring of risk (including self-hard risk), and providing information on how to cope with negative experiences, symptoms, and suicidal thoughts in schizophrenia.

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Conflict of Interests

The authors have no actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations.

Additional commentary for Chapter 4

Review Question

The review aim of Chapter 4 is to examine the best available evidence and potential gaps in the literature regarding the association between blunted affect and suicide in schizophrenia. Namely, the review question focuses on how blunted affect associates with suicide in schizophrenia.

Selection of Papers

Selected Papers include:

- Studies including participants with a diagnosis of schizophrenia, schizoaffective disorder, or psychosis, according to diagnostic criteria of DSM-V.
- Studies examining negative symptoms including blunted affect by using measures for these symptoms such as SANS and PANSS.
- Studies including patients who have experienced suicidal behaviour, attempted suicide, or died by suicide.

Quality assessment

Although quality assessment is important for judging the overall strength of evidence on the current review question, this review does not include one due to the limited sources extracted from the search. However, the quality assessment for included papers has been conducted manually by screening each title, abstract, keywords and main body of the papers by the people who contributed to the review (the candidate and the library staff who provided guidance).

Double Extraction of Data

This review does not follow the method of double data extraction due to limited time in the PhD and lack of a third author/reviewer.

Primary Outcome

The primary outcome of this review is to present the existing and best available work on the association between blunted affect and suicide in schizophrenia including further classifications such as suicidal behaviour and attempt. Furthermore, this review is an attempt to identify existing gaps in relation to the association between blunted affect and suicide in schizophrenia.

The terms used in the review (i.e suicidal behaviour, suicide attempt and suicide) have followed the definitions reported earlier in this thesis (Chapter 1, pages 41 – 42).

Meta- Analysis

This review does not include a meta-analysis as the included studies are not sufficiently homogeneous in terms of symptoms and outcomes. A meta-analysis in this review might potentially lead to misleading conclusions as selected studies present a diversity.

Evidence / Narrative Synthesis

No specific framework was used to guide the narrative synthesis such as Popay et al., 2006. The evidence synthesis was carried out by following the PRISMA checklist to track and complete all necessary steps for evidence synthesis manually. We started by understanding the theoretical framework and mainly the role of blunted affect in suicidal behaviour in people with schizophrenia. We divided the included papers in three categories (1) studies showed positive and direct association between blunted affect and suicidal behaviour, 2) studies showed positive and indirect associations between blunted affect and suicidal behaviour and 3) studies showed no association. We then organised the findings of included studies in certain categories such as sample size, diagnosis, scales used for measuring negative symptoms and suicidal behaviour and outcomes of each study such as number of attempts or suicides (See Table 4.1). Lastly, we attempted to draw conclusions about the direction and strength of the effect between blunted affect and suicidal behaviour. Also, further conclusions were reported about the involvement of other factors that have been suggested to be significant in the development of suicidal behaviour such as depression, hopelessness, and anxiety.

The candidate completed the narrative synthesis under library staff supervision who reviewed all the steps.

CHAPTER 5: BLUNTED AFFECT, SOCIAL WITHDRAWAL AND SUICIDE IN SCHZIOPHRENIA

5.1 Introduction

Blunted affect is one of the core negative symptoms in schizophrenia and it is explained as the lack of emotional expression, sensitivity and facial display (221). Findings in chapter 4 indicate that the level of existing evidence on the association between blunted affect and suicidality may warrant further examination. Examining blunted affect is of importance as it impacts and interacts with other functions such as social behaviour, emotion recognition and emotion processing; which are known to be relevant to schizophrenia and suicidal behaviour (203). For example, studies have documented that patients with schizophrenia who show less outward emotional expression also have high levels on emotional blunting (43,222). There is also evidence reporting difficulties in several expression modalities such as spontaneous emotional expression, smiling or gesture in schizophrenia (223). Difficulties in emotion expression are not limited to lack or reduced facial expression but are also strongly related to the social role and can influence whether people generally are willing to interact socially with others (224).

De la Ancioun et al., examined how social decision making is impacted by patient's intentionality and the way they interpret emotions. They developed an experiment in which participants had to choose whether they accept proposer's offer based on proposer's face and expression (happy, angry, sad, neutral). They found that higher order social decision making changed, based on the facial expression of the proposer; which lead the participant to accept or reject the offer only in healthy controls. Participants with schizophrenia were unable to make decisions based on proposer's facial expression and therefore were more likely to reject a fair offer compared to heathy control (225).

Blunted affect may be associated with other characteristics such as social avoidance, social withdrawal, emotional withdrawal, anhedonia (the inability to feel pleasure), alexithymia (the inability to identify one's feelings) and lack of empathy (50). Specifically, Hooker and Park identified that patients who showed a lack of emotional display also had difficulties in social behaviour (52). Meanwhile, Mueser et al., (51) found a link between facial emotion recognition and social competence. Namely, the ability to handle social interactions effectively and being able to form and maintain social interactions.

Emotional display is also important for social functioning and the development of people's behaviour. The social interchange that takes place when people present their emotions; such as display variations, variations in the intensity and onset of facial responses, constitute the foundation of emotional behaviour and influence the emotion regulation processes (226). Consequently, emotion responses can enrich the way emotion regulation processes work and therefore can influence the quality of any emotional experience. Studies in schizophrenia also suggested that emotion dysregulation has impact in triggering delusions; patients who cannot manage their emotional distress (mainly patients who experience anxiety and depression) are more likely to develop acute psychotic symptoms (227). Thus, emotional impairment may have significant impact on patients' life and in fact is directly correlated to negative, positive, and affective symptoms.

Current findings suggest suicidal thoughts are prevalent in people with schizophrenia or schizophrenia spectrum disorders at 40% approximately (229), while 5% -13% will eventually complete suicide (170). Existing systematic reviews consider depression, affective symptoms, socioeconomic factors and emotion dysfunction as high risk factors for suicidal behaviour and suicide (176). Since blunted affect impacts the way

people behave socially, the interest of this chapter is to examine whether blunted affect may relate to suicide in any way.

Suicide has been reported to be highly connected with social behaviour, social network and interaction (231). Shafer and Dazzi, (232), in their attempt to categorize symptoms into clusters in schizophrenia, included symptoms affecting social behaviour and emotion processing under the umbrella of Negative Symptoms . Thereby, suggesting the similar impact on social and emotional disturbances may have on patients' clinical presentation. Hopelessness is another risk factor for completed suicide consistently reported in the literature. Specifically, Beck (233), noted that ''the suicidal preoccupations… seem related to the patient's conceptualization of his situation as untenable or hopeless''. The suicidal patient develops the belief that suicide is the only solution and way out of their suffering. It would be reasonable to say that the critical role hopelessness has on suicidal behaviour is illustrated by the negative way the patient experiences the events along with other common features in schizophrenia such as depression (172).

In regards to negative symptoms, few papers have been conducted that directly explore the role of negative symptoms as suicide risk factors in schizophrenia. As rehearsed in chapter 1 p.28, the literature so far provides unclear findings regarding the impact negative symptoms have on suicidal behaviour possibly because of the lack of examination of negative symptoms individually. This is also justified from data presented in chapter 4, where only 12 papers examined potential links between specific negative symptoms such as blunted affect and suicidal behaviour in schizophrenia. Therefore, studies focusing on specific factors could be very informative in terms of understanding how significant each factor is on the development of suicidal behaviour and on potentially targeted interventions.

In addition, the different stages of psychosis such as first-episode psychosis (FEP), acute episodes or chronic schizophrenia differ in the rates and presentation of suicidal behaviour. In their 25 year study on schizophrenia mortality, Brown et al., (234), reported that higher percentages of completed suicide were more likely to be seen soon after the onset of psychosis, and in young people. Whereas, in a later phase a steep decline of suicide rates has been reported. Studies on lifetime suicide risk during and after hospitalization reported that the first weeks of discharge are also critical; as results indicate that suicide rates increase significantly during the first week or month after discharge compared to other periods (235,236). On the other hand, Dutta et al. (81), in their 40-year retrospective cohort study examined the long-term risk of suicide after the first episode of psychosis. They found that the risk can be persistent for up to 5.6 years after the first year of the episode although, with the first year remaining as the most critical. They also mentioned the importance of risk assessment even a decade later or more from the first presentation of psychosis, as evidence shows that risk exists even if clinical symptoms are not intense. Their results are consistent with Suokas et al., (237), who conducted a 14-year follow up study on suicide risk in FEP. They concluded that although suicide was more likely to happen shortly after the first attempt of the patient, the suicide risk remained elevated for more than a decade after the first attempt and was not limited on the onset of psychosis only (171). Other studies examined confounding factors such as depression, hopelessness, sleep disorder, substance misuse and history of suicide attempts (238–240).

Therefore, the gap remains in the knowledge of the role of blunted affect and related negative symptoms in suicidal behaviour. This may be particularly relevant in the early phases of psychosis when completed suicide, risk for suicidal behaviour, is at

its highest and clinical presentation is very acute. This is the main reason this chapter focuses on participants with FEP instead of schizophrenia.

5.2 Aim

The aim of this study is to investigate the strength of associations between the negative symptoms of blunted affect, social withdrawal, and suicidal behaviour in early stages of psychosis. I also aim to examine whether this association might impact suicidal behaviour and investigate the mediating potential of hopelessness in predicting suicidal behaviour in those with high levels of negative symptoms and social withdrawal.

The hypothesis is that there will be a positive association between the levels of blunted affect, social withdrawal, and suicidal behaviour. In addition, that the association between blunted affect, social withdrawal, suicidal behaviour, may cumulatively, or through indirect influence of hopelessness, impact on suicidal behaviour.

5.3 Methods

5.3.1 Study Design

Data was taken from the First Episode Psychosis-Autism (FEP-A) cohort study, examining the neurological overlap between autism and FEP (241). A cross-sectional design was used, consisting of a single assessment of interviewer and self-reported measures conducted and scored by a trained researcher and the candidate, who was trained with the support of staff members and researchers at University of

Birmingham. Consent was obtained from all participants. Ethical approval was granted by the UK Health Research Authority's National Research Ethics Service, reference number 13/WM/0213.

5.3.2 Sampling

Young people presenting to Birmingham and Solihull Mental Health Foundation Trust Early Intervention Services (EIS) were invited to take part in the research. EIS provides clinical services for young people presenting in the early stages of psychotic illness. The full sample was consisted of 99 patients, aged 16-35, with treated FEP at the time of recruitment. All the participants were on antipsychotic medication and received care-coordination and psychological interventions as part of EIS provision.

5.3.3 Inclusion/Exclusion Criteria

Individuals aged 16 years or above, with a diagnosis in keeping with ICD-10 F20-23, F25-29, which is the International Statistical Classification of Diseases and Related Health Problems (ICD), providing a medical classification list by the World Health Organization (WHO) satisfied all the inclusion criteria Exclusion criteria were a lack of capacity to consent (including a current psychotic episode) and non-English language speakers. Apart from past psychotic illness, past mental illness was not an exclusion criterion. EIS psychiatrists and care-coordinators were asked to identify individuals who met the inclusion and exclusion criteria. With the participant's consent their medical records were also searched for primary diagnosis (ICD-10 F20-

23, F25-29), diagnosis of autism, and medication. Participants were not antipsychotic-naive.

5.3.4 Demographic Details

Demographic information collected included age, gender, ethnicity, living situation, previous cannabis use, educational attainment, work/education status, parental age at birth, and family history of mental illness or autism.

5.3.5 Research Measures

Positive and Negative Syndrome Scale (PANSS) (242): The Positive and Negative Syndrome scale (PANSS) was used to measure positive, negative and general symptoms of schizophrenia. Each domain is assessed by a series of questions, which will then be used to rate on a 7- point severity scale. Based on the domains have been used in this analysis the minimum total score = 14 and the maximum total score = 98. PANSS showed good inter-rater reliability with internal consistency (alpha = 0.72) (243).

Shafer and Dazzi, (232), found five core factors in schizophrenia by grouping PANSS items in each cluster including positive symptoms, negative symptoms and general symptoms. The positive symptoms factor included Delusions (P1), Hallucinations (P3), Grandiosity (P5), Suspiciousness and persecution (P6), Unusual thought content (G9) Lack of judgment and insight (G12). The negative symptoms factor included Blunted affect (N1), Emotional Withdrawal (N2) Poor rapport (N3) Passive apathetic social withdrawal (N4), Lack of spontaneity (N6), Motor retardation (G7)

and Active social avoidance (G16). The negative symptoms cluster will be used in the analysis to test how they correlate to each other, and whether they have any power to predict suicidal behaviour.

Suicidal Behaviours Questionnaire- Revised (SBQ-R) (244): An accurate assessment of suicidality was designed to assess lifetime suicidal ideation and attempts, the frequency of suicidal ideation over the past year, the threat of suicidal behaviour, and the self-reported likelihood of future suicidal behaviour. The instrument has a good degree of internal consistency and a strong validity convergent (245). Scores on the SBQ-R have been shown to reliably differentiate between subgroups of suicidal-risk. Namely, there were two subgroups: if score >= 8 may indicate high suicidal behaviour, and score <=8 low suicidal behaviour. SBQ-R showed reliability with internal consistency (alpha = 0.88) (246,247).

The Beck Hopelessness Scale (BHS) (248): A multiple choice 20-item self-report measure of one's negative expectations regarding the future. It measures three major aspects of hopelessness: feelings about the future, loss of motivation, and expectations. The test is designed for adults and it measures the extent of the respondent's negative attitudes, or pessimism, about the future. It is also used as an indicator of suicidal risk in people who have made suicide attempts. BHS -Total has also been used as depended variable; as systematic reviews on suicide in schizophrenia regard hopelessness as one of the main factor impact the development of suicidal behaviour. BHS reported a good reliability with internal consistency (alpha = .97) for depressive subjects and alpha = .79 for control subjects. (176,188).

In addition, although not used in this analysis, participants completed the Autism-Spectrum Quotient (AQ; (249)), Social and Occupational Functioning

Assessment (SOFAS; (250)), Personal and Social Performance Scales (PSP; (251)), Quality of Life Scale (QoL; (232)).

5.4 Statistical Analysis

5.4.1 Descriptive Statistics

The main aim is to examine the relationship between negative symptoms of blunted affect and social withdrawal and suicidality in patients with schizophrenia.

A normality test was conducted for all continuous data using p-p plots , reporting data is not normally distributed, which is expected outside of very large samples (253). Non-parametric testing has been used accordingly where appropriate.

Explanatory analysis of socio-demographics and clinical features are presented using measures of means and standard deviation for continuous data.

Participants were grouped into those with high (>=8) and low (< 8) suicidality as assessed by the SBQ-R(Total) score in accordance with standard setting and previous literature (246,247).

To compare means of the demographic variables and PANSS in those with high and low suicidality, Mann–Whitney tests were conducted. Chi square tests of independence were also calculated to compare the frequency of suicidal behaviour in different a) gender and b) ethnic groups; for purposes of secondary exploration and to understand better the sample.

Spearman’s correlation co-efficient was used to investigate associations between individual negative symptoms, positive symptoms, hopelessness, and suicidal behaviour.

5.4.2 Multiple Linear Regressions

In order to explore whether the negative symptoms of blunted affect and social withdrawal can play a role in the development of suicidal behaviour over and above other known risk factors; a multiple stepwise linear regression was performed. The aim was to assess the impact of PANSS positive symptoms and negative symptoms clusters as defined by Shafer and Dazzi, together with those that the univariate analysis (Spearman's correlation) reported significantly associated with suicidal behaviour. (232).

A multiple linear regression has been conducted with SBQ-R(Total) as dependent variable. As mentioned, Ethnicity and Gender were also included as independent variables to test if they associate with the development of suicidal behaviour in schizophrenia, since they have been reported as potential factors which might influence the outcome (254,255). Hopelessness has also been added as independent variable in the regression for SBQ-R(Total) following the model of Shafer and Dazzi.

According to the precision efficacy analysis for regression (PEAR) methods for sample sizes in multiple linear regression, Brooks and Barcikowski,(257), suggested a minimum practical effect sample size of 20% in the case of multiple regressions (R^2 >= .20), which means that the hypothesis here should be applicable to at least 20% of the whole sample. Pohlmann, (258) suggested a minimum of 15 subjects per predictor which means that at least 30 participants needed (2 predictors – suicidality and hopelessness). In total 15 variables (Positive/Negative/General symptoms) were used as independent variables and two as dependent variable (SBQ-R(Total) and BHS(Total)) in the two multiple linear regressions.

Difficulties can arise in multiple testing; simultaneously evaluating many questions, testing many hypotheses, or comparing many variables (259). In this chapter, for instance, multiple PANSS items have been added in the regression as independent variables, which have an effect on suicidal behaviour and hopelessness. After conducting these multiple comparisons between the variables, is possible to end up with a Type 2 error. This poses a risk to wrongly conclude that there is at least one statistically significant variable which increases, whereas in fact there in no significance. To solve this problem and adjust multiple comparison, the Bonferroni correction was used to adjust the p value ($p<.001$) based on the total number of tests being performed (260).

5.4.3 Mediation analysis

A mediation analysis is commonly used to test a hypothetical causal chain where one variable i.e. X affects a second variable i.e. M (mediating variable) and, in turn, that variable affects a third variable Y (261). Potential mediating effects of significant factors from univariate analysis and regression analysis (i.e. Shafer and Dazzi negative symptoms cluster or hopelessness) on suicide in schizophrenia were examined. The aim was to determine whether negative symptoms cluster have any direct effect on suicidal behaviour or any indirect effect through hopelessness. To examine whether the effect of negative symptoms cluster on suicidality was mediated by hopelessness mediation analysis was conducted using version 26 SPSS Macro for Multiple Mediation (262).

5.5 Results

5.5.1 Sample Characteristics

Full sample consisted of 99 participants. A total of 85 individuals completed the assessments fully. Fourteen participants dropped out the study or were unable to finish the assessment (primarily due to clinical deterioration). Missing data from the 14 participants included complete SBQ-R (Total) and complete PANSS items. Therefore, these participants data were excluded from analysis. As whole questionnaire data was missing in those participants, this was not considered to be missing at random, rather potentially the result of lack of engagement or severity of illness. However, those who did not completed assessments did not significantly differ in age, gender, ethic group or mean score on available symptoms from those with complete data. The final sample consisted of 85 participants (See Table 5.1).

5.5.2 Suicidal behaviour

The mean SBQ-R score was 7.44 (range 0-15) (SD=4.07). 39 out of 85 participants scored high on suicide scale (SBQ-R(Total) >=8). 23 of participants (27%) had attempted suicide. The methods participants reported to have attempted suicide with were: overdose (n=15, 17.6%); cutting wrists/stabbing (n=7, 8.2%); attempted hanging (n=2, 2.3%); jump in front train tracks (n=1, 1.17%) or car (n=1,b1.17%); car crash (n=1, 1.17%); strangulation (n=1, 1.17%); drowning (n=2, 2.3%); starvation (n=1, 1.17%) and setting fire (n=1, 1.17%). Seven (8.2%) participants reported more than one suicide attempt and used a combination of methods. Two (2.3%) participants attempted suicide up to 4 times. Participants who attempted suicide more than once differed from those who attempted suicide once, as the first were

expressing their suicidal thoughts by writing notes or discussing about their thought to clinicians, whereas the later did not provide such evidence.

5.5.3 Demographic features

5.5.3.1 Age

A chi-square test of independence was performed to examine the relation between age and scores on SBQ-R(Total). There were no significant differences between the two variables (x^2 (83), N=85) = 85, p = 0.415) (see Table 5.1).

5.5.3.2 Gender

To test whether the two groups are differentiated by gender, a chi-square test of independence was performed to examine the relation between gender and SBQ-R(Total) scores. Results showed that there was a significant association between gender and SBQ-R(Total) scores. Females were more likely to score high on SBQ-R(Total) compared to males who scored low (x^2 (1), N=85)= 7.35, p = .007) (see Table 5.1).

5.5.3.3 Ethnicity

Out of those 39 participants with an SBQ-R(Total) score of >=8, significant differences were seen with regards to ethnicity, with white British participants (n=25, 64%) reporting higher levels of suicidal behaviour compared to those from other backgrounds. Black Caribbean and Asia Pakistani followed with 7.7% (both categories). Participants with Asian background scored lower in all areas including PANSS positive symptoms and negative symptoms, SBQ-R(Total) and BHS(Total).

Moreover, Asian patients reported lower suicide attempts compared to White (see Table 5.1).

Table.5.1 Demographic information, clinical measures and descriptive statistics information for total sample and high vs low group on SBQ-R(Total) scores.

	Total (N=85)	**High SBQ-R (>=8) (N=39)**	**Low SBQ-R (<8) (N=46)**	***p-value***
Age (mean)	25.4 (S.D=4.96)	25.05 (SD=5.61)	25.7 (SD=4.37)	.415
Gender Male Female	 55 (64.7%) 30 (35.3%)	1.43[a] 22 (56.4%) 17 (43.6%)	1.28[b] 33 (71%) 13 (28%)	**.007**
Ethnicity White Asian Black Other	 53 (63.4%) 14 (16.8%) 8 (9.4%) 10 (11.7%)	3.75 (SD = 3.75) 27 (69.2 %) 6 (15.5%) 4 (10.3%) 2 (5.1)	4.48 (SD=4.44) 26 (56.5%) 8 (17.6%) 9 (19.8%) 3 (6.6%)	**.000**
Occupation Employed or University Not in education or employment Other	 35 (41.1%) 44 (51.8%) 6 (7.8%)	 14 (36.4%) 20 (51.3%) 2 (5.1%)	 21(46.2%) 24 (53.3%) 4 (8.8%)	.752
Highest Completed Qualification University A-Levels /GCSE Other No qualification	 15 (17.7%) 57 (67.1%) 4 (4.7%) 9 (10.6%)	 5 (13.5%) 17 (72.9%) 3 (8.1) 4 (10.8%)	 10 (21.7%) 30 (65.3%) 1 (2.2%) 5 (10.9%)	.978
PANSS PS Total (mean)	11.84 (range 7-30) (SD=5.33)	13.69 (SD=5.8)	10.26 (SD=4.38)	**.001**
PANSS NS Total (mean)	11.98 (range 7-30) (SD=4.24)	12.13 (SD =3.48)	11.85 (SD=5.21)	.197
PANSS GS Total	26.02 (range 16-	28.59	23.85 (SD=6.79)	.102

(mean)	47) (SD=7.56)	(SD=7.72)		
BHS- Total (mean)	6.27 (range 0-20) (SD=5.28)	8.30 (S.D=6.08)	4.64 (SD=3.89)	**.000**
SBQ-R-Total (mean)	7.44 (range 0-15) (SD=4.07)	11.17 (S.D=2.8)	4.28 (SD=1.4)	--

PANSS PS = Positive Symptoms, PANSS NS = Negative Symptoms, PANSS GS = General Symptoms

[a] *Chi square for gender in high SBQ group (x^2 (1), N=39)= .641, p = .423)*

[b] *Chi square for gender in low SBQ group (x^2 (1), N=46)= 8.69,* ***p = .003****)*

[c] *Chi square for ethnicity in high SBQ group (x^2 (8), N=39)= 112, p = .000)*

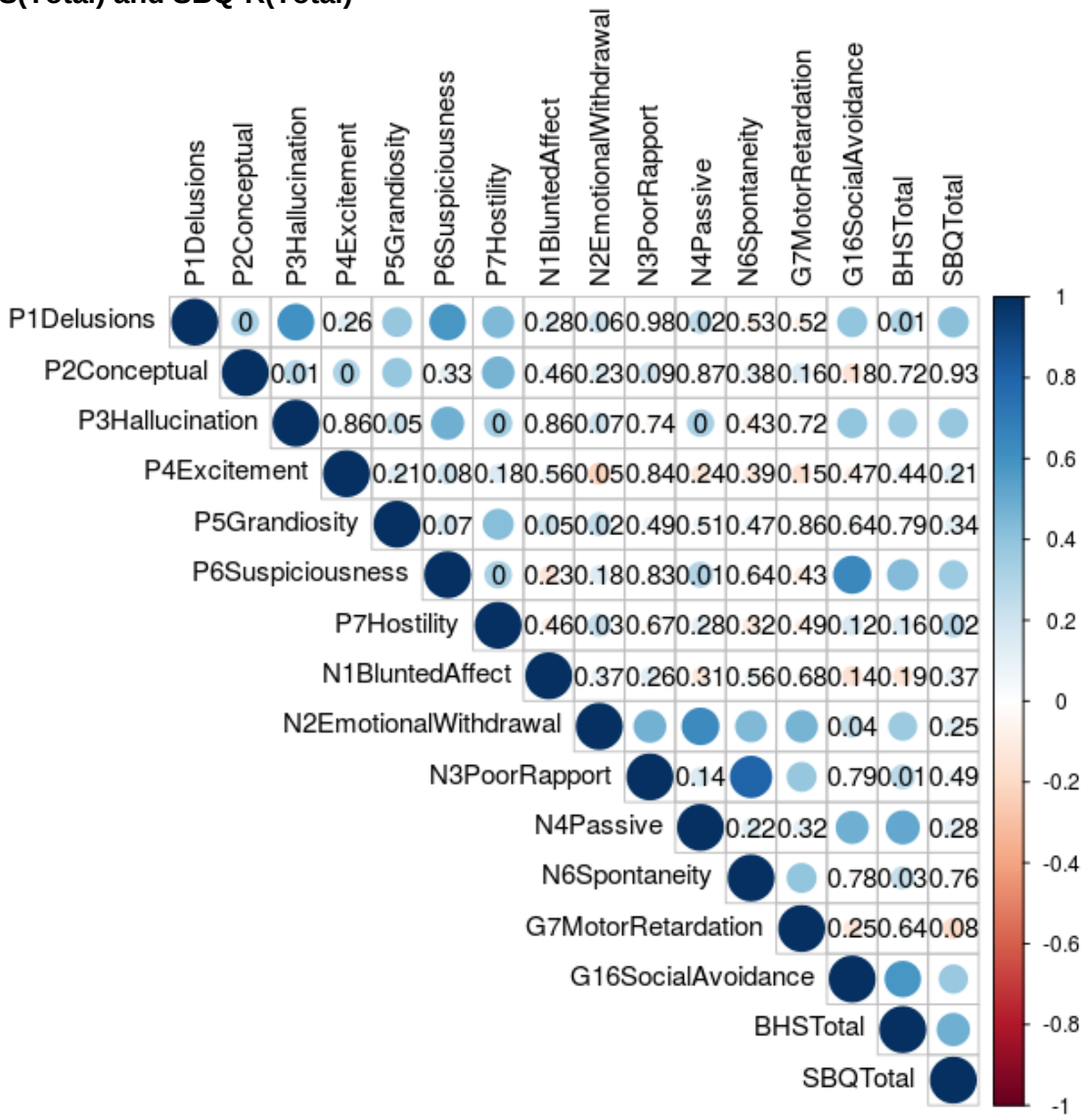
[d] *Chi square for ethnicity in low SBQ group (x^2 (11), N=46)= 98.5, p = .000)*

5.6 Univariate analysis

5.6.1 Spearman's correlation between PANSS symptoms, SBQ-R(Total) and BHS(Total)

A Spearman's correlation co-efficient was used to investigate associations between PANSS items, SBQ-R(Total) and BHS(Total), with, the selection of PANSS individual items of the negative symptoms (as detailed above), following Shafar and Dazzi (232) (See Figure 5.1).

Figure 5.1 Coefficient Correlations between Positive Symptoms, Negative Symptoms, BHS(Total) and SBQ-R(Total)



Note. Numbers indicate p value (sig level .001). The absence of numbers indicate there is no significance. Colours indicate whether the correlation is positive (blue) or negative (red).

5.6.2 PANSS Positive Symptoms

Figure 5.1 demonstrates a positive, significant, and strong correlation between specific positive symptoms and suicidal behaviour. There is a positive correlation between Delusions (P1) (r=.415, p=.000), Hallucinations (P3) (r=.381, p=.000),

Suspiciousness/Persecution (P6) (r = .337, p= 0.001) and Hostility (P7) (r= .263, p= .015) with SBQ-R(Total). Positive Symptoms also reported significant relationships with each other. For example, Hostility was significantly correlated with the majority of positive symptoms such as Delusions, Conceptual Disorganization, Hallucinations, Grandiosity and Suspiciousness/Persecution (see Figure 5.1).

5.6.3 PANSS Negative Symptoms

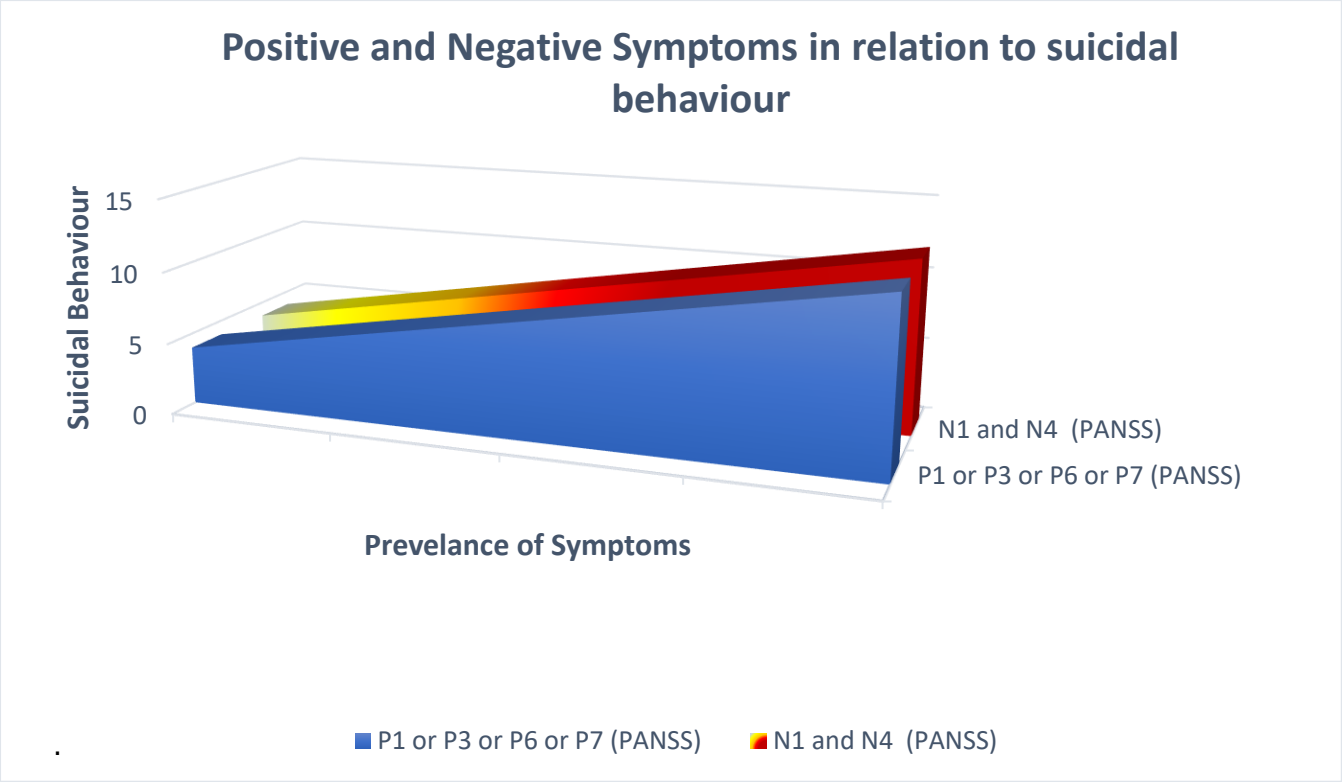
Figure 5.1 also shows that there is no significant direct correlation between the majority of specific negative symptoms and suicidal behaviour. There is a moderate correlation between Blunted affect (N1), Emotional withdrawal (N2) and Social withdrawal (N4) with SBQ-R(Total), but this did not reach statistical significance. Active social avoidance (G16) is the only item in negative symptoms factor that individually correlates significantly with suicidality (r=.371, p= .000).
Negative Symptoms also relate to each other: Emotional Withdrawal relates significantly with all the other symptoms in this cluster (Blunted Affect, Poor rapport, Passive apathetic/social withdrawal, Lack of spontaneity, Motor Retardation and Active social avoidance) (See Figure 5.1).

5.6.4 Positive and Negative Symptoms cumulative relationship to SBQ-R(Total)

Patients who scored high even on one item on PANSS positive symptoms reported higher scores on SBQ-R(Total). However, this is not the case in negative symptoms. Only patients who scored highly on 2 or more negative symptoms scored higher on SBQ-R(Total). Negative symptoms reported to have impact on SBQ-R(Total) only as

cluster/group of symptoms (i.e. blunted affect and social withdrawal or blunted affect, emotional withdrawal and social withdrawal) and not as individual factors. Data obtained shows that the impact an individual positive symptom has on SBQ-R(Total) equals the impact of 2-3 grouped negative symptoms have on SBQ-R(Total) (See Figure 5.2).

Figure 5. 2 Scoring high on one positive symptom has the same effect with scoring high on at least two negative symptoms on PANSS



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P1: Delusions, P3: Hallucinations, P6: Suspiciousness, P7: Hostility, N1: Blunted Affect, N4: Passive apathetic social withdrawal

5.6.5 Positive and Negative Symptoms in relation to BHS(Total)

3 out of 6 items in positive symptoms factor reported significant correlation with hopelessness BHS(Total), specifically delusions, hallucinations, and suspiciousness/preoccupation – see figure 5.1).

5 out of 7 negative symptoms relate significantly with hopelessness (BHS -Total). Specifically, these symptoms are Emotional Withdrawal (N2) (r=360, p= .001), Poor Rapport (N3) (r=.270, p =.015), Passive apathetic/social withdrawal (N4) (r= .513, p=.000), Lack of spontaneity (N6) (r=.236, p=.034) and Active social avoidance (G16) (r=.588, p=.000) (see Figure 5.1).

5.6.6 Blunted Affect and Social withdrawal in relation to SBQ-R(Total) and BHS(Total)

N1 (Blunted Affect) and G16 (Social Withdrawal) are the 2 symptoms of interest in this chapter. Based on Shafar and Dazzi model (217), both symptoms are included in negative symptoms cluster. However, they do not have the same impact on suicidality and hopelessness. Correlation outcomes report that N1 acts independently of suicidality whereas it seems to decrease when hopelessness increases. In contrast, there is a positive correlation between social withdrawal and both suicidality and hopelessness (see Figure 5.1).

5.6.7 Correlation between SBQ-R(Total) and BHS(Total)

Analysis indicates that there is a strong positive association between suicidality and hopelessness (r = .498, p = .002).

5.7 Multiple Linear regressions

5.7.1 Multiple linear regression with SBQ-R(Total) as the dependant variable

A multiple linear regression was calculated to test if examined symptoms influence patients' suicidal behaviour based on their positive and negative symptoms individual item score correlation's outcomes (figure 5.1) and those included in Shafer and Dazzi cluster model. Ethnicity and Gender have also been included as independent variables. SBQ-R(Total) is the dependant variable.

Using the stepwise method, a significant regression equation was found ($R^2 = .172$, F(1,83) = 17,240, p<.000). The results of the regression indicated that the two clusters of symptoms explain 17.2% of the variance. Specifically, results showed that delusions (β=.806, p = .004) and active social avoidance (β= .641, p =.024) significantly influenced suicidality rates. Blunted affect has also been used as an independent variable based on Shafer and Dazzi and showed no significant impact on suicide.

Overall, the scatter plot of the data reveals an approximate linear relationship between predicted and expected SBQ-R(Total) scores (see Figure 5.3).

The multiple linear regression equation used for this regression is

$$\hat{y} = b_0 + bX_1 + b_2X_2 + \ldots\ldots + b_{15}X_{15}$$

whereas:

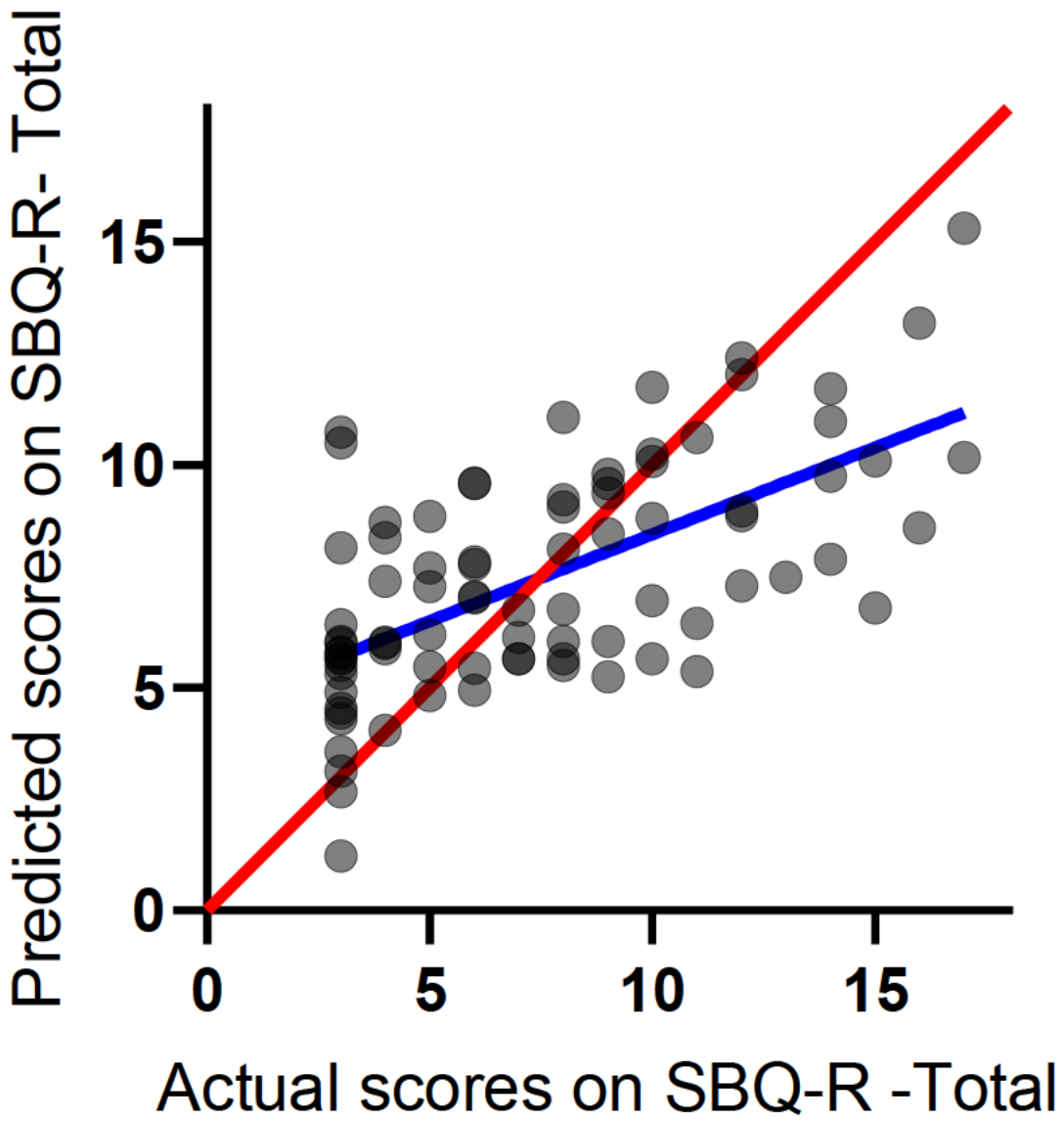
$\hat{y}$ = Depended variable (suicidality)

X_1 ….. X_{15} = Distinct independent or predictor variables (PANSS items),

b_0 = The value of $\hat{y}$ when all of the independent variables (X_1 ….. X_{15}) are equal to zero

b_1 …… b_{15} = The estimated regression coefficients. Each regression coefficient represents the change in $\hat{y}$ relative to a one-unit change in the respective independent variable.

Figure 5.3. Actual Vs Predicted plot for Multiple Linear Regression for SBQ-R(Total) as depended variable indicating most independent variables (X_1 ….. X_{15}) predict suicidality ($\hat{y}$).

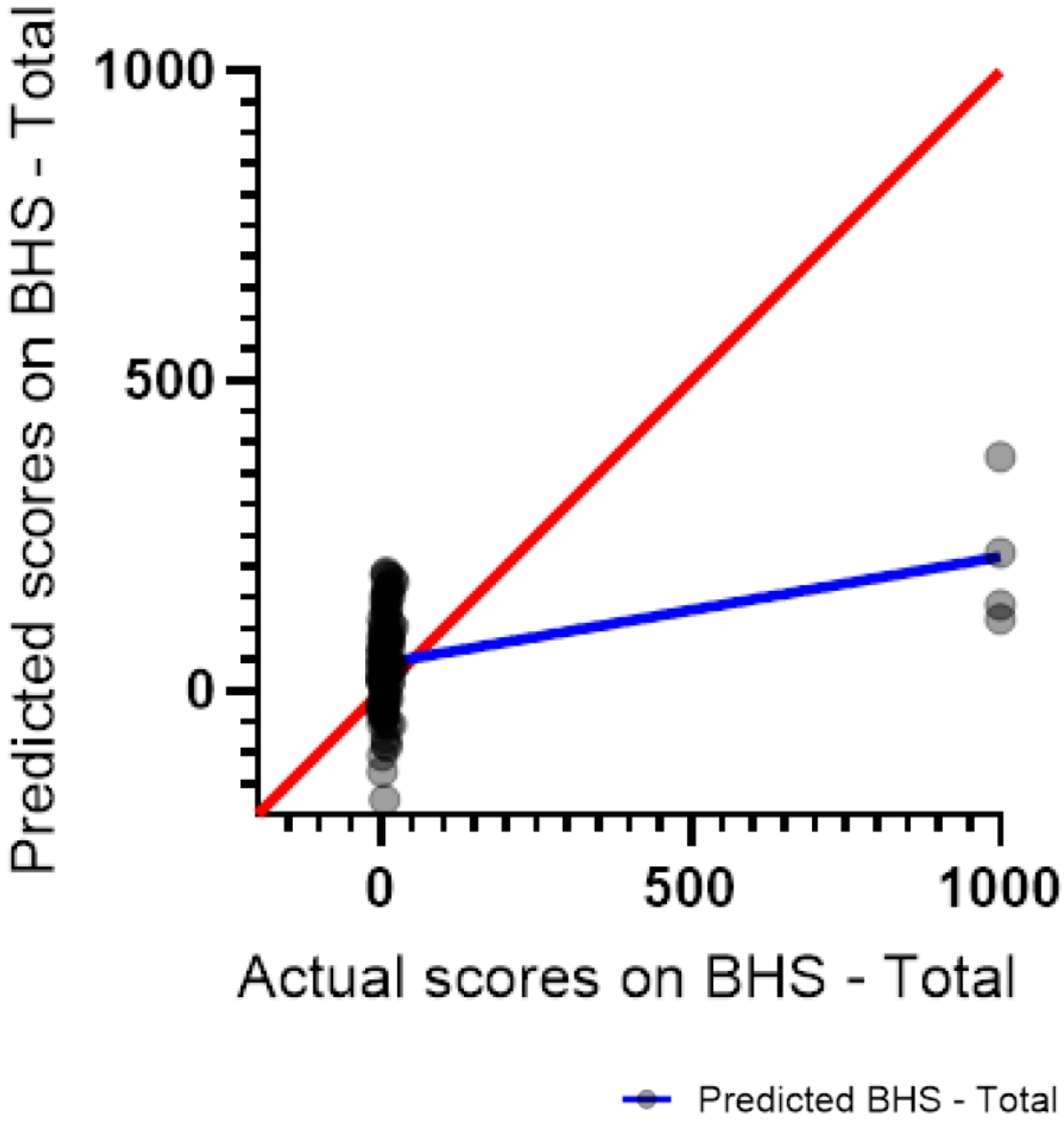


Note. *Red line indicates the line of perfect agreement (suicidality increases when scores on PANSS symptoms increase) whereas blue line indicates the line the data actually fit on. The figure demonstrates that the more symptomatic across PS and NS, the higher the suicidality score.*

5.7.2 Multiple linear regression with BHS(Total) as the dependant variable

A second multiple linear regression was carried out to investigate the relationship between positive symptoms and negative symptoms with hopelessness. Using the stepwise method it was found that negative symptoms explain a significant amount of the variance of hopelessness scores (R^2 = .471, F(3,80), 22.82, p <0.00,). Items on positive symptoms cluster did not report any significant prediction of hopelessness. Outcomes of the regression indicated two clusters of negative symptoms and explained 47.1% of the whole sample. Data report Active social avoidance (G16) (β = 1.60, p= .000), Poor rapport (N3) (β =1.51, p=0.06) and Social withdrawal (G16) (β=.802, p=.014) to predict significantly high rates of hopelessness. However, the group of independent variables used in this regression do not fit significantly with the expected outcome (see Figure 5.4). In this regression $\hat{y}$ = hopelessness whereas X_1 ….. X_{15} are the same distinct independent or predictor variables used in the previous regression (PANSS items).

Figure 5.4 Actual Vs Predicted plot for Multiple Linear Regression for BHS(Total) as depended variable indicating most independent (X_1 …. X_{15}) X variables) do not predict hopelessness ($\hat{y}$).



Note. Red line indicates the line of perfect agreement (hopelessness increases when scores on selected symptoms increase) whereas blue line indicates the line the data actually fit on.

Results from both regression analyses reported that positive symptoms largely predict suicidality whereas negative symptoms are more associated with hopelessness. Potentially, with a central role of hopelessness which is predicted by social withdrawal and is strongly related to suicidal behaviour. The important role of social withdrawal and hopelessness led to a mediation analysis to determine whether hopelessness plays a role of mediating any association between social withdrawal, active social avoidance, and suicidal behaviour.

5.8 Mediation Analysis

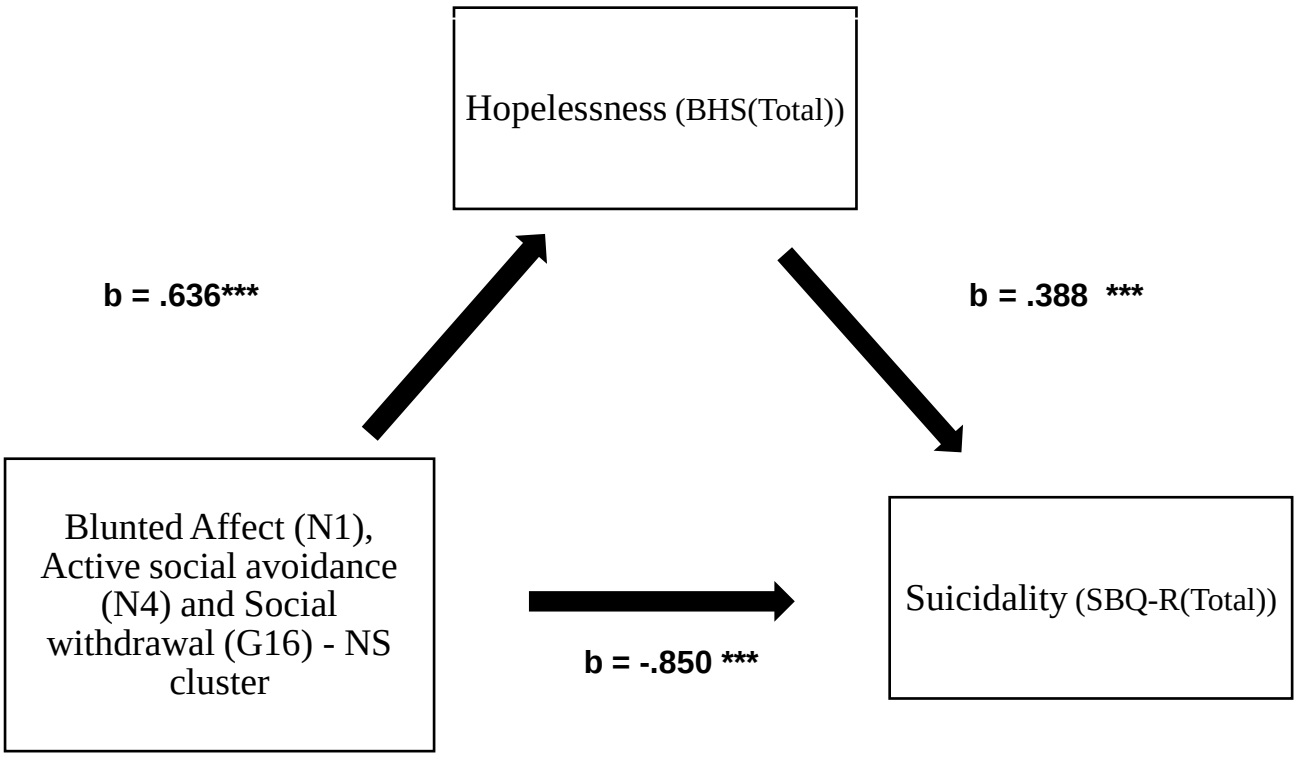
The mediation model focuses on the estimation of the effect of negative symptoms cluster of blunted affect, social withdrawal on suicide through the mediator variable of hopelessness; causally located between blunted affect, social withdrawal symptoms and suicide. Where N1, N4 and G16 are the input variable (X), suicide is output (Y) and hopelessness is the Mediating Variable (M_1).

The effect between X and Y was tested using a percentile bootstrap estimation approach with 1000 samples (263), implemented with the PROCESS macro Version 3.4 (262) in SPSS IBM Version 26.

Based on regression results negative symptoms cluster was associated with both suicidality and hopelessness. The potential model establishes two pathways which influence suicide by direct and indirect effect. The mediational analysis reports that negative symptoms cluster leads to suicide through hopelessness (M1).

The direct effect from negative symptoms cluster of blunted affect, active social withdrawal and social avoidance to SBQ-R(Total) score was negative (b=-.850, s.e= .3567, p= 0.01), indicating that the combination of these symptoms do not contribute on the development of suicidal behaviour, and indeed on their own may protect against this. However, the indirect effect of negative symptoms cluster to suicidality may be mediated by hopelessness with results indicating the positive association between negative symptoms cluster and hopelessness (b= .636, s.e = .4773, p= 0.01). Hopelessness is also positively associated with suicidality (b = .388, s.e = .0989, p= .002). This suggests that negative symptoms cluster can be considered as a significant risk for suicide when compounded by hopelessness (see Figure 5.5).

Figure 5. 5 Mediation model



Note: ***p<0.1; **p<0.05; ***p<0.01**

5.9 Discussion

The current study explored firstly the association between blunted affect, social withdrawal, and suicide in people with schizophrenia. Secondly, it examined the mediating potential of hopelessness in predicting suicidal behaviour in those with high levels of blunted affect and social withdrawal. The data suggests that from a negative symptoms cluster, only social withdrawal (G16) can be a direct predictor of suicidal behaviour whereas negative symptoms as a group associate more with hopelessness. Positive symptoms were also found to be predictors of suicidality, as stated in literature (176,188). Hopelessness has been reported to play a significant role as a mediator factor between negative symptoms and suicidal behaviour. The analysis in this chapter enables some insight regarding the relationship between the lack of emotion display, social withdrawal, suicidal behaviour, and hopelessness in schizophrenia.

It was hypothesised that suicide behaviour would increase in patients with high scores on blunted affect. However, results found that there is no such straightforward relationship and therefore the hypothesis has not been supported. Both correlations and regressions reported no significant association between blunted affect and suicidal behaviour. One explanation for this is that negative symptoms do not act independently as they can impact patients' clinical condition as a cluster of symptoms and not as independent factors. Emotional withdrawal relates significantly with all other negative symptoms including blunted affect, poor rapport, passive apathetic/social withdrawal. According to McGirr et al., (264) negative symptoms impacted on suicidal behaviour only as a group of symptoms. In comparison to positive symptoms, which are able to impact clinical condition independently from other symptoms or risk factors. Negative symptoms have been reported as "not

acute" and therefore as less powerful symptoms in terms of their individual intensity. McGirr and colleagues found consistent evidence with data in this thesis as patients who reported high levels of suicidal behaviour had scored highly on at least two negative symptoms. Another explanation why the hypothesis has not been supported, is in keeping with Tarrier's et al.,(265) study. They reported that the lack of emotional display might not lead to suicide; as it reflects a reduction in emotional responding of patient's emotional and psychological state, upon which suicidal thoughts and behaviour are elaborated. Since negative symptoms concern emotional impairments, then by their nature, they will limit or slow down the development of emotional reactivity. Thereby, it is less possible for a person with schizophrenia to develop strong and powerful suicidal thought.

In regards to the gender differences, existing literature suggests that males are more likely to complete suicide compared to females and the gender differential is most apparent at older ages (266). However, females are more likely to attempt suicide and experience non-fatal behaviours compared to males (267). This study justifies the current finding as 56.6% of females (17 out of 30) scored high on SBQ-R(Total) whereas 40% of males scored high on SBQ-R(Total).

The novelty in this study is how under-reported schizophrenia symptoms may impact suicidal behaviour. In the case of examining negative symptoms individually, there is no positive relationship between each negative symptom and suicidal behaviour in patients with schizophrenia. Results show that high scores on a single negative symptom only, cannot predict suicidal behaviour or it has no power to develop a suicidal behaviour in people with schizophrenia. However, participants who scored high on at least 2 -3 negative symptoms have been found to be at a high risk for developing a suicidal behaviour. For example, scoring highly on blunted affect only

does not put the patients into risk for a suicide attempt. Following this idea, if the same patient scores high on passive apathetic social withdrawal (N4) and active social avoidance (G16) then the risk for attempting suicide increases. This implies that negative symptoms may be considered as a suicide risk factor if there is an interaction between them.

Symptoms concerning emotional expression and social interaction lead to the lack of interest in involvement with people, absence of affective commitment to life events and lack of facial display of inner state (265). Therefore, these symptoms can impact suicidal behaviour indeed. However, previous studies suggest that these symptoms impact suicidal behaviour only through depression, hopelessness and feelings of dissatisfaction which have been suggested consistently to determine suicidal behaviour in schizophrenia (233,268). Taken together, blunted affect and emotional withdrawal are associated with suicide only in the case that these factors relate to depression and/or anxiety and hopelessness. Otherwise, they seemed to have a suppressive effect to suicide. This might provide further information regarding protective factors in suicidal behaviour, as it seems that the lack of motivation to act, the lack of energy and the suppressing nature might incommode the patient to attempt suicide.

However, blunted affect as a protective factor does not apply when other symptoms, potentially acting as mediators to suicidal behaviour, are present. Previous studies on depression and suicide are consistent with current findings as they reported that depressive symptoms were almost twice as common in the patients with suicidal behaviour compared to the control group. However, they also impacted other aspects of patients life such as social functioning and motor issues due to the comorbidity between depression and negative symptoms (270,271). Consequently, negative

symptoms of flattened emotional expression and social involvement may put people at risk for suicide only when features of depression and hopelessness are also present.

In contrast to negative symptoms, positive symptoms impact on suicidal behaviour in a much direct and acute way but at the same time drastically and independently, as they tend to determine patients' clinical presentation and behaviour. For example, with command hallucinations or acting on delusional beliefs. It has also been suggested that positive symptoms act as independent features not only regarding suicidal behaviour or negative symptoms but to other features such as intelligence which justifies the acute and determinant role of positive symptoms in schizophrenia (272). In their study Taylor et al., (273) reported that certain positive symptoms (mainly hallucinations and suspiciousness) not only impact suicidal ideation but are the most enduring symptoms in schizophrenia. Hence, they might contribute to perceptions of defeat and entrapment which develop perceptions of failure, loss without a way forward or means of escape (275).

Based on this idea, hopelessness has also been examined as a mediator since literature reports consistently that feelings of hopelessness are strongly associated to completed suicide in schizophrenia (215). Although the regression's results reported that positive symptoms likely be associated with suicide (182), they were not as relevant for predicting hopelessness. In contrast negative symptoms of social withdrawal and active social avoidance were associated with hopelessness. The relatively weak relationship between positive symptoms and hopelessness may be due to the experiences of hallucinations and delusions, which have a limited effect on persons' expectations of their future and ability to chase their goals over time (276). When hopelessness was used as depended variable in multiple regression, no item

from positive symptoms cluster predicted significantly high levels of hopelessness compared to negative symptoms cluster which predicted high levels on hopelessness. 3 out of 7 items in negative symptoms cluster were suggested as significant predictors for hopelessness. This finding has important implications as it demonstrates a) the power symptom clusters have on critical features for suicide such as hopelessness and b) that hopelessness may act as a mediator between negative symptoms and suicidal behaviour.

Results presented in this analysis are consistent with the literature suggesting that positive symptoms work as dominant and independent features where they can change dramatically patient's presentation, emotional state, and suicidal behaviour. Zubin and colleagues have reported that positive symptoms are predominantly episodic (277) which might be the reason positive symptoms fluctuate in such acute way. Another reason might be the timing positive symptoms occur. Research suggests that positive symptoms occurring at the first phase of psychosis and therefore have a significant prognostic importance for later functioning (278). They have also been named as the features that absorb all the initial attention from clinicians (279).

In contrast, negative symptoms, which may have a longer duration compared to positive symptoms, do not have such acute effect on patients' presentation (264). This finding is also justified by the idea that negative symptoms and other conditions such as depression are overlapping domains with distinct presentations (280). Literature reported negative symptoms to be persistent over time which is not the case with positive symptoms (272,279).

Regarding the mediation model, data demonstrated that social withdrawal as part of a negative symptoms cluster, links to suicide through hopelessness, but the question that arises is through what mechanism? There is some evidence suggesting that the key to answer this is to look at the role of anxiety in schizophrenia. Specifically, studies on anxiety and suicide in schizophrenia found that anxiety-related symptoms are a risk for higher levels on positive and negative symptoms. For example, poor social functioning as a negative feeling which links to social isolation and distorted thoughts about reality, self-esteem and poor rapport (281). In result, the individual is more likely to develop feelings of worthlessness, hopelessness and depression and therefore is at risk for a suicide attempt (282). Although, the role of anxiety has not been examined in this chapter. Examining anxiety might be providing insight on under what terms hopelessness acts as a mediator between social withdrawal and suicide and a new question to be examined in future research.

The current study is subject to strengths and limitations. The main strengths are that the study includes a relatively large sample, there is a use of in-depth multiple interviews and other assessment tools and it conducted while the patients were undergoing the acute phase of the disorder, which allowed us to see the nature and impact of certain symptoms. The main limitation this study presents it is the cross-sectional data, which do not allow us to observe patients' performance over time and therefore make predictions. Thus, longitudinal data is needed for examining the temporal relationship between experiences or symptoms to infer any real mediation or cause and effect, of the actual impact on symptoms and in turn on suicidal behaviour. A second limitation in this chapter is the absence of a control group. Having healthy controls in the case of negative symptoms and suicidal behaviour would provide a greater insight on the differences on symptomatology and outcomes

in the two groups. This would also provide evidence on whether suicidal behaviour is due to clinical symptoms, such as positive symptoms or other factors. We acknowledge that the lack of control group can bring clinical implications such as misunderstandings of whether clinical symptoms are the only risk factors for suicidal behaviour. However, the reason a healthy group has not been used in this thesis is because such data was not collected as part of this study, as the main aim of the FEP-A study was different form the research question of this thesis. The FEP-A study aimed to examine the association of autism spectrum traits, suicidal behaviour and depressing symptoms in people with psychotic experiences. A third limitation is the heterogeneity on PANSS and SBQ-R(Total) scores as there were not enough participants who scored high on both scales and vice versa. Moreover, a fourth limitation is the use of self- report measures, which infers validity problems. In the case of self-report measures, the patients may exaggerate or under-report the severity or frequency of symptoms. A fifth limitation is the imbalance between the number of men and women participating in the study, which might impact the representativeness of the results. One last limitation in this study is the clinical presentation of potential participants. The lack of engagement due to severe symptoms (recruitment conducted during FEP period) led to exclusion of those participants who could have provide a significant input to the research results.

Efforts to understand suicide risks in schizophrenia are of great importance and the findings presented in this study are relevant to clinical practice and research community. The lack of emotion display affects the way we behave socially, and our social interaction and behaviour affects the way we perceive life and how much we value our existence. Future examination on features that determine suicidal behaviour is needed if we aim to reduce suicide rates and build on the results

presented here. Further research on social isolation, loneliness, lack of emotion expression, anxiety could help build more accurate risk prediction and effective interventions.

In summary, this chapter explored the association between lack of emotion display, social withdrawal and suicide and presents findings on how negative symptoms may impact the development of suicidal behaviour in schizophrenia. Although individual negative symptoms do not directly appear to influence suicidal behaviour, the interaction between negative symptoms of social interaction and of social avoidance may have the power to impact suicidal behaviour in patients with schizophrenia. Lastly, negative symptoms are significant predictors of hopelessness, which occur with emerging social consequences in schizophrenia; serious social decline, emotional stagnation, feelings of worthlessness and should be considered as factors that may influence whether people with schizophrenia will choose death over life.

CHAPTER 6: BRAIN FUNCTIONING AND SUICIDAL BEHAVIOUR IN SCHIZOPHRENIA

6.1 Introduction

The field of neuroimaging has facilitated a paradigm shift in psychiatry research. Findings from multiple studies have clarified that mental disorders such as schizophrenia are associated with objective signs of changes in brain structure and function (283). Functional magnetic resonance imaging (fMRI) is a way to infer brain activity by measuring changes in blood flow. When the neuronal activity increases the demand for oxygen increases and therefore there is an increase in blood flow to regions of increased neural activity (284). fMRI is beginning to provide meaningful information in terms of how schizophrenia symptoms are associated with brain activity by identifying neural systems involved and how they relate to cognitive and behavioural dysfunctions (285). Studies on regional brain activity focusing particularly on the regions associated with the executive functions, and symptoms associated with the disorder, (101) lead to the development of new insights for clinical challenges such as suicide.

The lifetime risk of suicide in psychosis is approximately 5% (81,188,286). Furthermore, 15- 26% of patients with FEP are likely to have attempted suicide by their first treatment contact (at least once), and approximately 2–11% will attempt suicide over the first year after treatment onset (287). Examining suicidal behaviour and accurate prediction of it in first episode psychosis (FEP) can be a difficult task. Particularly, considering the multifactorial character of suicidal behaviour (288) and the severity of the symptoms the patients might experience. There is an urgency in exploring further the issue of suicide in this population.

The use of faces tasks in the early course of schizophrenia has previously shown profound and disabling deficits on emotion recognition and cognitive dysfunctions (289,290). Following this and as discussed in chapter 5, symptoms related to impairments on emotion processing such as social withdrawal may be associated with suicidal behaviour. Therefore, the use of a faces task could be a suitable tool to investigate functional differences in brain areas associated with emotional processing, negative symptoms, and social withdrawal. This is an exploratory chapter. It aims to investigate the whole brain activity in patients with schizophrenia, who report high or low measures of suicidal behaviour, in order to provide new insights into the underlying mechanisms.

6.1.1 Previous cognitive and neuroimaging studies in suicide and schizophrenia

In suicidal behaviour investigation, Keilp et al., (291) found that ‘‘high lethality attempters’’ (the people who reported increased number of prior suicide attempts, suicide planning and substance use immediately prior to the attempt) scored lower on tasks on attention, memory, and general intellectual functioning. That was in comparison to low-lethality attempters. He hypothesised that pre frontal cortex (PFC) activity is impaired in patients who have a history of significant suicidal behaviour. Following this, Desmyter et al., (217) in their review attributed activity in suicidal patients to PFC dysfunction, mainly in the areas regarding problem solving abilities. They also found that the same participants reported a higher propensity to act on negative emotions and therefore higher possibilities to develop hopelessness and other condition that contributes on suicide.

Low activation in PFC and orbitofrontal (OFC) cortices, have been suggested to be of great importance in suicide as they are involved in executive (decision-making and other cognitive functions), reward processing – which associates with our motivations, intentions and drives - and communicate directly with emotional processes such as emotion regulation and social behaviour (95). This is because frontal cortices (PFC and OFC) are areas related to the encoding of the value of the outcome we want to achieve (how important this outcome is for us) (292). Therefore, a poor function of these processes might lead to higher risk for suicide. In other words, these brain regions are necessary not only for decision-making and problem solving but also for making predictions about our decisions based on current information we hold (293). Our behaviour and actions are guided by the information processed regarding the reward outcome (our goal) and that may be key to maintaining hope in adverse circumstances.

Studies focusing on suicidal behaviour in schizophrenia, consistently point to the relationship between these frontal cortices and emotion-related areas such as the amygdala (119,288). Previous studies have also reported that amygdala have effect on disturbances on emotional processing in patients with schizophrenia (50), and contribute to abnormalities on prefrontal areas and influence impulse dysregulation which has been reported to play a role on suicidality (295). Specifically, there is evidence suggesting that the OFC-amygdala network plays an important role on impulsiveness and emotion disturbances. For instance, emotional numbness (feeling emptiness or despondency) which is potentially linked to suicidal behaviour in schizophrenia (296).

The limbic system is the brain region involved in our behavioural and emotional responses, and is very important especially when it comes to responses such as fight

or flight or survival-related responses. Hence, it seems to have an important role in suicidal behaviour in schizophrenia and it may be related to how patients develop social behaviour and process their emotions (297–299). Although the common view is that amygdala's role is to process stimuli related to threat or danger, it seems that its role is much broader. Research shows that amygdala plays an important role in choosing which people we trust (105,300) and also it impacts the size and the complexity of our social network (301). A research demonstrated that patients with larger amygdala volume tend to have more complex and bigger social network size compared to people with smaller amygdala volume. This is based on the notion that amygdala's processing capacity it is likely to depend on its size (107). This is important to mention as social isolation and lack of interaction with community has been suggested as main suicide risk factors in schizophrenia. Keeping up with these results, other fMRI findings on suicidal behaviour report an interaction between frontal cortices and limbic system. Existing studies suggested that a diminished PFC activation might result in dysregulation of mood and contribute to poor decision-making and impulsivity in suicide attempters (302,303).

Additional studies suggested that dysfunction in both frontal and emotion related areas such as amygdala are involved in multiple functions. Namely, emotional, and cognitive control and therefore may also play a significant role on suicidal behaviour development (305). In their study, Jollant at al., (304) drawn attention to the relationship between abnormalities in frontal cortices and impairments in decision-making in people who experience suicidal behaviour. They suggested that people experiencing such abnormalities reported higher scores on suicidal behaviour, particularly if depression was present. In another study, examining suicidal behaviour, Hercher et al., (305) reported that anterior cingulate cortex (ACC) is the

brain area that connects limbic structures and the frontal lobes ,and it integrates cognitive activity with affective experience. Therefore, a reduced function of ACC may indicate potential alterations in emotion related areas and increase the risk for a suicide attempt.

However, differences in people with and without suicidal behaviour in schizophrenia are not limited to the functional neuroimaging. Minzenberg et al., (306) compared patients with and without history of suicidal tendency (attempt or ideation), and reported that the patients who attempted suicide showed significant volumetric reduction with a network of frontal brain regions such as the left middle frontal gyrus. Furthermore, several other brain areas such as left superior, left medial, right middle, and right medial, premotor cortex and dorsal anterior cingulate were associated with suicidal ideation. They suggested that suicidal behaviour in schizophrenia is directly related to the structural differences in multiple frontal areas. This may imply difficulty in forward planning and abnormalities on ‘‘proactive control’’ function which impact patients’ ability to plan ahead, control and manage their life.

Research on brain connectivity also provides insight on suicidal behaviour in schizophrenia. In their study, Zhang et al., (307) observed reduced connectivity of the anterior cingulate gyrus and PFC in high suicide risk in patients with schizophrenia compared to the patients with low suicide risk (305). The results demonstrated that patients with a high risk of suicide may have difficulty in decision-making processes through reduced communications between emotion and executive decision-making regions in the brain. Although, evidence on structural MRI and connectivity contribute significantly to the field of neuroscience, this chapter uses fMRI as it is the most accurate tool we have for examining face recognition. Since faces are the most important visual pattern for humans, and provide important information regarding

emotion expression, which is the main focus in this thesis. Another reason for the preferred use of fMRI over other methods, is because it provides precise outcomes on how the face/emotion recognition develop in our brain. Also, how we respond to emotional/social stimuli which associates significantly to suicidal behaviour (308).

Therefore, the heterogeneity of suicidal behaviour makes it difficult to characterize accurately, although it may involve maladaptive attentional and decision-making processes; and emotion disturbances, which affect many aspects of patients' function. Examining the whole brain activity in response to emotional faces may provide a general picture of how brain function in people with suicidal behaviour by eliminating the risk of potentially excluding additional or novel areas of interest.

6.1.2 The role of facial expression in suicidal behaviour in schizophrenia

The ability to recognise emotions based upon facial expression is critical because it is the foundation of the construct of social cognition and adaptive behaviour (309). People who display emotions themselves and recognise emotions in others can influence their social behaviour too. In their study on social cognition, Adolphs et al., (310) found that people with impairments in limbic system, judged as approachable faces that people with no impairments considered as the most unapproachable. This might suggest that such impairments of how we judge people based on their face expression or how we perceive others' emotions, might lead to our decision to approach or to disconnect socially from those people; due to the lack of feelings of trust these faces develop in us.

As rehearsed in chapter 5, social withdrawal, and other related symptoms, can affect the development of suicidal behaviour in schizophrenia (blunted affect relates to

suicide indirectly). Kiosses et al.,(311) examined the relation between emotion and suicide in an older psychiatric population and introduced a model based on a diathesis of emotional expression, in which suicide is linked with the poor ability to express even negative emotions (e.g. feeling sad or fearful). According to the same study, social cognition, decision-making, and emotional regulation are impaired and become mediating factors for suicide in those with mental disorders, including schizophrenia. Further studies have reported the important role of social behaviour and emotion processing in suicidal behaviour in schizophrenia suggesting that such abnormalities can be a high risk for suicide in clinical population (297,298).

Other disciplines also highlight the importance of facial recognition not only in human beings, as it allows an animal to distinguish animals from the same, or a different, species to ensure its survival (312). The field of evolutionary psychology has demonstrated evidence suggesting that the importance of face recognition in primates lies on the fact that it appears to be a ‘special’ ability that has been selected for, through evolutionary pressures, and conserved across species (313). Therefore, it is of high significance on individuals’ lives. Furthermore, disciplines such as cognitive psychology report that faces are somehow perceived differently by the brain than other patterned objects individuals might see, and thus, may represent a special stimuli and information (314).

Understanding emotion-related abnormalities in schizophrenia will lead to the development not only of better tools to extract data regarding these functions but also of the development of targeted interventions. Therefore, understanding and focusing on emotion-related functions can be of great importance in suicide research. Since suicide risk factors such as depression and hopelessness are emotion-oriented

conditions; related directly to emotion processing dysfunctions (315) which are characterized by strong feelings of sadness, guilt or worthlessness (316–318).

6.1.3 Using face task in examination of suicidal behaviour in schizophrenia.

The use of a faces task in neuroimaging is a common way to extract outcomes in relation to neural activity during fMRI. A face task is a short visual input of gray-scale images of faces during an fMRI scan, showing either happy, sad, and fearful, angry or neutral expressions (319). The importance of using faces task, though, lies on the kind of information we extract by using such tools. One of the main reasons we need such information is because such processes are vital mechanisms, which allow people to recognise emotions, shape social behaviour and communicate. Therefore, it is important to test whether they function properly.

There is no doubt that the better understanding the nature of suicidal behaviour in schizophrenia is increasing over years. Several studies using fMRI have contributed on identifying certain brain areas related to suicidal behaviour in schizophrenia, including the frontal cortices and regions from the limbic system such as amygdala (120,288). Although this chapter focuses on functional evidence, other studies on structural MRI noted a significant link between a variety of genetic, biochemical, brain abnormalities and suicidal behaviour in schizophrenia (320–322).

However, gaps in the literature still exist. Although most of the neuroimaging studies examined specific brain areas that may have an effect on suicidal behaviour, less focus has been given in examining the whole brain function. Focusing on specific areas might provide precise examinations on how each area impacts suicidal behaviour. However, this can lead to a significant limitation as conducting a region of

interest (ROI) analysis might lead to compounded type 1 errors. This chapter, thus, will investigate whether people with high versus low suicidal behaviour show different whole brain function during exposure to fearful vs neutral faces.

6.2 Aims and Hypothesis

The aim of this chapter is to examine the differences in brain activation during the faces task in FEP patients with high vs low levels of reported suicidal behaviour.

I hypothesise that patients with FEP reporting high levels of suicidal behaviour will show different brain activation potentially in the amygdala and PFC (including OFC) during the fearful vs neutral faces compared to patients with low levels of suicidal behaviour.

6.3 Methodology

6.3.1 Study Design

A cross-sectional design was used consisting of two sessions (clinical assessment and brain scan) by interviewer. Self-reported measures conducted and scored by trained researchers and a functional Magnetic Resonance Imaging using the Faces Task.

6.3.2 Setting

All participants were recruited from the Birmingham Early Intervention Services (EIS). EIS aim to provide intensive support from a specialist team to young people with a

first episode of psychosis for the first 3 years of their illness. It is an attempt to reduce duration of untreated psychosis and provide early access to treatment (Bird et al., 2010). It has been shown that the provision of such services provides better clinical outcomes compared to general services (such as GP services) and they are also cost effective.

Recruiting participants from Birmingham was also an interesting attempt as it is a city with more than 1 million citizens and characterized by cultural diversity including large communities of Black and Muslim people (323). In Birmingham, there are four early intervention teams (North, South, East, West).

6.3.3 Participants

Data was collected as part of the BioPoP pilot study (Biological Correlates of dimensional symptoms of psychosis). The aim of the BioPoP study, was to examine whether specific biomarkers can be identified for positive symptoms, depression, and poor functioning in first episode psychosis. Informed consent was obtained from all participants. Ethical approval was granted by the UK Health Research Authority's National Research Ethics Service, reference number: 15/WM/0255.

The PhD candidate was responsible for recruitment of 18 out of a total of 24 subjects. Both males and females from all ethnic backgrounds recruited with age range 18-35. The inclusion/exclusion criteria provided in Table 6.1.

Table 6.1 Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• First Episode Psychosis • Current Positive Symptoms as defined by 3 or more on at least 1 item from PANSS positive scale • Within 12 months of treatment onset • Capacity to consent • Demographic Details of age, gender and ethnicity	• Significant risk to self or others • Contraindications for MRI (i.e. Pregnant, implanted metal device, history of working with metal) • IQ< 70 • Significant Neurological disorder • DSM-V defined dependence on alcohol or illicit substances

6.3.4 Procedure

Participants' recruitment took place in Early Intervention South Team NHS in Birmingham. After the researcher explained study's criteria and aims to clinical staff in the team, the care coordinators screened for eligible participants and discussed with the researcher regarding their eligibility. According to the protocol, the care coordinator discussed the study with the potential participants and if pre-consent given then the researcher arranged to visit the participant at home with the care coordinator present. After providing the relevant documents (Participant's Information Sheet - see Appendix A-16) and informed the participants about the aim of the study. The patients could ask questions then and any other time before and after consenting to participation in the study. The researcher allowed 24 hours to the participant to decide whether they want to take part in research. After 24 hours, the researcher contacted the participants and if the response was positive then the researcher booked the first appointment with the participant. All participants were

screened for conditions for which fMRI would represent a health risk or other conditions such as experiencing severe symptoms and lack of engagement and would have been excluded if any contraindications were present.

Participants were informed that they may terminate the study at any time without needing to provide a reason. All study participants received comprehensive written information and had the opportunity to discuss any aspect of it with the researcher. When participants were satisfied with the aim of the study and information received, written consent was obtained, signed by the participant and the researcher (the candidate and one more researcher involved in this study - see contributions p.12). The researcher asked the participants to consent for their GP to be contacted regarding their participation in the study and in cases where any brain abnormalities were detected, for their GP to be informed of the findings. The researcher also explained that confidentiality will be maintained by assigning a unique identifier to all data. Name and contact details would be stored separately from the data obtained. Personalized data would only be available to immediate members of the research team. After completion of the project, raw data and results will be archived in a database at the University of Birmingham and stored.

6.3.5 Measures Used

Participants were assessed on a battery of measures as below:

1. Demographic information on a datasheet created for the purpose of this study.
2. Positive and Negative Syndrome Scale (PANSS) (242)
3. Suicidal Behaviours Questionnaire- Revised (SBQ-R) (244)
4. Mini- International Neuropsychiatric Interview (M.I.N.I.) (324)

5. Calgary Depression Scale for Schizophrenia (CDSS) (325).
6. World Health Organization Disability Assessment Schedule (WHODAS) (326).
7. Scale for the Assessment of Negative Symptoms (SANS) (327).
8. Affective Lability Scale Short Form (ALS-S) (328).
9. Young Mania Rating Scale (YMRS) (329).
10. Psychotic Symptom Rating Scales (PSYRATS) (330).

The three scales used for the analysis in this chapter are described below:

1) The Positive and Negative Syndrome Scale (PANSS) was used for measuring the positive, negative, and general symptoms of schizophrenia and psychosis. Each domain was assessed by a series of questions, which will then be used to rate on a 7- point severity scale (1-7). Based on the domains that have been used in this analysis the minimum total score = 14 and the maximum total score = 98.

2) The Suicidal Behaviours Questionnaire- Revised (SBQ-R) is an accurate assessment of the suicidality in early psychosis designed to identify risk factors for suicide. Scores (1-15) on the SBQ-R are shown to differentiate between subgroups of suicidal-risk and non-suicidal participants reliably; if score >= 8 equals high suicidal behaviour, score <=8 equals low suicidal behaviour (246,247).

3) The Mini- International Neuropsychiatric Interview (MINI) was designed as a brief structured diagnostic interview to meet the need for a short but accurate structured psychiatric interview for multicentre clinical trials and epidemiology studies. Also, to be used as a first step in outcome tracking in clinical settings with high validity and reliability. Main domains examined for this analysis are depression, anxiety, social

phobia, substances use and panic attacks. The structure of the assessment is set up like a decision tree or branching flowchart that leads to the specific diagnosis only if several criteria are met (based on patient's responses – Yes or No) (324).

6.3.6 fMRI Task

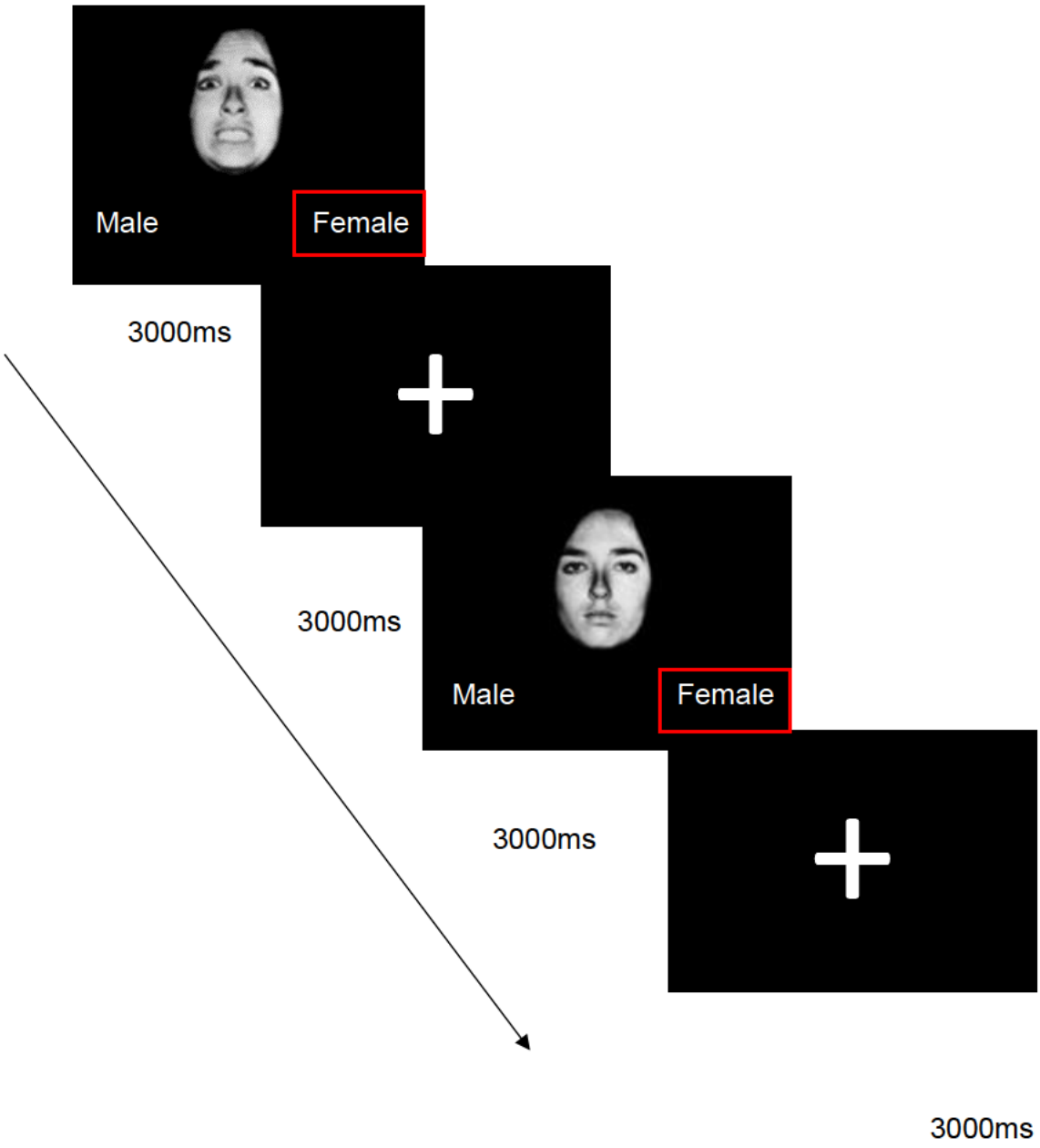
The faces task on BioPoP study consisted of blocked presentation of faces including neutral, happy, sad, and fearful emotions and rest blocks. Faces were presented in alternation in the following order: neutral, happy, neutral, sad, neutral, fearful, rest blocks. Face images were taken from the Ekman & Friesen (331) facial affect series. Pictures were gray-scale and cropped, using the same contour to hide the hair and neck. Visual faces were back-projected onto a screen at the end of the scanner bore and viewed through an angled mirror (see Appendix A-23 & A-24). A black background and central white crosshair remained present throughout the experiments. The faces were each displayed individually (one after the other) for 3 seconds and repeated 3 times (128 images displayed in total) and a total of 36 functional images were extracted.

The faces were never presented in the same order twice. Participants were instructed to press the right or left button with their dominant hand using their index finger and middle finger on a button- box to indicate face's gender (male or female) and to respond as accurately as possible. Therefore, the participants' focus was not on the emotional expression, rather determining gender; however, they were presented with a randomised sequence of male/female faces with neutral, happy, sad, and fearful facial expression. Stimulus gender (50% male) was fully randomized. Subjects received all the information about the task before they entered the scanner. All participants completed a condensed practice version outside of the scanner just

before entering to ensure they understood the task and instructions. Participants were also reminded about the instructions before the task began. Another reason this was important to be done prior to the actual brain scan was to make participants familiar with the process and the task. Therefore, reducing the risk for anxiety feelings or other behaviours that might put the participant in risk. Total time of task was 8 minutes. Behavioural measures including accuracy and reaction times were collected throughout the task.

The focus of this study was the contrast between fearful faces vs neutral faces as existing evidence suggest that patients with schizophrenia show most marked differential responses in brain activity (i.e medial PFC and amygdala) during processing of fearful faces compared to other emotional stimuli (325). There is also evidence that schizophrenia patients experiencing particularly psychotic symptoms, have increased levels of fear and arousal (326), compared to other emotions. Therefore, targeting this emotion reaction can be quite informative. Other studies suggest that exposure to fearful faces in schizophrenia shows significant differences in activations in the PFC compared to other samples (327,328).

Figure 6.1. Face task during fMRI (fearful face followed by a blank slide with a fixtion cross and then by a neutral face)



6.3.7 fMRI data acquisition and pre-processing

Neuroimaging data acquisition for BioPoP study was undertaken at the Birmingham University Imaging Centre (BUIC) using a 3T Philips Achieva MR scanner equipped with a 32 channel SENSE head coil. The neuroimaging procedure involved a) A structural MRI: Whole Brain T1 Weighed Structural MRI Imaging was performed using 3D volumetric spoiled gradient eco imaging, b) a Functional MRI Task in which participants participated in a faces task. Accuracy and reaction time during facial recognition task was recorded using E-Prime Professional 2.0 software (332).

Thirty-six functional slices were acquired with zero slice gap, parallel to the anterior-posterior commissure line using gradient-echo planar imaging (EPI) sequence with an echo time of 35 ms, matrix= 64 x 64, a flip angle of 90°, a repetition time (TR) of 2.2 s and a voxel size 3 x 3 x 3 mm. A total of 175 volumes were acquired. The total imaging procedure time including participant's preparation was 60 minutes in total with the Faces task taking a total of 8 minutes (for structural images -T1- please see Appendix A-25).

Initial pre-processing steps were used in accordance with typical fMRI analysis procedures to increase validity and accuracy of the data, considering the external noise or individual's amount of movement. The preprocessing of images was carried out using Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, University College London, UK http://www.fil.ion.ucl.ac.uk/spm/Wellcome) and Matlab (Mathworks, Natick, MA, USA). All images were reoriented to the anterior-posterior commissure, slice time corrected with the middle slice being the reference, realigned to the first image in the series to correct for head movement, co-registered to the T1-weighted anatomical

image, and normalized to the Montreal Neurological Institute reference space. Normalized images were smoothed with a 6mm full width/half-maximum Gaussian kernel.

In terms of images quality, poor and excluded scans refer to those with ringing, blurring or distortion, whereas good scans refer to those with clear details in brain regions. Artefacts due to head movement or physiological noise were corrected using the ArtRepair toolbox (Centre for interdisciplinary brain science research, Stanford University, USA; http://spnl.stanford.edu/tools/ArtRepair/ArtRepair.htm). Corrected images that still presented a poor quality with no clear details (even after correction) were excluded too.

6.3.8 Data analysis

6.3.8.1 Demographic, clinical, and behavioral data

The demographic data was described using descriptive statistics. Behavioural data was collected using E-Prime Professional 2.0 (332) and analysed using SPSS IBM version 26. Accuracy and reaction time were recorded for each participant in the study. A t-test conducted to compare reaction time and accuracy between High SBQ and Low SBQ-R group for both factors. Clinical data such as PANSS, SBQ-R(Total) and MINI scores, was analysed using SPSS IBM version 26 as well.

6.3.8.2 fMRI Analysis

The GLM approach implemented in SPM 12 was utilized for fMRI data modelling and analyses. The most widely used technique for this kind of analysis capitalizes on changes in blood flow and oxygenation associated with neural activity (the hemodynamic response), and on the differing magnetic properties of oxygenated and deoxygenated blood (BOLD method). Each epoch type (neutral faces, happy faces, fearful and sad faces) was modelled in a boxcar design. In the GLM, the predictors of the epochs included the onsets of epochs, and six movement parameters (i.e. three translation and three rotation parameters) from the pre-processing analysis.

A block analysis was carried out using for the fearful faces versus neutral faces. The contrast image produced for each of the above and the contrast vector were entered into second level random-effects analyses.

The single group second level analysis consisted of voxel wise one-sample *t-test* for fearful versus neutral faces. The criterion for inclusion of a voxel in a cluster was set at $p < .05$ (uncorrected) and a cluster was considered as significance at level of $p < .05$ FWE (Family wise error) corrected for multiple comparison across the entire brain

The between-group (Low SBQ group>High SBQ group) comparison was done using two sample t-tests with the significance criterion based on the spatial extent of suprathreshold voxel clusters, a method proposed by Friston et al., (333). The criterion for inclusion of a voxel in a cluster was set at $p < .05$ (uncorrected) and a cluster was considered as significant at level of $p < .05$ (FWE corrected). All the results reported in MNI152 coordinate standard system.

6.4 Results

6.4.1 Demographic data analysis

Over the period 2016-2018, 24 patients were recruited. Out of 24 recruited participants, 12 completed the brain imaging. Participants who dropped out mainly reported being overwhelmed and anxious regarding the scan which was quite noisy. This was mainly due to patients being claustrophobic. Two participants dropped out before getting into the room, seven experienced feelings of panic and sweating, making them unable to carry on the research and three participants were unable to do the brain scan due to piercings or coloured tattoos.

Out of 12 participants who completed neuroimaging procedures, 8 participants had data that were suitable for brain imaging analysis. Reasons for exclusion of 4 participants' data were: 1) stretched T1 (one participant) and functional images (one participant) and 2) missing behavioural data (two participants who did not press the buttons fully on the face task or forgot to press the button entirely). These four participants did not report higher scores on PANSS than the participants who were included in the data analysis. All 8 participants who had suitable brain imaging data completed all clinical assessments including PANSS and SBQ-R(Total).

6.4.2 Demographic data

Whole sample consisted of 24 participants, with 14 males and 10 females. Age ranges from 20 to 36. Most of the participants were White British (10 out of 24) and smokers (14 out of 24) (see Table 6.2). Of the 8 participants (5 males and 3 females) with usable brain imaging data, the mean age was 26.5. Half of the included participants are Asian (Indian, Pakistani, Bangladesh and Chinese), 3 are White

British and 1 is Black African. 4 out of 8 participants have school qualifications. 3 participants have graduated from college and 1 participant has no qualifications (see Table 6.2)

Table 6.2 Demographic data including mean and Std.D for eligible participants.

	Total sample (n=8)	**Percentage %**	**S.D**
Age (mean)	26.5		6.90
Gender			
Male	5	62.5%	
Female	3	37.5%	
Ethnicity			4.80
White(all)	3	37.5%	
Asian(all)	4	50%	
Black (all)	1	12.5%	
Highest Qualification			0.70
Collage (A-Levels, BTech etc)	3	37.5%	
School leaving qualifications	4	50%	
No qualification	1	12.5%	

6.4.3 Clinical data

The participants were divided into 2 subgroups based on their scores on SBQ-R(Total). Both high and low SBQ groups included 4 participants. High SBQ group

was consisted of 3 males and 1 female aged 20-33 whereas the low SBQ group was consisted of 2 males and 2 females aged 21-36 (see Table 6.2). The cut off point for allocating each participant in the right group was number 8 (if score >= 8 equals high suicidal behaviour, if score <=8 equals low suicidal behaviour) (246,247). In SBQ-R(Total), four out of eight participants scored low (<=7) with the lowest score being 3, and four scored high (>=8) with the highest score being 11.

Table 6.3 Scores on other clinical domains in whole sample

Note: *MINI: Mini- International Neuropsychiatric Interview, PS PANSS: Positive Symptoms in PANSS, NS PANSS: Negative Symptoms in PANSS*

Participants	Depression MINI	Anxiety MINI	Panic Attack MINI	Substance Dependence MINI	Social Phobia MINI	PS PANSS TOTAL	NS PANSS TOTAL	SBQ-R TOTAL
High SBQ Group								
#1103	Current	Current	n/a	Over the last year	Current	21	8	11
#0579	n/a	Current	Lifetime	Over the last year	Current	17	13	9
#A4E6	Current	Current	n/a	Over the last year	Current	25	22	7
#A4B5	Current	Current	Lifetime	n/a	n/a	21	15	9
Low SBQ Group								
#1314	n/a	n/a	n/a	n/a	Current	10	15	3
#1145	n/a	n/a	n/a	n/a	n/a	16	9	3
#A4BD	n/a	n/a	n/a	n/a	Current	9	27	4
#A4BE	n/a	n/a	n/a	n/a	Current	11	14	3

Furthermore, the two groups reported differences on other factors apart from suicidal behaviour including depression, anxiety, substances use, social phobia, and panic

attacks. 3 out of 4 participants who reported high suicidal behaviour also met the criteria for depression, substance use and social phobia. All the participants in this groups reported experiencing anxiety but only two participants met the criteria for panic attacks. In contrast, participants who reported a low suicidal behaviour did not meet the criteria for depression, anxiety, substances use or panic attacks. However, 3 out of 4 participants in this group met the criteria for social phobia (See Table 6.3).

6.4.4 Behavioural analysis

There was significant difference in task response accuracy (number of correct responses), where participants with high suicidal behaviour (M=1.75, SD=.95) made more accurate responses in face task compared to low suicidal behaviour (M=5.50, SD = 4.12), (t (3) = 3.65, p = .035). There was no significant difference between the groups regarding their reaction time.

6.4.5 fMRI data analysis

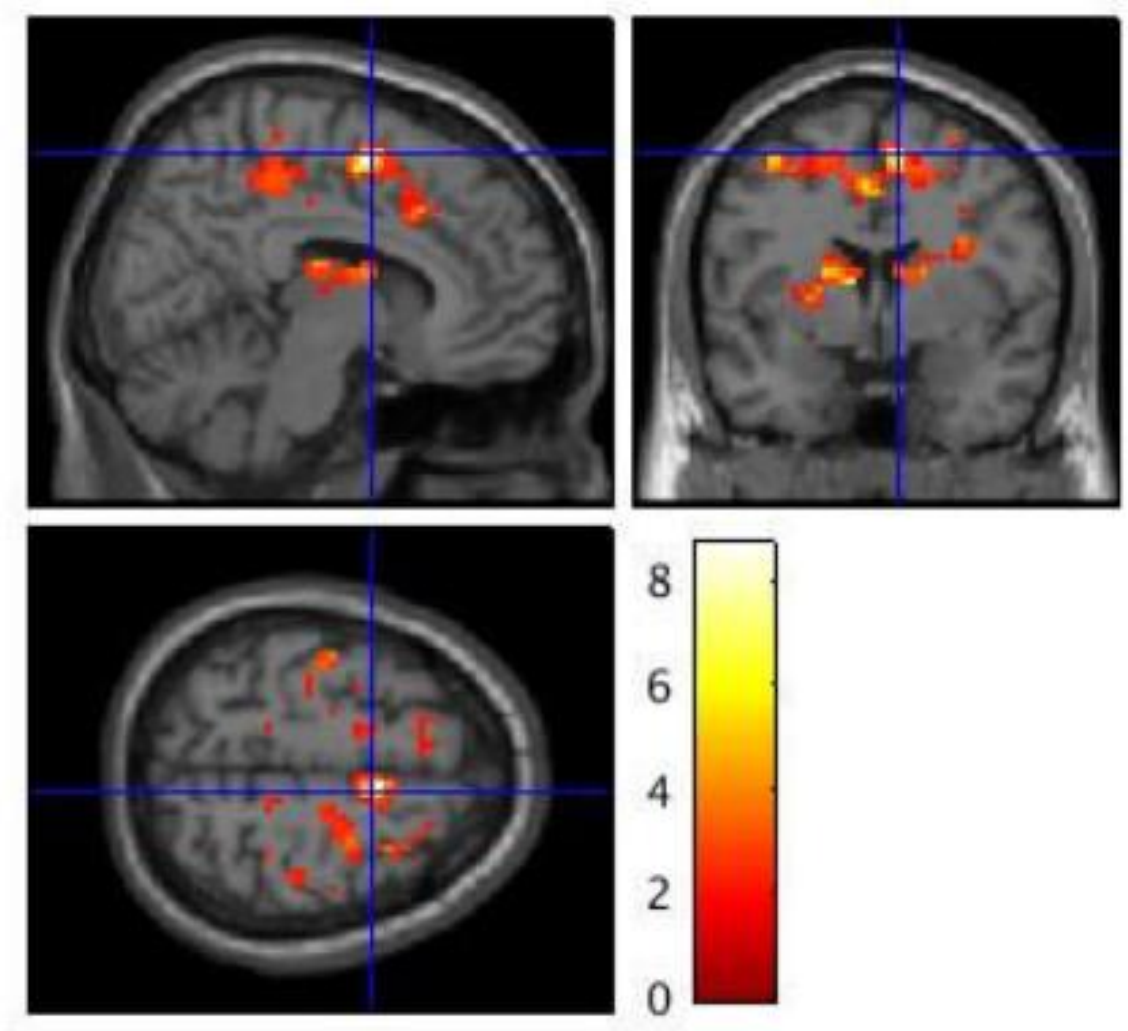
A one sample t-test conducted comparing all eight participants during the faces task (fearful face versus neutral face). Results from the whole group analysis demonstrated the right medial frontal gyrus and right thalamus to be the areas with the highest activation during the faces task. All other regions did not demonstrate any significant differences. Please see Table 6.4 and Figure 6.2.

Table 6.4 One sample t-test in all participants (fearful face > neutral face).

Brain Region	Hemisphere	BA	MNI Coordinates			T	*P* value*
			x	y	z		
Medial frontal gyrus	R	6	9	2	55	8.73	.001
Thalamus	R	---	15	-16	17	7.05	.001
Thalamus	R	---	21	-34	5	6.72	.001

(FWE corrected)

Figure 6.2 One sample t-test: Neural activations are shown for the whole group during the face task (Contrast: Fearful face > Neutral face). Note: The lighter the colour of the activation suggests the areas are more significantly activated. Crosshairs emphasize the peak voxel.



A two- sample t-test was then conducted between low SBQ group > high SBQ group on the fearful face versus neutral face contrast of the faces task. Extent threshold is 0 voxels and significance level p<0.001 (FWE corrected).

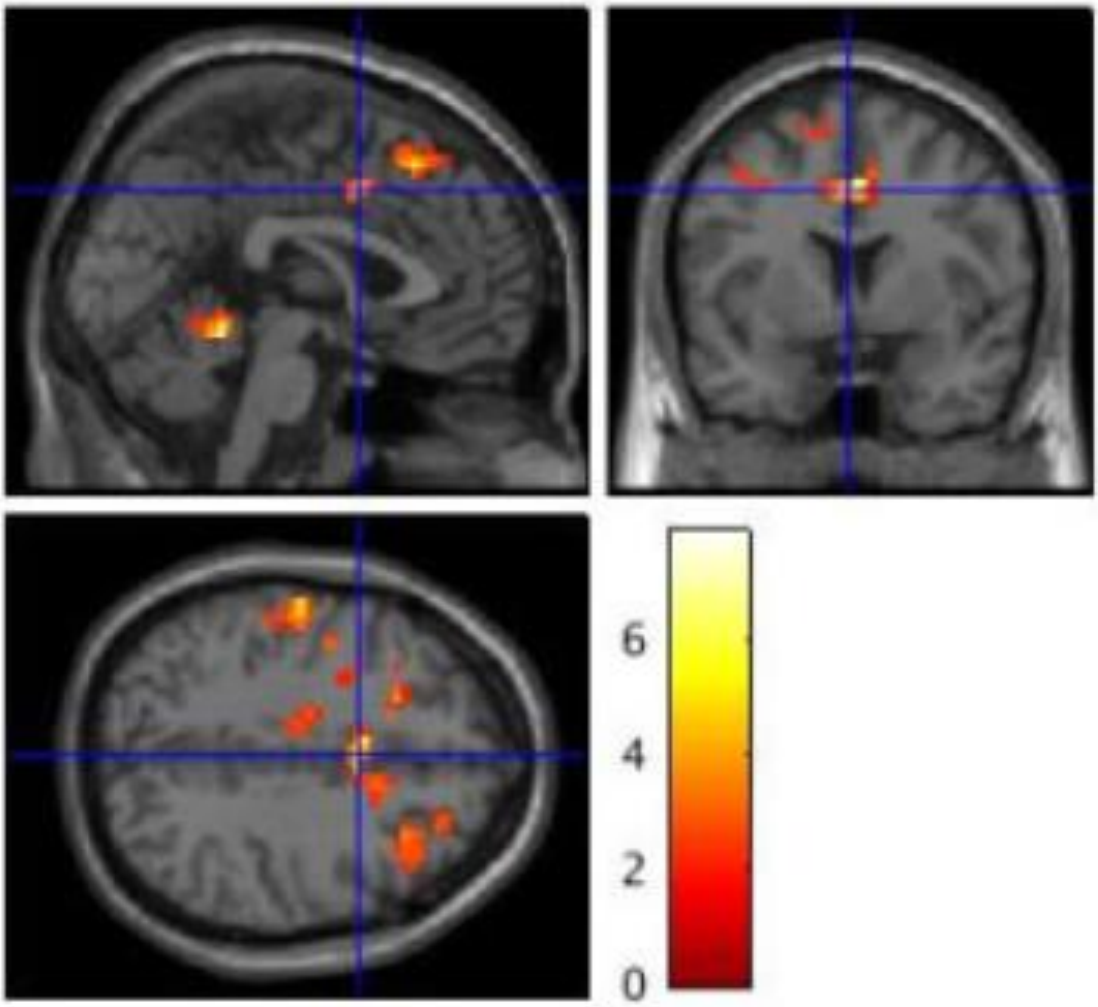
Comparison between the two groups demonstrates that during the task, people who scored lower in SBQ-R(Total) showed greater activation in the right anterior-cingulate gyrus and both right and left medial frontal gyrus (See Table 6.5), in contrast the high SBQ group (See Figure 6.3).

Table 6.5 Two sample t-test in SPM for low SBQ versus High SBQ group (Low>High) during the face task (Fearful face > Neutral face).

Brain Region	Hemisphere	BA	MNI Coordinates			T	*P* value*
			x	y	z		
Anterior-cingulate gyrus	R	24	0	5	41	7.85	.001
Medial frontal gyrus	L	6	-12	-16	39	6.45	.001
Medial Frontal gyrus	R	8	3	26	50	6.18	.001

(FWE corrected)

Figure 6.3 Two sample t-test: Neural activations are shown for low SBQ versus High SBQ group (Low>High) during the face task (Contrast: Fearful face > Neutral face). Note: The lighter the colour of the activation suggests the areas are more significantly activated. Crosshairs emphasize the peak voxel.



6.5 Discussion

Following existing models that utilise the faces task in schizophrenia research, this chapter examined the differences in brain function in groups with high and low suicidal behaviour during the fearful vs neutral faces task. Results indicated that patients with low reported levels of suicidal behaviour showed greater activation in anterior cingulate gyrus and bilateral medial frontal gyrus compared to patients with high suicidal behaviour. Results are partially consistent with the literature suggesting that PFC and PFC-related brain areas such as ACC and MFC showed different brain activation on the faces task in FEP patients with high suicidal behaviour (330,331). However, no differences were reported in the limbic system and particularly in the amygdala. Findings justify partially the hypothesis that brain activation will be different in high vs low SBQ groups. Some of the areas the literature suggested being involved in suicidal behaviour development demonstrated different activation between the two groups.

Existing literature, suggests a minimum of 12 subjects is required to obtain 80% power at a significance level of p =0.05 at the single voxel level (337). However, the current study needs to be considered an exploratory analysis because despite the recruitment of a moderate sample of 24 subjects, only 12 participants underwent fMRI, with 8 having usable brain imaging data. The fact all participants were in their first year in EIS, and potentially still symptomatic, might explain why a high number of participants (four) were excluded when examining the collected data.

Studies on factors which commonly lead participants to drop out MRI and fMRI studies have reported that stress and anxiety can be significant factors for disengagement and termination of the scan. This may lead not only to premature

termination of the procedure but also to impaired data quality. Premature termination is mainly due to the mood changes and hormonal fluctuations that participants experience during the scan (336). In the case of schizophrenia and psychotic disorders this can be more obvious as based on reviews on MRI studies, participants are likely to experience further symptoms in addition to mood and anxiety and therefore more likely to complete a study with a small sample (344,345). Muehlhan et al., reported that fMRI procedure in patients may elicit subjective and neuroendocrine stress reactions that can lead to participants' drop out or even change functional activation patterns during scan (336). Consequently, although drawing firm conclusions is not appropriate, I aim to discuss possible associations that might guide future research.

High reported on suicidal behaviour in schizophrenia has also been shown to be associated with decreased BOLD response in the PFC by Potvin et al., in 2018 (338). Lower PFC function in high SBQ group might demonstrate a reduced PFC function, which might have important implications on executive/cognitive process and decision-making processing, and this might explain current outcomes. Such abnormalities seem to link to a distorted way a patient with suicidal behaviour processes emotions and to poor decision making, which may increase the chances to evaluate decisions wrongly. Therefore, these abnormalities might potentially lead to suicidal behaviour due to failures on decision making process (339). Specifically, participants who scored high on SBQ-R(Total) reported lower activation in the anterior cingulate and medial frontal cortex which form part of the PFC. Previous studies reported that anterior cingulate is increasingly responsible for conflict detection and the emotional evaluation of error (307). It has been also shown to associate with mood regulation, emotional valence of thoughts and depression

(91,311) . Thereby, this may explain why high SBQ group demonstrated a reduced activation on this area.

Other findings report that people with higher suicide risk present dysfunctions in cognitive/executive processes related to goal-representation functions since the PFC is involved in aspects of cognition that are impaired in schizophrenia (such areas include working memory, reward-related learning, executive function) (285). For example, Lewis, (340) reported that people with schizophrenia report reduced activation in PFC, particularly when they perform cognitive tasks. Therefore they face bigger challenges when it comes to execution, control and thought regulation. Minzenberg et al., (306), also provided evidence suggesting that frontal cortices failures could be a great risk in schizophrenia, leading to suicidal thoughts and behaviours over time due to the wrong evaluation of thoughts and how to attain goals.

Consistent with previous studies and current results, Monkul et al, (302) suggested that abnormalities on frontal areas, such as impaired PFC function, infer problems on how information is received from the limbic network (which encodes whether a stimulus is emotionally significant and sends the information to frontal areas) is used. Therefore, the behaviour is built on wrong information in terms of individual's needs. This explanation could be given in the context of the 'dual brain pathology' theory proposed by Tebartz van Elst et al., (341). They examined anterior cingulate, and dorsolateral prefrontal volumes at the same time as amygdala and hippocampal volumes and suggested that abnormalities on frontolimbic area may explain why these patients also experience emotional instability, mood symptoms or even impulse behaviour; all of which are frequently seen in suicidal behaviour in schizophrenia. This is also consistent with current results in this chapter as 3 out of 4 participants

who scored high on SBQ-R(Total) also reported high rates on depression and anxiety compared to low SBQ group.

Moreover, participants in the high SBQ group reported more positive symptoms compared to the ones in low SBQ group, showing that positive symptoms are more prevalent in high SBQ group (consistent results with Chapter 5). However, this was not the case when negative symptoms were assessed. Both groups (high and low SBQ groups) had similar results on negative symptoms, making negative symptoms less of a determinant for suicide risk factor. This might happen due to the prevalence of positive symptoms during the early stage of the disorder (344) since all participants were recruited during their first year of treatment. Evidence suggests that the presentation and prevalence of negative symptoms is more likely to happen in a later stage of schizophrenia (277) which is not the case here as there was no difference between group scores on negative symptoms in this study of FEP. This might be due to the very limited sample.

Abnormalities in brain function, though, do not occur in isolation. In terms of clinical presentation, high SBQ-R participants reported high scores on depression, axienty, panic disorder, and substance misuse. The data here are in conjunction with existing systematic reviews on suicidal behaviour reporting cumulative symptom load as suicide risk factrors in schizophrenia (79,188).

In this thesis cumulative symptoms also contribute to the idea of rational suicide in schizophrenia even when the patients experience brain dysfuntion. Symptoms such as depression, anxiety and substance misuse in schizophrenia should not be considered as random signs of psychopathology. Such symptoms might exist earlier than we estimate or might contribute to the duration of untreated psychosis (DUP) (342). This follows that the experiences, feelings and emotions of people with

schizophrenia might turn into obstacles and lead to the experience of life as a devastating condition. Therefore, other solutions to the problem might arise such as suicide. Furthermore, and consistent with existing findings, higher rates of depression and anxiety in schizophrenia, were suggested to be associated with lower general life satisfaction and lower satisfaction with daily activities, social relationships, finances and health (80) .

My argument here is that, as brain dysfunction does not occur in isolation from other risk factors, such as clinical symptoms, it might be possible that the idea of rational suicide can still be applied in the case in schziophrenia even when objective brain dysfunction is present.

Results did not find differences in brain function in the regions associated with emotional processing such as the amygdala. An explanation for this might be a type 2 error due to low sample size or absence of effect as 12 out of 24 participants dropped out. However, it is not unexpected that the results reported no significant amygdala responses, as the amygdala is very small and can be easily missed with a small sample and whole brain analysis. A larger sample would be able to provide more accurate results regarding the relationship between suicidal behaviour and the brain areas involved in suicidal behaviour, such as the amygdala.

Furthermore, there is a limitation regarding the scales used to decide whether patients were at low or high risk. The scales were completed by the participants and therefore the outcome was subject to participants' evaluation on the SBQ-R(Total), a self-reported questionnaire, and not based on clinician's judgment, which might be an implication as some patients may exaggerate in terms of their behaviour or underestimate the risk. The high suicidal behaviour group, as discussed above, had

higher scores on depression and positive symptoms: thus, the differences in ACC, PFC and MFG activation could equally be a marker of illness severity, rather than directly related to suicidal behaviour.

A third reason this study is limited is due to the study design. As this is a cross sectional study, we do not have the opportunity to assess patients longitudinally. Although this chapter has no longitudinal hypothesis, it would be useful to test brain function over time. The fact participants have been assessed during their first 12 months in the service allows us to assess patients during the early stages of illness only and it is difficult to determine changes after the initial phase of the illness. However, this is in contrast with previous findings on the timing of suicide. Some studies reported that patients at illness onset are more likely to attempt suicide due to their psychotic experiences (182,188). On the other hand, other studies report that chronic patients or patients 3-4 years after admission are more vulnerable to risk due to depressive symptoms and subjective distress that are more prevalent in a later phase of schizophrenia (346,347). The design of this study allowed us to measure suicide risk at a specific time which means that we may consider patients who scored lower on SBQ-R(Total) as patients who are not at risk. However, this does not necessarily guarantee that the same patients will not be at risk for a suicide attempt at a later time point. The last limitation in this study is the absence of a healthy comparison sample in terms of psychosis, and therefore suicidal mechanisms not related to pathological conditions, such as schizophrenia, remain under-examined here.

Although no clear conclusions can be drawn here as this is an exploratory study, this study can still provide some potential insight on how aberrant brain function may provide the basis of emotional dysfunction and subsequent isolation that are

intricately related to suicidal behaviour. It also addresses the need of integrated studies as there are many and multidimensional risk factors underlying suicidal behaviour in patients with schizophrenia. Existing literature suggests that suicidal behaviour in people with schizophrenia is a result not only of clinical symptoms or brain dysfunction but also of other factors. such as family history of suicide, social status, education, traumatic events (79), later environmental factors such as adverse life events and substance abuse (348), genetic factors (349), and brain abnormalities on structural activity and connectivity (335). In future, longitudinal studies which recruit a larger sample and examine patients at different points in time (in terms of progression of illness), would be more appropriate to draw conclusions, as it would show a light on how suicidal behaviour differs with progression and duration of the illness. The implementation of a holistic approach (including neuroimaging, clinical and social data) and longitudinal design is required to test multifactorial and complex conditions such as suicide. The importance of conducting integrated research is determined by the complexity of the problem, as the more complex and multifaceted the problem is, the more significant the involvement in an interdisciplinary effort will be. Therefore, to study about mental health challenges, brain function, strategies and skills related to specific problems will complement and expand the interventions with which we are already familiar, and enhance the possibilities to become more efficient in identifying critical conditions and outcomes in schizophrenia and other disorders (350).

CHAPTER 7: GENERAL DISCUSSION

7.1 Thesis overview

The overall aim of this thesis was to examine suicidal behaviour in schizophrenia from multiple perspectives, with focus on the under-examined symptoms of blunted affect and social withdrawal and to extend the examination to include brain function to further elucidate aetiological processes behind reasoned actions and contribution to suicidal behaviour. Studies and data included in the thesis investigated these aims using a novel approach by integrating disciplines of philosophy, psychology, psychiatry, and neuroimaging.

7.2 Significant Findings

7.2.1. The role of rationality in suicide

The principles of instrumental rationality examined in chapter 3, include the constitutive principles of rational agency and volitional activity, which relate directly to the means the individual adopts to achieve specific goals. Rationality, therefore, is a fundamental condition to examine in the case of completed suicide, as suicide is an action itself. It is also important to note that instrumental rationality does not concern the moral character of the means or the actions ones adopts (this examination would fit in ethics or moral philosophy). Instead, it refers to the process or the principles someone follows to reach their ends. The major requirement for someone to be instrumentally rational is the consistency between the means and the ends. In other words, instrumental rationality reflects the consistency between the willingness (intention) to do something and the behaviour (outcome). In chapter 3, I argued that the action of suicide can be a rational action in many cases, and therefore there are

‘‘good reasons’’ for it, namely that suicide can be seen as a sensible and appropriate action, that keeps with one's fundamental interests (92).

The argument in chapter 3 is that patients with schizophrenia might be prone to report such consistencies between their intentions and behaviours, since the choice to complete suicide could be based on conditions that are unbearable to cope with. Therefore, the reasons to end their life seem in favour of their interests (relief) and consistent with their goal which is to escape from their suffering and pain. Hor and Taylor (188) in their systematic review, suggested that: insight, hopelessness, depression and negative symptoms are common symptoms observed in patients with suicidal behaviour and can occur significant suffering in patients’ life, particularly due to high rates of insight. There is also evidence that the decision to end life is often directed by emotional disturbances, impulsivity, anxiety, depression, loss of control, cognitive distortions, impaired problem-solving ability or disrupted social relations (215). These factors have been consistently reported to reduce quality of life and develop significant emotional distress to one’s life in both clinical and non-clinical populations. However, patients experiencing these factors, should not be regarded as irrational agents, as rationality does not concern the content of the reason or moral status of suicide (i.e. Is it moral for a patient to end their life based on these reasons?) but rather it concerns the patient’s volitional activity (i.e. Does the individual adopt the right means to achieve their end?).

Moreover, there are theoretical accounts that interpret suicide as a decision taken in the context of exhausted individual, family, and social network resources or even an action due to despair and persistent physical and emotional pain (352). Hence, whilst suicide in schizophrenia is often considered as an action outside the realm of logical thought and therefore patients who die by suicide are likely to be considered as

irrational agents. It would be a mistake we often fall in, to define situations or actions we cannot understand as irrational or distant from the reality. Indeed, understandability occurs only when we are able to apply empathy to that person, identify the person's situation, feelings and values and experience somehow their experience.

Another reason that rationality is a crucial topic to explore as the start point to better understand suicide in schizophrenia, is the fact that suicide may be still considered differently in those with mental illness compared to those who suffer from physical disorders. Such distinction occurred due to the historical and traditional statements that people with mental disorders lack capacity, autonomy or even personhood. Therefore, any action by them does not reflect any free will or cognitive process. Although, existing research and policies on stigma and mental health awareness managed to weaken such statements, there are still cases where suicide as a goal is evaluated differently between mentally and physically ill people.

For example, there is a claim that patients who wish to die because of irreversible, and likely terminal physical suffering, should be allowed to do so. In the context of the care and treatment of people who have a physical disorder, extreme and untreatable physical pain are likely to be accepted not only as rational reasons for suicide but also acceptable and legal (i.e. in countries that have legalised euthanasia and have gained support from local governments to do so). This happens mainly because the person possesses cognitive coherence and reports an ability to appreciate the consequences of their actions (91,345) realistically.

In contrast, in schizophrenia, accepting that suicide is rational is less clear-cut and may be controversial, as people with schizophrenia can be considered to lack mental

capacity, and therefore are not autonomous (352). They may also be considered as people who cannot report cognitive coherence between their intentions and actions, mainly because of certain symptoms that influence perception and cognitive function. Therefore, suicide could be only seen as an irrational action. However, people with physical disorders also report problems on decision-making and cognition, indicating that the effects of such impairment may appropriately be considered as a barrier to adequate decisional capacity to physically ill people as well (353). This possibly happens because a poor quality of life influences recovery, treatment effectiveness, clinical decision and increases the emotional pain that is present for the disorder and hence the capacity for decision making can be impaired in physical disorders too (356).

The point of my argument here is that suicide can be a result of a rational decision in schizophrenia. To put things into perspective, the situational evidence here could be all the symptoms, that drive the patient to think of suicide or to end their life. Such situational evidence is the suicide risk factors presented above and examined in this thesis. As previously mentioned in chapters 3, 4 and 5; depression, hopelessness, negative evaluation of the self, emotional overwhelming, blunted affect, and social withdrawal contribute significantly to suicidal behaviour. Not only that they develop associations between them which can increase the risk even more (i.e. the association between depression and hopelessness) (79). Thus, a suicide occurring under these circumstances (the presence of these symptoms and associations) could be defined as a rational action.

In the case of negative symptoms, the possibility of someone struggling each day with real-life challenges and suicidal ideation, is quite common. In the case of negative symptoms the patient may attribute despair or hopelessness in the right

context and meaning, since higher levels of depression and negative symptoms seem to relate to better insight compared to positive symptoms (174). Subsequently, negative symptoms and negative feelings do not impact the perception of the reality compared to other symptoms such as psychotic experiences. Following this, a suicide driven by negative symptoms is mainly driven by patient's intention to stop overwhelming situations, which have been developed in time. Such intentions should not be defined as something irrational or odd. Instead, a suicide, driven by such symptoms which lead to certain intentions about ending life, should be considered as a rational suicide. However, it is important to mention that psychopathology of schizophrenia, associates to underlying brain dysfunction, and therefore such dysfunctions could still be seen as situational evidence for a rational suicide since they can potentially make such experiences more devastating for the patient (due to potential changes in perception, cognitive and emotion functions (303).

The role of rationality in suicide research in schizophrenia should be considered with seriousness for three reasons. Firstly, it makes clear that suicide should not be examined only in terms of its moral character but rather as a frequent outcome in serious mental illness, which addresses the need of prevention. Secondly, it underlines that considering suicide in schizophrenia as an irrational action, meaning that we can regard mentally disordered people as people who lack capacity, autonomy and therefore personhood. This in turn may lead to stigmatization and serious unethical statements where we use a health disorder as a primary indicator to consider someone as autonomous or not. Thirdly, factors such as blunted affect, social withdrawal, emotional distress, or other frequent factors such as depression and hopelessness are present enough to potentially offer a rational choice for someone to choose actively and rationally death over life, and therefore should not

underestimate their impact neither should regard an action driven by such symptoms as irrational.

7.2.2 The association between blunted affect and suicide in schizophrenia

Chapter 3 introduced a novel avenue to examine and interpret suicide in schizophrenia by adopting a philosophical approach. One of the main suggestions is to examine further how certain negative symptoms may be related to suicide as they are potentially contributors to rational suicide in schizophrenia. Reviewing existing research about this association informs current concepts and models of suicide driven by negative symptoms and whether these symptoms can be targeted for prevention and intervention purposes.

Following PRISMA guidelines I included 12 papers examining negative symptoms including blunted affect, and suicide (including suicidal ideation, suicidal behaviour, suicide attempts and completed suicide) in schizophrenia. The findings indicate a positive association between blunted affect and suicide. However, this potential association is not direct but may be mediated by other factors such as emotional withdrawal, depressive symptoms, hopelessness, low self-esteem, negative evaluation of the self and poor social functioning. The results reveal that suicide should be examined as a multifactorial problem in which not only clinical factors might play a significant role. Furthermore, as many papers in the review reported a close link between blunted affect and individual's social functioning, it would be beneficial for research to examine this relationship furthermore and how it might associate to suicide.

7.2.3 The role of blunted affect and social withdrawal in suicidal behaviour

Research on negative symptoms is urgently needed, as they impact significantly on the long-term morbidity, chances to recovery, daily function, and the quality of life in schizophrenia and, as reported above, may also contribute to rational suicide. However, in general terms, research on suicide prevention in mental disorders suggests that implementing interventions that improve rehabilitation, social interaction and quality of life can likewise prevent people from developing suicidal behaviour in schizophrenia (68,358). This has also been shown in chapter 4, as factors related to social interaction and emotional health seem to act as mediators between negative symptoms such as blunted affect and social withdrawal and suicide.

Blunted affect and social withdrawal are clinical features in schizophrenia which are part of the broader term of emotional dysfunction in schizophrenia (other emotional deficits are for example abnormalities in hedonic pursuits or inability to connect emotionally with others). They are critical because they have implications for the ability of others to interpret and respond to facial expressions, which is a key skill for efficient and effective interaction, social bonding, and general functioning outcomes. These abilities though, might also lead to an elimination of the risk for developing suicidal behaviour. As seen in chapter 5, high scores on social withdrawal an emotional withdrawal were associated with high scores on suicidal behaviour. In this sense, an improvement in the ability to be socially connected and emotionally expressed could potentially act as an intervention for reducing the risk (359).

Ekman explained this idea very well by suggesting that the face sends various signals about mood and emotions of a person; a ‘‘multimessage system that informs

other people' about age, emotion state, mood, attitudes, attractiveness, and even intelligence'' (360). We could say that facial expressions are the starting point of social interaction, since the process of forming social interactions presupposes the ability to respond to others' emotional states and facials cues. However, individuals with schizophrenia who experience blunted affect do not display these expressions or respond to the emotional states of others in the way people without such symptoms do. The implications of such dysfunctions can be seen when it comes to how individuals with blunted affect function socially. Robertson et al., (361) in their study, suggested that the potential impact of negative symptoms severity, including blunted affect, social withdrawal and anhedonia, as predictors of diminished social skills (skills that required for real-world social functioning) appears to be much greater than that of social competence or even depression. The former symptoms are directly related to substantial social deficits in schizophrenia. However, social deficits in schizophrenia do not concern only the clinical presentation or the daily tasks of the patients. They also concern other domains such as brain activity and function (106).

Results in chapter 5 reported that although blunted affect does not associate directly with suicidal behaviour, it reports a direct relationship to social withdrawal. This suggests that a patients' inability to express their emotional state may lead to narrowing their social network and detachment from others. Furthermore, participants with higher levels of blunted affect also scored higher on active social avoidance which may be seen as a step to social isolation (362). Interestingly, participants with blunted affect reported very low levels of positive symptoms; this may be due to the timing of sampling, as positive symptoms are more likely to be present during acute exacerbations of psychosis, which might not allow participants with significant positive symptoms to be recruited into the study. In contrast, negative

symptoms are expressed along a continuum and even if they are present in the early phase there is a possibility to remain undetected (363).

Results in chapter 5 also reported a significant association between emotional withdrawal and blunted affect in schizophrenia, which may also lead to difficulties in forming social relationships due to the impact of diminished facial expression. The implications of blunted affect may also lead to severe deficits in real-world social functioning such as social competence, motivation, ability to cope with everyday activities, and to remain connected or even cognitive strength (338). Such implications are also reported as adequate and rational reasons for a suicide which in turn highlights blunted affect as a crucial feature to consider in future research.

In multivariate regression analysis in chapter 5, blunted affect and social withdrawal predicted high scores on hopelessness and association with suicidal behaviour. Lippi et al., (364) also suggest that patients who completed suicide scored high on blunted affect, social withdrawal, hopelessness and depression. Therefore, we should regard hopelessness not only as a suicide risk factor but also as a potential mediator factor between negative symptoms and suicide (see figure 5.2, chapter 5). Although this mediation model seems to work well in terms of predictability, when blunted affect was examined individually it showed no correlation to suicidal behaviour. In this case that implies that negative symptoms might act as complementary factors rather than singularly determinant factors. Such dynamic changes in the power and impact of blunted affect might create a difficulty in management and risk monitoring, as the impact blunted affect has on patients' life is determined from several other factors (such as other negative symptoms and hopelessness). Therefore, the role blunted affect will have on suicidal behaviour increases may be individual to each patient circumstances and symptom profile. In contrast to this, is the case of positive

symptoms, which appear to show a more direct and stable relationship with suicidal behaviour in schizophrenia (272).

Further, findings in chapter 5 report the relationship between other symptom clusters and suicidal behaviour. For example, participants who scored high on the SBQ-R(Total) scored also high on at least one positive symptom or at least two negative symptoms (mainly blunted affect and social withdrawal) Further endorsing the point that positive symptoms have a clear impact on suicidal behaviour, compared to blunted affect and social withdrawal, which present a more dynamic relationship in combination with mediating factors need to also be present (i.e. hopelessness).

In addition to its relevance to suicidal behaviour, hopelessness is a core feature of depression. Findings in the systematic review and brain imaging chapters agree with the current literature that depression is a common symptom in schizophrenia and demonstrated that patients with high rates of hopelessness and depression reported lower levels of PFC activation. However, the exact association between depression and negative symptoms needs further examination and might need a detailed approach as depression is associated with poor prognosis and seems to affect the development of suicidal behaviour (280). There are studies consistent with the role of depression in suicidal behaviour and findings in chapter 5, which report that people with schizophrenia who are less able to recognize emotional expressions accurately have a more negative social outcome and higher risk of developing depression (302). Existing findings suggest that conditions of depression, social isolation, emotional withdrawal, and deficits in social cognition not only contribute to negative clinical outcomes such as the development of suicidal behaviour may be related to underlying brain dysfunction. Such dysfunction might enhance the risk of suicidal behaviour, particularly when other risks are present (and towards changes in certain

brain regions that regulate emotion stability, cognitive coherence and decision making processes (369).

In summary, associations between blunted affect, emotional and social withdrawal and suicidal behaviour might contribute to the development of suicidal behaviour, particularly when hopelessness acts as a mediator. These factors should be seen as adequate for a rational reason to choose suicide, and may present novel and modifiable risk factors for suicide prevention in schizophrenia.

7.2.4 The role of brain activation in suicidal behaviour in schizophrenia

The results in chapter 6 are partially in agreement with existing evidence which is suggesting that people with schizophrenia show impairments in PFC and limbic system, compared to healthy controls, and that there is an impaired functional connection between these two regions (370). Deficits in emotion processing might manifest a deficit not only in expressing emotions (such as blunted affect) but also impairments in executive and cognitive functions and decision making due to the interaction between frontal cortices and emotion-related brain regions (372).

The ability to understand facial expressions allows us to recognise others' emotions, it is a key component of how we interact socially (373) and allows others to predict our actions. Expressing emotions is a powerful form of rapid communication and connection within people, as they convey emotional states to other people via facial features (372). Emotion expression is a tool to communicate our intentions and desires and influence others' emotional states (375), and increasing social connectedness and interaction, which may be a mechanism that prevents suicidal behaviour.

Results on PFC activation are keeping up with Bijttebier et al., (335) who explained that groups at high risk of suicidal behaviour may show reduce PFC activity because of the reduced strength in connectivity in frontal and occipital regions related to anxiety and hopelessness. This is also consistent with findings in chapter 5 and 6, as both anxiety and depression were found to be higher in the high SBQ-R group. Furthermore, reduced activation in PFC function has also been reported to create a greater propensity to act on suicidal or impulsive feelings (322) and therefore to contribute significantly to suicidal behaviour, particularly if other factors such as cognitive impairments, depression and emotional disturbances co-exist (120).

Such evidence reinforces the argument of rational suicide in schizophrenia. If PFC impairments create impulsive feelings or drive suicide risk factors such as hopelessness and depression, then this could lead patients think about suicide as an end to suffering. Furthermore, following existing evidence, the presence of emotional dysfunction that has been consistently reported to be the case in suicidal behaviour in schizophrenia (322) might also make suicide look as a rational choice; as the patients might experience these conditions in a much more intense and devastating way people without brain dysfunctions do.

In addition to this, patients who reported high rates in SBQ-R and PFC impairment also reported high sores on clinical factors such as anxiety, substance misuse, social phobia, and panic attacks. These conditions might prevent the patients of living a manageable life and stop them from coping with the triggers efficiently. For example, the role of anxiety in schizophrenia has repeatedly been reported as a high-risk factor for suicidal behaviour whereas at the same time it has been suggested by philosophers to play a significant role in maintenance of inner peace and feelings of emotional satisfaction (75). Thus, the existence of such factors in a patient's life

might not only lead to brain dysfunctions but also enhance the idea of rational suicide as the patient experiences and realizes the difficulty of overcoming such conditions.

In summary, chapter 6 suggests that examination of complex brain pathways in response to facial expression might contribute to understanding suicidal behaviour in patients with schizophrenia.

7.3 General Limitations

As this is a cross sectional study, the first limitation refers to that lack of longitudinal data. Cross sectional data does not allow us to track individuals' progress over time nor allow us to evaluate whether interventions have any impact on suicidal behaviour. Whilst I have presented correlation and a mediation analysis, longitudinal data would be needed to fully conclude blunted affect and social withdrawal may influence suicidal behaviour via hopelessness.

The second primary data study included self-report, structured interview data and neuroimaging (fMRI). In this study fMRI data added to the examination of suicide in schizophrenia by addressing whether any biomarkers relevant to facial processing could be identified. In this neuroimaging study, although 24 participants completed the clinical assessments, only 12 participants completed the fMRI scan. The second limitation of this thesis is therefore the relatively small sample size in one of the two studies included in this thesis. Main reasons participants dropped out the study were anxiety and overwhelming feelings, and thus more severely ill patients have been excluded. Other reasons were piercings or tattoos.

The quite significant limitation in the data chapters for this thesis is the absence of a control group. Healthy controls would provide a greater insight on what factors

contributing to suicidal behaviour by demonstrating which factors may be indicative of clinical status, rather than specifically suicidal behaviour. This would also provide evidence on whether suicidal behaviour is due to clinical symptoms such as positive symptoms or other factors.

Although large longitudinal studies with participants diagnosed with schizophrenia have been published in the past years, this thesis is the first attempt to integrate clinical, neuroimaging and philosophical aspects on suicide in schizophrenia, providing a novel approach. I suggest that clinical concepts of schizophrenia can be modulated by underlying theoretical considerations, and that this may help clinicians' practice. In particular, emphasis needs to be placed on social withdrawal and hopelessness to prevent suicidal behaviour, and blunted affect may be an identifiable antecedent. Beyond the limitations this study has, the underlined strength considers a new, holistic method on suicide examination in clinical population which can improve not only clinical practice but the effectiveness of interventions.

7.4 Clinical implications

A number of potential recommendations and further avenues for clinical practice could be taken from results presented in this thesis in terms of suicide prevention, clinical practice, and efficient interventions. Research on individuals with schizophrenia and suicidal behaviour has shown that there is a need to focus on early phases of an individual's behaviour and presentation (376). The psychological consequences for someone who is feeling hopeless and suicidal may exist long before the clinician assigns a diagnosis (377). This is a statement that has been consistently reported in existing literature and therefore many studies consider the

early detection and practice on people with suicidal behaviour as a very important area of research.

The personal and societal cost of suicide also reinforce the importance of effective preventive measures. Suicide prevention requires a multifactorial approach involving community, clinical practice and broader health care, workplaces and schools (378). Existing evidence estimates that 30% of patients with FEP attempt suicide at least once in their lifetime (379). Furthermore, approximately 14% of patients who make serious suicide attempts will be re-admitted to the hospital for a suicide attempt at some point in their life (380). Therefore, interventions aimed at improving and maintaining social connections in patients with blunted affect implemented by early intervention services, could potentially help reduce completed suicide.

This thesis suggests that an effective approach for reducing the risk of suicide attempts may be a stronger continuum and consistent care between clinical practice and community, which would improve connectedness and social outcomes in people who are at risk. Improving the quality of care received by those who seek help in clinical settings and addressing accurately and on real time the problems is of great importance. I suggest that better evaluation of the process and quality of care patients receive from such settings (i.e. crisis teams, early intervention, emergency departments) can lead to better mental health care for suicidal patients and substantially reduce the future burden of suicide.

Appropriate use of assessment and screening tools including measures of hopelessness, social withdrawal and blunted affect can help paint a better picture of patients' circumstances and consequently monitor risk better. Every patient seen in an emergency department, or any mental health unit with suicidal behaviour should

receive a comprehensive suicide risk assessment; including the assessment of blunted affect and social connection, hopelessness with focus on increasing meaningful recovery would be justified.

The role of social withdrawal, hopelessness, and blunted affect (as other negative symptoms) can bring benefits not only in suicide prevention and risk monitoring, but also on the contribution to the recommendations for improving quality of life. For example, negative symptoms and particularly social withdrawal associated with social isolation and depression and have been reported to contribute to increasing rates of loneliness (psychological embodiment of the feeling of social isolation) (359). The rates of depression and loneliness on the other hand, reveal the urgency to rethink the concept and the importance of communication and connectiveness between people. Loneliness and social isolation should be seen as key targets as they are conditions that significantly contribute to the impact of schizophrenia and other mental disorders. Evidence suggests that loneliness in schizophrenia is associated with impaired social cognition and functioning, drug abuse/dependence, metabolic syndrome, broad-based morbidity, anhedonia and subjective thought disorder, and therefore examination of such factors might allow clinicians to implement more efficient interventions (381).

Following findings in this thesis it clear that there is a necessity of hope and social belonginess that may contribute significantly to a patients' recovery, reduced rates of depression, stigma and suicide (382). Implementing, such strategies focusing on peer support, community activities and interaction that aim to eliminate stigma could enhance the quality of life, prevent negative outcomes such as suicide and build resilience, thereby, allowing people to find better mechanisms to cope with other conditions such as stress and seek support in time.

7.5 Future research on negative symptoms and suicidality in schizophrenia

Over the last years, there has been increased understanding of complex models of suicide risk factors instead of analysing factors independently. This is a new era on suicide research, in which researchers begin examining correlations between factors by adopting concepts from other fields such as philosophy, sociology, and economy. This thesis highlights many points regarding future research on negative symptoms and suicidality in schizophrenia.

Firstly, the value of focussing on individuals with schizophrenia lies in the fact that they are agents who can make decisions rationally and do not differ from other people in terms of their autonomy, personhood and mental capacity (94). Therefore, improving interventions and treatments broadly here not only makes sense but also contributes significantly in the broader community and society.

Secondly, it is clear that longitudinal studies are needed to examine changes in blunted affect and social withdrawal over the developmental course of suicidal behaviour in schizophrenia. Longitudinal studies would also substantiate how blunted affect contributes to social isolation and loneliness which are main areas mental health research closely relates to suicidal behaviour.

Thirdly, advances of study designs would help to examine whether blunted affect and social withdrawal are specific deficits in schizophrenia that come under the umbrella of negative symptoms or whether they are deficits that can be related to other symptoms such as positive symptoms. Even combined treatment packages tailored to individual symptom and risk profiles might contribute to reducing suicidal behaviour.

7.6 Conclusion

This thesis aimed to provide an integrated multidisciplinary investigation that considers suicidal behaviour as a rational act in schizophrenia. All knowledge presented here can be utilised as potential foundations to develop new holistic accounts of suicide in schizophrenia and suicide prevention intervention targeting patients who are socially withdrawn, have difficulty with emotional expression compounded by hopelessness. Understanding the importance of emotion expression and social functioning in people with schizophrenia will help us to highlight areas for intervention, community involvement, social skills, and outreach work. This thesis is an attempt to present a novel, multidisciplinary approach of the problem of suicide in schizophrenia ultimately aiming to add to the literature that will guide interventions that improve quality of life and maintain life through the significant challenges people with schizophrenia face.

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APPENDICES

A-1 Poster/Leaflet advertising the FEP-A Study

Would you like to take part in research?

We are looking for young people (ages 16-35) to take part in a study about brain development in **mentally healthy** adolescents and young adults at the University of Birmingham.

What does the research involve?

- A screening questionnaire to see if you are eligible
- Brain scanning session that lasts approximately 45 minutes
- You will receive **£10** for your time



Want to know more?

Call: kjhlhkljlkj

Text: lklm;kl;k

Email: ljljhlijj;ok;k;lk;lk;lk

A-2 Participant information sheet for the FEP-A study

PARTICIPANT INFORMATION

Study Title: The clinical and neurobiological overlap between autism and psychosis

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

The purpose of the study:

The aim of this study is to investigate the symptoms of psychosis and if or how they may be related to autism-like traits.In some ways, the symptoms of psychosis and autism are quite similar. There is also evidence that the disorders share common risk factors and biological mechanisms. Not much is known about this potential overlap between the disorders and what this might means in terms of diagnosis, treatment and outcome. In this study, we will investigate symptoms, functioning and brain activity in an attempt to understand if or how psychosis and autism may be linked.

Why have I been chosen?

We are inviting young people in the Early Intervention Service at the Birmingham and Solihull Mental Health NHS Foundation Trust to take part in this study.

Do I have to take part?

No – involvement in this study is voluntary. If you decide to take part, you are still free to withdraw at any time without giving a reason. If you do decide to take part, and later change your mind you can withdraw from the study at any time, or ask that the information you have given us is removed from the study.

A decision to withdraw at any time, or a decision not to take part, will not affect the standard of health care you receive now or in the future.

What will happen to me if I take part?

The researcher will meet with the University of Birmingham, at your home or at a health centre to carry out the assessments with you. These will consist of an interview and questionnaires asking about different symptoms and feelings (that might or might not relate to you) and other aspects of your life and personal history. The interview will take approximately one and a half hours to complete and you will receive £15 in recognition of your time and expenses. We will ask your permission to send a summary of your results to your care coordinator.

If you wish to take part in the brain scan, this will take about 45 minutes and you will receive £10.

The brain scan is known as magnetic resonance imaging (MRI) and is a way to take pictures of the inside of the body, and for this study, specifically of your brain. The process uses intense magnetic fields and radio waves to create these images. We will get information about both the structure and function of your brain. You will be asked to go through a safety questionnaire with a scan operator before being allowed into the scanner itself. You will be asked to lie completely still on your back while the machine will surround the upper part of your body.

What are the possible side effects of taking part?

We do not expect that any part of this study will cause harm to anyone taking part in it. Some people might find it difficult discussing their symptoms, life events or other personal information. You don't have to answer anything that you are not comfortable with and you can stop at any time. If you experience distress and would like to discuss it with someone, we will organise this for you.

The brain scan is considered to be extremely safe and non-invasive. However, the scanner is noisy so all participants will wear earplugs and headphones. The scanner is a small space and can cause distress for people who are afraid of small places. If you think you may feel claustrophobic, please discuss this with us and we can do a practice run in a mock scanner. If this is uncomfortable for you, we don't need to proceed.

The main risks of the brain scan are because of people taking metal objects into the scanning room. This is particularly dangerous if you have metal in your body from surgery (for example, a pacemaker), or from an accident (such as having metal filings in your eye from welding or grinding metal). We will ask you questions about this, and it is important for you to tell us if there is a chance you have metal in you.

You will be carefully introduced to the scanner and you are allowed to leave at any stage. While lying motionless on the scanner bed, you may experience back and neck pain. This will be minimized by the use of comfortable padding and positioning.

There is no known extra risk in conducting brain scans on women who are pregnant. However, it is conventional to exclude women who are pregnant from research using MRI scans. A pregnancy test kit will be available, should women wish to use it before undergoing a scan.

Whilst in the scanner, you can talk to the operator at any time and will be holding an emergency button which you can squeeze during a scan in the event of distress. This will activate an alarm and cause the operator to immediately stop the scan.

It is unlikely that we will find anything unexpected in the scan of your brain. If we do find anything unexpected we will let you know immediately and advise you of what actions need to be taken.

What are the possible benefits of taking part?

On a personal level, participants from previous studies have found that talking to a study researcher and sharing issues that might contribute to the mental health issues they are experiencing to be helpful. Although we cannot promise the study will help you, the information we get from this study may help other young people dealing with similar kinds of problems.

What will happen when the research study stops?

The data will be put into a database and analysed together with data from other participants who took part in the study. The results of the study will be written up for publication in health professional journals and will be presented at conferences in the UK and abroad. Your identity will never be revealed. We will ask you at your appointment if you would like to see the results of the study when it is finished.

Will my taking part in this study be kept confidential?

All information collected as part of this research will be kept in a locked filing cabinet and stored securely on a computer at University of Birmingham. We will give you an individual code, and all data from your interview will be stored using this code, not your name. In the future, we may also send some of your data to colleagues in other universities, but we will never send information that could identify you. Your clinician and GP will be informed of your participation, but only the research team have access to your personal information. We will ask your permission to send a summary of your results to your care coordinator, but will not do so without your consent. The data will be stored for a minimum of ten year. All your information will be kept confidential, unless you tell us something that gives us reason to believe that you or others are in danger (e.g. having strong suicidal thoughts). In this event, we will talk with you about it before we share the information (e.g. telling your care coordinator).

Who is organising and funding the research?

The research is sponsored by The University of Birmingham in partnership with the Birmingham and Solihull Mental Health NHS Foundation Trust.

What if there is a problem?

If you are worried or concerned about any aspect of the study you should talk to the researcher. If they are unable to address your concerns or you wish to make a complaint about the study, you can contact your local Patient Advice and Liaison Service - call 0800 953 0045; text 07985 883 509; email pals@bsmhft.nhs.uk.

Who has reviewed the study?

All research in the NHS is examined by an independent group of people called a Research Ethics Committee. Their job is to protect your safety, rights, wellbeing and dignity. This study has been reviewed by the NRES Committee West Midlands - Edgbaston.

Contact for Further Information

Please contact Katharine Chisholm (Project Coordinator) on . We are situated at School of Psychology, University of Birmingham.

Thank you for reading this.

A-3 Screening Questions for FEP-A Study

Screening Questions

Have you ever been diagnosed with a mental health condition?

1. Has there ever been a period of time when you were feeling so good, 'high', excited or hyper that you got yourself into trouble? Was that more than just a good feeling? • **IF NO:** What about a period of time when you were so irritable that you found yourself shouting at people, or starting fights or arguments? (Either in the last month, or anytime in the past?)	1	2 3 **Go to Current Manic Episode**
2. For the past couple of years, have you been bothered by depressed mood most of the day, more days than not?	1	2 3 **Go to Dysthymic Disorder & PMDE**
3. Have you ever had a panic attack when you suddenly felt frightened or anxious or suddenly developed a lot of physical symptoms? **IF YES:** Have these attacks ever come on completely out of the blue – in situations where you didn't expect to be nervous or uncomfortable?	1	2 3 **Go to Panic Attack**
4. Were you ever afraid of going out of the house alone, being in crowds, standing in a queue or traveling on buses or trains? **IF YES:** Do you avoid these situations? **IF NO AVOIDANCE:** When you are in one of these situations, do you feel very	1	2 3 **Go to AWOPD**

uncomfortable or like you might have a panic attack?

5. Is there anything that you have been afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing? **IF PUBLIC SPEAKING FEARS ONLY:** Do you think that you are more uncomfortable than most people are in that situation?	1	2 3 **Go to Social Phobia**
6. Are there any other things that you have been especially afraid of, like flying, seeing blood, getting an injection, closed places, or certain kinds of animals or insects? **IF YES:** Do you always feel frightened when you (CONFRONTED WITH PHOBIC STIMULUS)? **IF YES:** Did you think that you were more afraid of (PHOBIC STIMULUS) than you should have been (or made sense)?	1	2 3 **Go to Specific Phobia**
7. Have you ever been bothered by thoughts that didn't make any sense and kept coming back to you even when you tried not to have them… thoughts like hurting somebody, or being contaminated by germs? **IF YES:** When you had these thoughts, did you try hard to get them out of your head? (What would you try to do?)	1	2 3 **Go to OCD**
8. Was there ever anything that you had to do over and over again and couldn't resist doing, like washing your hands again and again, counting up to a certain number or	1	2 3 **Go to OCD**

checking something several times to make sure you'd done it right?
IF YES: Why did you have to do (COMPULSIVE ACT)? What would happen if you didn't do it?

9. Sometimes things happen to people that are very upsetting, things like being in a life threatening situation like a major disaster, very serious accident or fire, being physically assaulted or raped, seeing another person killed or dead or badly hurt, or hearing that something horrible has happened to someone you are close to. At any time during your life have any of these sorts of things happened to you? **IF ANY EVENTS LISTED:** Sometimes traumatic experiences like (TRAUMAS LISTED ABOVE) keep coming back in nightmares, flashbacks, or thoughts that you can't get rid of. Has that ever happened to you? **IF NO:** What about being very upset when you were in a situation that reminded you of one of these terrible things?	1	2 **Go to PTSD**	3
10. In the last six months have you been particularly nervous or anxious? **IF YES:** Do you also worry a lot about bad things that might happen? **IF YES:** During the past 6 months, would you say you have been worrying more days than not? **IF YES:** When you are worrying this way, do you find that it's hard to stop yourself?	1	2 **Go to GAD**	3
11. Over the last several years, what has your	1	2	3

physical health been like? **IF BAD:** How often have you had to go to a doctor because you weren't feeling well? (What for? Was the doctor always able to find out what was wrong, or were there times when the doctor said there was nothing wrong but you were still convinced that something was wrong?		**Go to Somatisation Disorder**
12. Have you been to see a doctor because of physical pain? **IF YES:** How much does the pain interfere with your life? Has it made it hard to do your work, or be with friends?	1	2 3 **Go to Pain Disorder**
13. Do you worry a lot that you have a serious disease that the doctors have not been able to diagnose? **IF YES:** What makes you think so? (What do you think you have?) **IF YES:** What have your doctors told you?	1	2 3 **Go to Hypochondriasis**
14. Some people are very bothered by the way they look. Is this a problem for you? **IF YES:** You've said that you have been bothered by (DEFECT IN APPEARANCE). How often do you think about it? **IF PREOCCUPIED WITH PERCEIVED DEFECT:** How much does this bother you? What effect has this had on your life? (Has it made it hard for you to do your work or be with friends?)	1	2 3 **Go to Body Dysmorphic Disorder**

15. Have you ever had a time when you weighed much less than other people thought you ought to weigh?

IF YES: At that time, were you very afraid that you could become fat?

1 2 3

Go to Eating Disorders

16. Have you often had times when your eating was out of control?

IF YES: During these times, do you often eat within a 2 hour period what most people would regard as an unusual amount of food? Tell me about that.

1 2 3

Go to Bulimia Nervosa

17. Did anything happen to you just before (onset of current disturbance)?

Note: Ask this question only if there is a current disturbance, and none of the above questions have been answered positively.

1 2 3

Go to Adjustment Disorder

18. Has there ever been any time in your life when you had five or more drinks (beer, wine or spirits) on one occasion?

IF YES: When in your life were you drinking the most? (How long did that period last?)

DATE AND PATTERN OF HEAVIEST USE:
_____
_____
_____
_____

During that time…

How often were you drinking? What were you drinking? How much?

1 2 3

Go to Alcohol Use Disorders

During that time…

Did your drinking cause problems for you? Did anyone object to your drinking?

IF ALCOHOL DEPENDENCE SEEMS LIKELY, CHECK HERE__ AND GO TO ***ALCOHOL DEPENDENCE***

IF ANY INCIDENTS OF EXCESSIVE DRINKNG OR ANY EVIDENCE OF ALCOHOL-RELATED PROBLEMS, GO TO ***ALCOHOL ABUSE***

19. Have you ever used street drugs? Such as cannabis, cocaine etc. 1 2 3

Go to Non-Alcohol Substance Use Disorders

20. Have you ever gotten 'hooked' on a prescription medication or taken a lot more of it than you were supposed to? 1 2 3

Go to Non-Alcohol Substance Use Disorders

Note: In addition, please check the following diagnostic entities:

Do you know what an MRI scan is?
Describe

Have you had one before?

Would you consent to having an MRI scan?

Are you claustrophobic?

Do you suffer from any medical condition that may be relevant (e.g. epilepsy, diabetes, asthma)?

Is there any reason that you may have metal in your body? (e.g. welder, machinist, grinder or worked with metal without eye protection)

Do you have any tattoos or body piercings (other than earrings)?

Do you wear dentures, a dental plate or a brace (not fillings)?

Do you have any transdermal skin patches (e.g. nicotine patch)?

(Females only) Are you or could you be pregnant?

Do you have a cardiac Pacemaker, pacing wires or defibrillator?

Have you ever had any surgical procedures whereby you have had metal placed in your body? (Such as having cardiac Pacemaker, pacing wires or defibrillator)

When are you available to come for a scan? What sorts of dates/ times?

A-4 Participant Consent Form for FEP-A Study

PARTICIPANT CONSENT FORM:
Consent to be contacted for future research

Study Title: The clinical and neurobiological overlap between autism and psychosis

Put initials in box to confirm agreement

I give permission for researchers to use my data from all aspects of this study for future research projects, and to share my data with co-investigators and other researchers on request as long as no information is used which could identify me ☐

I agree to be contacted by researchers in the future if a new study is proposed that I might be interested in participating in. ☐

_____	_____	_____
Full name	Date	Signature

A-5 Questionnaires and Measurements for FEP-A Study

The following questions are about your background, thoughts, feelings and behaviours. Please ask the researcher if anything is unclear or if there is something that you don't understand.

What is your ethnicity?

White-British

White- Irish

White-Other

Asian-Indian

Asian-Pakistani

Asian-Bangladeshi

Other Asian background

Black-Caribbean

Black-African

Other Black background

Mixed-White and Black Caribbean

Mixed-White and Black African

Mixed-White and Asian

Other Mixed Backgrounds

Other – please specify_____

Have you ever used cannabis? ***(please circle)*** Yes No

If yes, at what age did you first _____

How old was your mother when you were born?_____

How old was your father when you were born?_____

What is your current marital status? *(select one only)*

Single/never married

Boyfriend/girlfriend (less than 3 months)

Boyfriend/girlfriend (more than 3 months)

Married/ civil partnership/living with partner more than 6 months

Divorced

Separated but not divorced

Widowed

Which of the following best describes your current accommodation? *(select one only)*

Live in the family home

Live alone

Live with housemates

Live with partner

Live in a boarding house/hostel

Homeless

Other – please specify _____

What is the highest educational qualification you have completed? (*select one only*)

No school certificate or any other qualification
GCSE/NVQ level 1 or 2
A-level/GNVQ/BTEC/NVQ level 3
NVQ level 4 or above
Higher National Diploma (HND)
Undergraduate degree

Postgraduate degree

Which of the following best describes your current work/education status? (*select one only*)

Not in education or employment
Full-time employment
Part-time employment - specify number of hours per week?_____
Secondary school
College full-time
_____ University full-time
College part-time – specify number of hours per week?_____
University part-time - specify number of hours per week?_____
_____ Other – please specify _____

A-6 AQ for FEP-A Study

		definitely agree	slightly agree	slightly disagree	definitely disagree
1	I prefer to do things with others rather than on my own.				
2	I prefer to do things the same way over and over again.				
3	If I try to imagine something, I find it very easy to create a picture in my mind.				
4	I frequently get so strongly absorbed in one thing that I lose sight of other things.				
5	I often notice small sounds when others do not.				
6	I usually notice car number plates or similar strings of information.				
7	Other people frequently tell me that what I've said is impolite, even though I think it is polite.				
8	When I'm reading a story, I can easily imagine what the characters might look like.				
9	I am fascinated by dates.				
10	In a social group, I can easily keep track of several different people's conversations.				
11	I find social situations easy.				
12	I tend to notice details that others do not.				
13	I would rather go to a library than a party.				
14	I find making up stories easy.				
15	I find myself drawn more strongly to people than to things.				
16	I tend to have very strong interests, which I get upset about if I can't pursue.				
17	I enjoy social chit-chat.				
18	When I talk, it isn't always easy for others to get a word in edgeways.				

19	I am fascinated by numbers.				
20	When I'm reading a story, I find it difficult to work out the characters' intentions.				
21	I don't particularly enjoy reading fiction.				
22	I find it hard to make new friends.				
23	I notice patterns in things all the time.				
24	I would rather go to the theatre than a museum.				
25	It does not upset me if my daily routine is disturbed.				
		definitely agree	slightly agree	slightly disagree	definitely disagree
26	I frequently find that I don't know how to keep a conversation going.				
27	I find it easy to "read between the lines" when someone is talking to me.				
28	I usually concentrate more on the whole picture, rather than the small details.				
29	I am not very good at remembering phone numbers.				
30	I don't usually notice small changes in a situation, or a person's appearance.				
31	I know how to tell if someone listening to me is getting bored.				
32	I find it easy to do more than one thing at once.				
33	When I talk on the phone, I'm not sure when it's my turn to speak.				
34	I enjoy doing things spontaneously.				
35	I am often the last to understand the point of a joke.				
36	I find it easy to work out what someone is thinking or feeling just by looking at their face.				
37	If there is an interruption, I can switch back to what				

	I was doing very quickly.				
38	I am good at social chit-chat.				
39	People often tell me that I keep going on and on about the same thing.				
40	When I was young, I used to enjoy playing games involving pretending with other children.				
41	I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).				
42	I find it difficult to imagine what it would be like to be someone else.				
43	I like to plan any activities I participate in carefully.				
44	I enjoy social occasions.				
45	I find it difficult to work out people's intentions.				
46	New situations make me anxious.				
47	I enjoy meeting new people.				
48	I am a good diplomat.				
49	I am not very good at remembering people's date of birth.				
50	I find it very easy to play games with children that involve pretending.				

A-7 CTQ for FEP-A Study

These questions ask about some of your experiences growing up as a child and a teenager. Although these questions are of a personal nature, please try to answer as honestly as you can. For each question mark the box under the response that best describes how you feel.

	When I was growing up...	Never True	Rarely True	Sometimes True	Often True	Very Often True
1.	I didn't have enough to eat.					
2.	I knew that there was someone to take care of me and protect me.					
3.	People in my family called me things like "stupid", "lazy" or "ugly.					
4.	My parents were too drunk or high to take care of the family.					
5.	There was someone in my family who helped me feel that I was important or special.					
6.	I had to wear dirty clothes.					
7.	I felt loved.					
8.	I thought that my parents wished I hadn't been born.					
9.	I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.					
10.	There was nothing I wanted to change about my family.					
11.	People in my family hit me so hard that it left me with bruises or marks.					
12.	I was punished with a belt, a board, a cord, or some other hard object.					
13.	People in my family looked out for each other.					
14.	People in my family said hurtful or insulting things to me.					
15.	I believe that I was physically abused.					

16.	I had the perfect childhood.					
17.	I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor.					
18.	I felt that someone in my family hated me.					
19.	People in my family felt close to each other.					
20.	Someone tried to touch me in a sexual way. Or tried to make me touch them.					
21.	Someone threatened to hurt me or tell lies about me unless I did something sexual with them.					
22	I had the best family in the world.					
23	Someone tried to make me do sexual things or watch sexual things.					
24	Someone molested me.					
25	I believe that I was emotionally abused.					
26	There was someone to take me to the doctor if I needed it.					
27	I believe that I was sexually abused.					
28	My family was a source of strength and support.					

A-8 SIAS and SPS for FEP-A Study

For each question, please mark the box to indicate the degree to which you feel the statement is characteristic or true of you. The rating scale is as follow:

0 = **Not at all** characteristic or true of me

1 = **Slightly** characteristic or true of me

2 = **Moderately** characteristic or true of me of me

3 = **Very** characteristic or true

4 = **Extremely** characteristic or true of me

		Not at all	Slightly	Moderately	Very	Extremely
1	I get nervous if I have to speak with someone in authority (teacher, boss, etc.)					
2	I have difficulty making eye contact with others.					
3	I become tense if I have to talk about myself or my feelings					
4	I find it difficult to mix comfortably with the people I work with.					
5	I find it easy to make friends my own age.					
6	I tense up if I meet an acquaintance in the street.					
7	When mixing socially, I am uncomfortable.					
8	I feel tense if I am alone with just one other person.					
9	I am at ease meeting people at parties, etc.					
10	I have difficulty talking with other people.					
11	I find it easy to think of things to talk about.					
12	I worry about expressing myself in case I appear awkward.					
13	I find it difficult to disagree with another's point of view.					
14	I have difficulty talking to attractive persons of the opposite sex.					
15	I find myself worrying that I won't know what to say in social situations					
16	I am nervous mixing with people I don't know well.					

17	I feel I'll say something embarrassing when talking					
18	When mixing in a group, I find myself worrying I will be ignored.					
19	I am tense mixing in a group.					
20	I am unsure whether to greet someone I know only slightly					

0 = **Not at all** characteristic or true of me

1 = **Slightly** characteristic or true of me

2 = **Moderately** characteristic or true of me

3 = **Very** characteristic or true of me

4 = **Extremely** characteristic or true of me.

		Not at all	Slightly	Moderately	Very	Extremely
1	I become nervous if I have to write in front of other people					
2	I become self-conscious when using public toilets.					
3	I can suddenly become aware of my own voice and of other listening to me					
4	I get nervous that people are staring at me as I walk down the street.					
5	I fear I may blush when I am with others.					
6	I feel self-conscious if I have to enter a room where others are already seated.					
7	I worry about shaking or trembling when I'm watched by other people					
8	I would get tense if I had to sit facing other people on a bus or a train.					
9	I get panicky that others might see me to be faint, sick or ill.					
10	I would find it difficult to drink something in front of a group of people.					
11	It would make me feel self-conscious to eat in front of a stranger at a restaurant.					
12	I am worried people will think my behaviour odd.					
13	I would get tense if I had to carry a tray across a cafeteria					
14	I worry I'll lose control of myself in front of other people.					
15	I worry I might do something to attract attention of others.					

16	When in an elevator I am tense if people look at me.					
17	I can feel conspicuous standing in a queue.					
18	I get tense when I speak in front of other people.					
19	I worry my head will shake or nod in front of others					
20	I feel awkward and tense if I know people are watching me					

A–9 BHS for FEP-A Study

This questionnaire consists of 20 statement. Please read the statements carefully one by one. If the statement describes your attitude **for the past week including today**, tick TRUE. If the statement does not describe your attitude, tick FALSE. Please be sure to read each statement carefully.

		TRUE	FALSE
1	I look forward to the future with hope and enthusiasm		
2	I might as well give up because there is nothing I can do about making things better for myself		
3	When things are going badly, I am helped by knowing that they cannot stay that way forever		
4	I can't imagine what my life would be like in ten years		
5	I have enough time to accomplish the things I want to do		
6	In the future, I expect to succeed in what concerns me most		
7	My future seems dark to me		
8	I happen to be particularly lucky, and I expect to get more of the good things in life than the average person		
9	I just can't get the breaks, and there's no reason I will in the future		
10	My past experiences have prepared me well for the future		
11	All I can see ahead of me is unpleasantness rather than pleasantness		
12	I don't expect to get what I really want		

13 When I look ahead to the future, I expect I will be happier than I am now

14 Things just don't work out the way I want them to

15 I have great faith in the future

16 I never get what I want, so it's foolish to want anything

17 It's very unlikely that I will get any real satisfaction in the future

18 The future seems vague and uncertain to me

19 I can look forward to more good times than bad times

20 There's no use in really trying to get anything I want because I probably won't get it

A-10 SBQ-R for FEP – A and BioPoP Study

Please tick the statement or phrase that best applies to you.

1. Have you ever thought about or attempted to kill yourself? (tick one only)

Never

It was just a brief passing thought

I have had a plan at least once to kill myself but I did not try to do it

I have had a plan to kill myself and really wanted to die

I have attempted to kill myself, but did not want to die

I have attempted to kill myself, and really hoped to die

2. How often have you thought about killing yourself in the past year? (tick one only)

Never

Rarely (1 time)

Sometimes (2 times)

Often (3-4 times)

Very often (5 or more times)

3. Have you ever told someone that you were going to commit suicide, or that you might do it? (tick one only)

No

Yes, at one time, but did not really want to die

Yes, at one time, and really wanted to die

Yes, more than once, but did not really want to do it

Yes, more than once, and really wanted to do it

4. How likely is it that you will attempt suicide someday? (tick one only)

Never

No chance at all

Rather unlikely

Unlikely

Likely

Rather likely

Very likely

5. If you have ever attempted to kill yourself, what did you do?

A-11 SPQ_b for FEP-A Study

Please answer each item by marking the box under Yes or No.

Please answer all items even if you are unsure of your answer

		Yes	No
1	People sometimes find me aloof and distant.		
2	Have you ever had the sense that some person or force is around you, even though you cannot see anyone?		
3	People sometimes comment on my unusual mannerisms and habits.		
4	Are you sometimes sure that other people can tell what you are thinking?		
5	Have you ever noticed a common event or object that seemed to be a special sign for you?		
6	Some people think that I am a very bizarre person.		
7	I feel I have to be on my guard even with friends.		
8	Some people find me a bit vague and elusive during a conversation.		
9	Do you often pick up hidden threats or put-downs from what people say or do?		
10	When shopping do you get the feeling that other people are taking notice of you?		
11	I feel very uncomfortable in social situations involving unfamiliar people.		

12	Have you had experiences with astrology, seeing the future, UFOs, ESP or a sixth sense?
13	I sometimes use words in unusual ways.
14	Have you found that it is best not to let other people know too much about you?
15	I tend to keep in the background on social occasions.
16	Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?
17	Do you often have to keep an eye out to stop people from taking advantage of you?
18	Do you feel that you are unable to get "close" to people?
19	I am an odd, unusual person.
20	I find it hard to communicate clearly what I want to say to people.
21	I feel very uneasy talking to people I do not know well.
22	I tend to keep my feelings to myself.

Structured Clinical Interview

FOR THE POSITIVE AND NEGATIVE SYNDROME SCALE (SCI-PANSS)

Data on **LACK OF SPONTANEITY** and **FLOW OF CONVERSATION**, **POOR RAPPORT** and **CONCEPTUAL DISORGANISATION.**

notes

Hi, I'm ….. We're going to be spending the next 20 or 30 minutes talking about yourself and your reasons for being here. Maybe you can start by telling me something about yourself and your background? (Allow at least 5 minutes for a non-directive phase serving to establish rapport in the context of an overview before proceeding to the specific questions listed below.)

Data on **ANXIETY.**

notes

1. Have you been feeling worried or nervous in the past week?

No ↓

yes **2. Would you say that you're usually calm and relaxed?** ↓

→ **3. What's been making you feel nervous (worried, uncalm, unrelaxed)?** ↓

4. Just how nervous (worried, etc.) have you been feeling? ↓

5. Have you been shaking at times, or has your heart been racing? ↓

6. Do you get into a state of panic? ↓

7. Has your sleep, eating or participation in activities been affected?

Data on **DELUSIONS (GENERAL)** and **UNUSUAL THOUGHT CONTENT.**

Notes

1. Have things been going well for you?



2. Has anything been bothering you lately?



3. Can you tell me something about your thoughts on life and its purpose?



4. Do you follow a particular philosophy?



5. Some people tell me they believe in the Devil; what do you think?



6. Can you read other people's minds?

Yes



no **7. How does that work?**



8. Can others read your mind?

Yes



9. How can they do that?

no



10. Is there any reason that someone would want to read your mind?



11. Who controls your thoughts?

Data on **SUSPICIOUSNESS/PERSECUTION, PASSIVE/APATHETIC SOCIAL WITHDRAWAL, ACTIVE SOCIAL AVOIDANCE** and **POOR IMPULSE CONTROL.**

notes

1. How do you spend your time these days?

2. Do you prefer to be alone?

3. Do you join in activities with others?

No

4. Why not? … Are you afraid of people or do you dislike them?

If 'yes'

yes **5. Can you explain?**

If 'yes'

6. Tell me about it?

7. Do you have many friends?

If 'no'

8. Just a few? (If 'yes' go to Q. 11)

If 'no'

yes **9. Any? (If 'no' ask Why?)**

If 'yes'

10. Why just a few friends?

11. Close friends?

If 'no'

yes **12. Why not?**

13. Do you feel you can trust most people? (If 'yes' go to Q15)

No

14. Why not?

15.Are there some people in particular that you don't trust?

Notes

Yes

16. Can you tell me who they are? (If 'no go to Q.22)

Yes

17. Why don't you trust people (or named specific person)?

(If 'don't know' or 'don't want to say')

18. Do you have a good reason not to trust?

no

19. Is there something that … did to you?

20. Perhaps might do to you now?

(If 'yes')

21. Can you explain to me?

22. Do you get along well with others?

No

yes **23. What's the problem?**

24. Do you have a quick temper?

Yes

25. Do you get into fights? (if 'no' go to Q29)

Yes

26. How do these fights start?

no

27. Tell me about these fights?

28. How often does this happen?

29. Do you sometimes lose control of yourself?

30. Do you like most people?

No

yes

31. Why not?

32. Are there perhaps some people who don't like you?

yes

no

33. For what reason?

34. Do others talk about you behind your back?

yes

35. What do they say about you?

no

36. Why?

37. Does anyone ever spy on you or plot against you? (If 'no' go to next page)

yes

38. Do you sometimes feel in danger? (If 'no' go to next page)

yes

39. Would you say your life is in danger? (If 'no' go to next page)

yes

40. Is someone thinking of harming you or even perhaps thinking of killing you? (If 'no' go to next page)

yes

41. Have you gone to the Police for help?

42. Do you sometimes take matters into your own hands or take action on those who might harm you? (If 'no' go to next page)

yes

43. What have you done?

notes

Data on **HALLUCINATORY BEHAVIOUR** and **ASSOCIATED DELUSIONS.**

Notes

1. Do you once in a while have strange or unusual experiences?

2. Sometimes people tell me that they can hear strange noises or voices inside their head that others can't hear. What about you?

No

3. Do you sometimes receive personal communication from the radio or TV?

4. From God or the Devil? (If 'no' go to Q20)

Yes

5. What do you hear?

yes (if voices)

6. Are these as clear and loud as my voice?

7. How often do you hear these voices (noises, messages, etc)?

8. Does this happen at a particular time of day or all the time?

Go to Q20

9. Can you recognise whose voices these are?

10. What do the voices say?

11. Are the voices good or bad?

12. Pleasant or unpleasant?

13. Do the voices interrupt your thinking or your activities?

14. Do they sometimes give you orders or instructions?

15. For example?

notes

16. Do you usually obey these orders (instructions)?

17. What do you make of these voices (or noises): Where do they really come from?

18. Why do you have these experiences?

19. Are these normal experiences?

Go back to Q3

20. Do ordinary things sometimes look strange or distorted to you?

21. Do you sometimes have 'visions' or see things that others can't see?

yes

22. For example?

no **23. Do these visions seem very real or life-like?**

24.How often do you have these experiences?

25. Do you sometimes smell things that are unusual or that others don't smell?

yes

no **26. Please explain.**

27. Do you get any strange or unusual sensations from inside your body?

no

yes

28. Tell me about this.

Go to next page

Data on **SOMATIC CONCERN.**

Notes

1. How have you been feeling in terms of your health?

if other than 'good'

if 'good'

2. What has been troubling you? (Go to Q5)

3. Do you consider yourself to be in top health? (If 'yes' go to next section)

No

4. What has been troubling you?

5. Do you have any medical illness or disease?

6. Has any part of your body been troubling you?

No

yes

7. How is your head? Your heart? Stomach? The rest of your body?

8. Could you explain? (if appropriate)

9. Has your head or body changed in shape or size?

no

Yes

10. Please explain.

Go to next section

11. What is causing these changes?

Data on **DEPRESSION.**

Notes

1. How has your mood been in the past week: mostly good, mostly bad?

if 'mostly bad'

if 'mostly good'

2. Have there been times in the past week that you were feeling sad or unhappy?

no

Yes

3. Is there something in particular that is making you sad?

Go to next section

notes

4. How often do you feel sad?

5. Just how sad have you been feeling?

6. Have you been crying lately?

7. Has your mood in any way affected your sleep?

8. Has it affected your appetite?

9. Do you participate less in activities on account of your mood?

10. Have you had any thoughts of harming yourself?

11. Any thoughts about ending your life?

yes

no

12. Have you attempted suicide?

Go to next section

Data on **GUILT FEELINGS** and **GRANDIOSITY.**

notes

same (go to Q5)

1. If you were to compare yourself to the average person, how would you come out: a little better, maybe a little worse, or about the same?

worse

2. Worse in what ways?

better

3. Just how do you feel about yourself? (go to Q5)

4. Better in what ways? (go to Q5)

Notes

5. Are you special in some ways?

Yes

6. In what ways?

no

7. Would you consider yourself gifted?

8. Do you have talents or abilities that most people don't have?

Yes

no

9. Please explain.

10. Do you have any special powers?

Yes

11. What are these?

12. Where do these powers come from?

13. Do you have extrasensory perception (ESP), or can you read other people's minds?

no

14. Are you very wealthy?

Yes

15. Explain please.

no

16. Can you be considered to be very bright?

Yes

17. Why would you say so?

18. Would you describe yourself as famous?

no

yes

go to Q21

notes

19. Would some people recognise you from TV, radio or the newspapers?

if 'yes'

no

20. Can you tell me about it?

21. Are you a religious person?

yes

no

22. Are you close to God?

yes

23. Did God assign you some special role or purpose?

no

no

24. Can you be one of God's messengers or angels?

yes

25. What special powers do you have as God's messenger (angel)?

no

26. Do you perhaps consider yourself to be God?

yes

27. Do you have some special mission in life?

yes

28. What is your mission?

no

29. Who assigned you to that mission?

30. Did you ever do something wrong; something you feel bad or guilty about?

no

yes

31. Just how much does that bother you now?

no

32. Do you feel that you deserve punishment for that?

go to next section ← Yes

33. What kind of punishment would you deserve?

34. Have you at times thought of punishing yourself?

no → go to next section

Yes

35. Have you ever acted upon these thoughts?

Notes

Data on **DISORIENTATION.**

1. Can you tell me what is today's date (i.e. the day, the month, the year)?

2. What is the name of the place you are in now?

3. (If hospitalised) What ward are you on?

4. (If hospitalised) What is the address of where you now stay?

5. If someone had to reach you by phone, what number would they call?

6. What is the name of the doctor who is treating you?

7. (If hospitalised) Can you tell me who else in on the staff and what they do?

8. Do you know who is now the Prime Minister?

9. Who was the Prime Minister before?

10. Who is the leader of the opposition party?

Notes

Data on **DIFFICULTY IN ABSTRACT THINKING.**

notes

1. I'm going to now say a pair of words, and I'd like you to tell me in what important way they are alike. Lets start for example, with the words … see Appendix A. How are they alike- what do they have in common?

if any other answer

if correct answer

2. Good. Now what about….? (Select three other items from the similarities list at varying levels of difficulty and based upon the interview stage and record the responses. Then go to Q4)

(If we use 'apple & banana' as the items) The incorrect answer will be either CONCRETE ('they both have skins' or 'you can eat them'), TANGENTIAL ('they're small), or IDIOSYNCHRATIC ('monkeys like them') – record this in the notes section to the left.

3. Okay, but they're both… give answer. Now how about … : how are these alike? (Select three other items from the similarities list at varying levels of difficulty and based upon the interview stage and record the responses.)

4. You've probably heard the expression… select proverb from Appendix B. What does this really mean?

5. What about when people say… select second proverb from Appendix B. What do they mean?

6. There's a very old saying… see Appendix B for third proverb. What is the deeper meaning of this proverb? (Select 1 other proverb from the final set in Appendix B)

Data on **LACK OF JUDGEMENT and INSIGHT.**

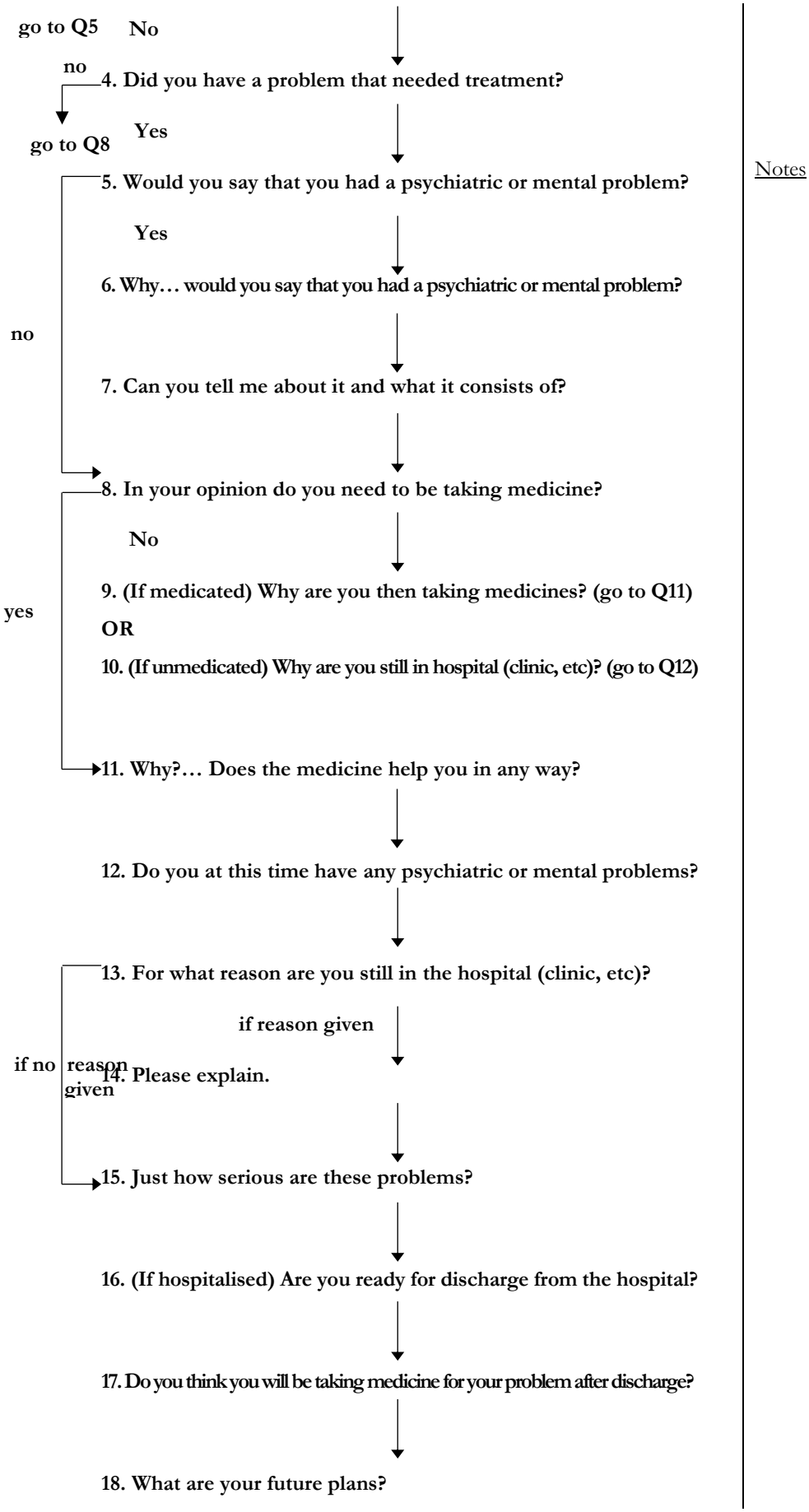
notes

1. How long have you been in the hospital (clinic etc)?

2. Why did you come to the hospital (Clinic, etc)?

yes

3. Do you need to be in the hospital (Clinic, etc)?


go to Q5
No
no
4. Did you have a problem that needed treatment?
go to Q8
Yes
5. Would you say that you had a psychiatric or mental problem?
Yes
6. Why… would you say that you had a psychiatric or mental problem?
no
7. Can you tell me about it and what it consists of?
8. In your opinion do you need to be taking medicine?
No
9. (If medicated) Why are you then taking medicines? (go to Q11)
yes
OR
10. (If unmedicated) Why are you still in hospital (clinic, etc)? (go to Q12)
11. Why?… Does the medicine help you in any way?
12. Do you at this time have any psychiatric or mental problems?
13. For what reason are you still in the hospital (clinic, etc)?
if reason given
if no reason given
14. Please explain.
15. Just how serious are these problems?
16. (If hospitalised) Are you ready for discharge from the hospital?
17. Do you think you will be taking medicine for your problem after discharge?
18. What are your future plans?

Notes

19. What about your longer-range goals? … Well that's about all I have to ask of you now. Are there any questions that you might like to ask of me? … Thank you for your co-operation

Appendix A: Items for assessing SIMILARITIES in the evaluation of **DIFFICULTY IN ABSTRACT THINKING.**

2-year assessment **Baseline/6mth assessment** **1-year/Discharge/18mth assessment** **Acute ward assessment**	1. How are a ball and orange alike? 2. Apple and banana? 3. Pencil and pen? 4. Nickel and dime?
2-year assessment **Baseline/6mth assessment** **1-year/Discharge/18mth assessment** **Acute ward assessment**	5. Table and chair? 6. Tiger and elephant? 7. Hat and shirt? 8. Bus and train?
2-year assessment **Baseline/6mth assessment** **1-year/Discharge/18mth assessment** **Acute ward assessment**	9. Arm and leg? 10. Rose and tulip? 11. Uncle and cousin? 12. The sun and the moon?
2-year assessment **Baseline/6mth assessment** **1-year/Discharge/18mth assessment** **Acute ward assessment**	13. Painting and poem? 14. Hilltop and valley? 15. Air and water? 16. Peace and prosperity?

Appendix B: Items for assessing PROVERB INTERPRETATION in the evaluation of **DIFFICULTY IN ABSTRACT THINKING.**

What does the saying mean:

2-year assessment **Baseline/6mth assessment** **1-year/Discharge/18mth assessment** **Acute ward assessment**	1. "Plain as the nose on you face"? 2. "Carrying a chip on your shoulder"? 3. "Two heads are better than one"? 4. "Two many cooks spoil the broth"?
2-year assessment **Baseline/6mth assessment** **1-year/Discharge/18mth assessment** **Acute ward assessment**	5. "Don't judge a book by its cover"? 6. "One man's food is another man's poison"? 7. "All that glitters is not gold"? 8. "Don't cross the bridge until you come to it"?
2-year assessment **Baseline/6mth assessment** **1-year/Discharge/18mth assessment** **Acute ward assessment**	9. "What's good for the goose is good for the gander"? 10. "The grass always looks greener on the other side"? 11. "Don't keep all your eggs in one basket"? 12. "One swallow does not make a Summer"?
2-year assessment **Baseline/6mth assessment** **1-year/Discharge/18mth assessment** **Acute ward assessment**	13. "A stitch in time saves nine"? 14. "A rolling stone gathers no moss"? 15. "The acorn never falls far from the tree"? 16. "People who live in glass houses should not throw stones at others"?

Panss Rating Form **Name**_____ **Date**___

		absent	minimal	mild	moderate	moderate severe	severe	extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7
G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7

G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

A-13 Volunteer Expenses Claim form for FEP-A study

The National Autistic Society

Volunteer's Name: _____

Volunteer's Address: _____

Service Volunteer is from: _____

Reason for claim: _____

DATE	DETAILS OF EXPENSE BEING CLAIMED	NO. OF MILES	MILEAGE CLAIM @ 45P/MILE	PUBLIC TRANS-PORT*	OTHER AGREED COSTS*	TOTAL	ADMIN USE ONLY
				OVERALL TOTAL CLAIMED			

*** Please ensure a copy of your telephone bill is enclosed with highlighted calls, otherwise your claim will be rejected.**

PLEASE INSERT BANK DETAILS FOR PAYING EXPENSES DIRECTLY INTO YOUR BANK ACCOUNT
Name and Address of Bank holding your account:

Account Name – Your name or Name of Account Holder:	**Bank Account Number:**	**Sort Code:**

If claiming for mileage - *I certify that my vehicle is in good condition and has been serviced in accordance with the manufacturer's recommendations at a vat registered garage.*

Signed by Volunteer: **Date:**

Signed by Co-ordinator: **Print name:**
Date:

FOR ATTENTION OF FINANCE ONLY:

T Codes T1: T2: T3: Nominal code: 43140

For any queries about this claim please email 'STAFF MEMBERS EMAIL ADDRESS'

A-14 Poster advertising the BioPoP Study

UNIVERSITY OF BIRMINGHAM

Version 1
02.6.2015

ForwardThinking Birmingham

Birmingham Children's Hospital NHS
NHS Foundation Trust

Biological correlates of dimensional symptoms of psychosis (BioPoP)

Are you **aged between 16 and 35**?

Do you have **no experience of mental health difficulties**?

Are you interested in taking part in research?

What is the study investigating?

We are running a study at the University of Birmingham looking to use brain images and blood samples to further understand the biological markers of the different types of symptoms which occur in psychosis.

What will the study involve?

- It will take part at the University of Birmingham
- You will have a short interview about different kinds of experiences
- You will have an MRI brain scan
- You will have a blood sample taken

You will be paid **£20** upon completion of the study.

How do I get involved?

If you are interested in taking part, please contact:

[redacted]

Birmingham and Solihull Mental Health NHS Foundation Trust

25 Vincent Drive
Birmingham, B15 2FG

PALS Patient Advice and Liaison Service Customer Care **Mon – Fri, 9am – 5pm**

Telephone: 0121 333 8403 **E-mail: pals@bch.nhs.uk.** **Website: www. forwardthinkingbirminghan**

A-15 Leaflet advertising the BioPoP Study for CPN

BioPoP

Biological correlates of dimensional symptoms of psychosis

Five point introduction of the BioPoP study to explain to your clients:

1. This study aims to determine specific biomarkers (by this we mean biological tests such as results from a blood test) for dimensional symptoms (such as positive symptoms, depression and poor functioning) in FEP.
2. Assessments last 3 hours; 2 hours completing questionnaires/interview assessing their symptoms, a blood test and cognitive assessment, and then a 1 hour MRI scan.
3. Participants will receive £20 to compensate their time for the MRI scan
4. Would you like to hear more about taking part?

Does your client meet the inclusion criteria?

Inclusion Criteria	*Exclusion criteria*
First Episode Psychosis	Significant risk to self or others
Current Positive Symptoms as defined by 3 or more on at least 1 item from PANSS Positive scale	Contraindications for MRI (Pregnant, implanted metal device, history of working with metal)
Within 12 months of treatment onset	Dependence on alcohol or illicit substances
Capacity to consent	Significant neurological disorder, or IQ< 70.

For more information, contact

[redacted]

A-16 Participant information sheet for the BioPoP study

Biological correlates of dimensional symptoms of psychosis (BioPoP)

Participant Information Sheet

We would like to invite you to take part in a research study. Before making any decisions, you need to understand why this research is being done and what the study would involve for you. Please read the following information carefully and, once you have finished, feel free to ask any questions. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

For some other mental health difficulties, such as depression, researchers have been able to identify specific biological markers of the illness; however this still remains relatively unclear for psychosis. A biological marker is something that can be identified in a test such as a blood sample, X-ray or MRI scan that tells doctors if an illness is present or not. The aim of this research study is to use brain images and blood samples to further understand the biological markers of the different types of symptoms which occur in psychosis. We hope that this will help to improve the accuracy of diagnosis and improve the specificity of treatments in the future.

Why have I been chosen?

You have been asked to take part because you are currently experiencing your first episode of psychosis, and you have expressed an interest in taking part in research.

What does taking part involve?

If you decide to take part, a short interview will be carried out which relates to different kinds of experiences which you may or may not have had. This interview will take about an hour and will be conducted by trained researchers. It will cover topics such as your past medical history, past history of symptoms and your current level of symptoms. This information will be used to see if we can identify biological markers of specific symptoms such as low mood or hallucinations. You will also have a blood sample taken. In addition, a Magnetic Resonance Image (MRI) scan will be carried out at the Birmingham University Imaging Centre (BUIC), which will take no longer than an hour. This is a painless and safe brain scanning technique, which involves lying down with your head in a tunnel. You will hear intermittent loud noises, but are still able to communicate with professionals through the intercom – which is inside the scanner. We will ask you to complete a short task, for which instructions will be fully explained to you on the day. This task will involve looking at different pictures when you are in the scanner. We will ask some participants, those who are not taking any medication, to have a second blood test in about 6 weeks' time. We will also ask if you would be interested in being contacted in 12 months to complete some of the questionnaires and interviews by the research team.

Do I have to take part?

No, you do not have to take part – it is completely up to you to decide. If you agree to participate, however, we will ask you to sign a consent form to show that you have read and understood the information sheet, and contact your GP to inform them of your participation. You can withdraw your participation at any point throughout the study. If you decide to withdraw, you do not have to offer an explanation and your decision will, in no way, affect your future treatment.

Will I be compensated for my time?

You will receive **£20** for you time and we will pay for your travel expenses to and from the Birmingham University Imaging Centre (BUIC).

What are the risks?

MRI is a completely non-invasive and painless technique, which does not involve radiation. Some people may find the scan noisy; therefore, all participants will wear earplugs and headphones. The MRI machine itself has a trolley that you will lie down upon, moving in to a donut shaped space of about 70 cm. This small space may cause distress for people who are afraid of small places. We are able to do a practice run in a mock scanner, and not proceed if you find this uncomfortable. Professionals will remain close-by should you, at any point, wish to stop the procedure. You will be in the scanner for up to 60 minutes.

The main risks of MRI are due to people taking metal objects into the scanning room. This is particularly dangerous if a person has metal in their body from surgery (for example a pacemaker), or from an accident (such as having metal filings in his/her eye from welding or grinding metal). Participants are, thus, thoroughly screened for. Neck and back pain may be experienced by the participant, however, this can be minimised by the use of comfortable padding and positioning.

There is no known extra risk in conducting MRI scans on women who are pregnant. Despite this, it is conventional to exclude women who are pregnant from research using MRI scans. A pregnancy test kit will be available, should women wish to use it before undergoing a scan.

Whilst in the scanner, participants can talk to the operator at any time and will be holding an emergency button, which they can squeeze during a scan in the event of distress. This will activate an alarm and cause the operator to immediately stop the scan. In the event that the MRI scan reveals any unexpected findings the participant will be informed of this as will their clinical team.

In addition, there are no known risks of blood sampling, which will be carried out in accordance with standard safety procedures. You will have one needle only. You may feel nervous about this and some patients feel slightly faint after a blood test. You will be put at ease as much as possible and the researcher will be with you at all times.

What are the benefits of taking part?

There may be no direct benefit to you as a consequence of participating in the study; however, the results may help improve the treatment of other people in the future.

In addition, whilst the blood samples and MRI scan are not subjected to any routine testing, should any incidental findings arise we will contact you and alert your GP. Consent to contact your GP with your involvement in the study and any new health information will be included on the consent form.

What will be done to ensure confidentiality?

All images and blood results will be anonymised, and personal details that might identify you will be removed so that you cannot be identified in any published reports. Data will be stored on a secure database and hardcopies kept in a locked cabinet for 10 years (the minimum time stipulated by the University of Birmingham). Only members of the research team will have access to this data.

What if there is a problem?

If you have any questions regarding the study, you can contact Markella Grigoriou, Carl Krynicki or **Dr. Rachel Upthegrove**, the principle investigator, on

If you are unhappy or wish to make a complaint, please contact Carl Krynicki in the first instance. All concerns will be dealt with promptly, and information will subsequently be provided either by telephone or in writing to inform you of how the problem has been addressed. Should Carl Krynicki be unable to resolve your problem, or if your complaint is about the team, please contact the Patient Advice and Liaison Service (PALS) on free phone number 0800 953 0045.

What will happen to the results of the study?

The data obtained from this study will be analysed, and we hope to publish the results in scientific journals. If you would like to, you will be provided with a summary of what has been found and, if requested, a copy of the final published article.

Who has reviewed this study?

This study has been reviewed by the Edgbaston Research Ethics Committee (15/WM/0255).

Thank you for taking the time to read this information sheet. If you would like further information or have any questions, please contact:

Dr Rachel Upthegrove

Birmingham and Solihull Mental Health NHS Foundation Trust
25 Vincent Drive
Birmingham, B15 2FG

A-17 Letter to participant's GP of the BioPoP Study

The Barberry, National Centre for Mental Health
25 Vincent Drive
Birmingham, B15 2FG

<Date>

Biological correlates of dimensional symptoms of psychosis (BioPoP)

WM/15/0255 Principal Investigator Dr. Rachel Upthegrove

Re: <Patient's name>

Date of Birth: <date of birth>

Our research team are currently doing a study which aims to identify the biomarkers of different symptom domains in psychosis.

Your patient <insert name> has agreed to participate and, as part of the study, will take part in a detailed clinical interview with the researcher. As part of the study, <insert name> will also provide a blood sample and an MRI brain scan.

<insert name> has consented to you being informed of their involvement, and is aware that his/her participation in the study, or decision to withdraw at any point, will in no way affect his/her routine treatment.

Should any incidental or clinically important information be revealed in the study, you will be informed. The research team will be working closely with participants' mental health teams at the participating NHS trusts, who will likewise be informed of any new information.

If you would like further information about this project, please contact Research Associate Carl Krynicki or Principal Investigator Dr Rachel Upthegrove on

Yours sincerely,

Dr Rachel Upthegrove

Senior Lecturer and Honorary Consultant Psychiatrist

A-18 MRI Participants information sheet for BioPop study



Centre for Human Brain Health

www.birmingham.ac.uk/chbh

The University of Birmingham

Edgbaston

PARTICIPANT INFORMATION SHEET

PROJECT: BioPoP

GENERAL INFORMATION

Introduction to the research and invitation to take part:
You are being invited to take part in a MRI research project. It is important that you understand why the research is being done and what it will involve before you decide whether or not to take part. Please read the following information carefully, and please discuss this with others if you wish. Feel free to ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the project? [Please adjust to fit your project]
The project will be examining the relations between brain structure and brain function using magnetic resonance imaging.

What will happen during the experiment?
[Please adjust to fit your project, describing what it involves. If there are specific things the subject needs to know or consider before agreeing, e.g. painful stimuli will be delivered, this is the place to describe them] The stimuli will be visual images (pictures, words), sounds or tactile input. Any stimuli that might potentially be distressing will be shown to you beforehand to enable you to judge if you feel distress. You will be able to withdraw from the project at any time (see below).

Do I have to take part?
No. It is up to you whether or not to take part. If you do, you will be asked to fill in and sign a consent form. A copy of this information sheet and your signed consent form will be available for you to keep. You are still free to withdraw at any time and without giving a reason. Withdrawing

from the project will not affect you in any way including any current or future relationship with the University of Birmingham.

What will happen to me if I take part?
You will undergo an MRI scan and you may also be asked to carry out a task while in the scanner. As you carry out the task we will measure changes related to brain activity which will inform us about how brain areas operate while a task is being undertaken. The scanning session will last about 1 hour, during which time you will be asked to lie as still as possible to keep your head from moving.

What is magnetic resonance imaging?
Magnetic resonance imaging involves changes to the gradient of a magnetic field to produce shifts in the alignment of atoms in the body and brain of the person being scanned. The changes in alignment can be used to measure details of the structure and function of the tissues in the brain. The procedure is non-invasive and carries no known harm outside of safety issues for operating in a high magnetic field (e.g. if you have a cardiac pacemaker). For this reason you will be asked go through a safety screening questionnaire with an authorised scan operator prior to being allowed to proceed into the scanning environment.

What are the possible benefits of taking part?
By learning more about how the brain works, by using MRI, we will be able to improve understanding of brain structure and function, develop better ways of diagnosing changes in brain function, and we will learn about how to improve brain function to optimise performance.

Can I get a picture of my brain or the raw data of my brain picture?
Depending on the particular experimental protocol of the project principle investigator, you may be offered an picture of your brain, typically an image (e.g. in jpeg format) or paper copy showing views of your brain from different orientations. Generally this will not be available for some time after the scan session as the data will need to be reconstructed and converted into a format you can easily view. Raw data for MRI scans are not available to research volunteers. These are generally very large files in data formats that require specialized software to open them.

What happens at the end of the research project?
The results will be written up in a scientific publication or presented in other academic formats. In addition results may be reported in a newsletter to be distributed to participants or to hospitals involved with the project. All data arising from this project will be reported anonymously.

How will my data be shared?
Research data collected from the MRI scan will initially only be shared between the project principal investigator and collaborators working on the project. Typically, these project collaborators may include the graduate students or postdoctoral researchers who are supervised and managed by the principal investigator. This data will be pseudoanonymized. This means that a particular code will be used to replace your name in the MRI data so that it will not be possible to identify you from this code alone.

In the ethics consent form we also ask if you are willing to share the data we collect from you with other researchers. There are two levels of data sharing. Firstly, local sharing of your data (in a pseudoanonymized format) within the University of Birmingham. Secondly, sharing of your data (in a fully anonymized format) outside of the University. If you agree to share your data you may also be asked to fill in a short health and demographic questionnaire.

In the first case, your data may be copied to an internal University of Birmingham data server and made available for other University of Birmingham researchers to use in their work. For example, in the future you may volunteer to be a participant in a new MRI study. Rather than needing to scan you again on a standard MRI protocol that has already been collected from you (a process which may be time consuming) the principal investigator of the new project can instead retrieve your earlier scan without needing to be a collaborator on the current project, provided you have given your consent here.

In the second case, typically your data may be made available to other researchers via an open access database. It is now standard, as part of the publication process, for many scientific journals to require that researchers upload an anonymised copy of the data being presented to some form of data repository so that other researchers can examine and reanalyze the data. Such sharing of data is now highly encouraged. This is considered best practice and is consistent with current government and international policies on scientific data. In this case all shared data will be fully anonymised and will never contain any personal details about you (name, address etc). A random code will be used to replace your name in the data so that it will impossible for anyone to identify you.

Will I be recognisable from my data?

In case of MRI data, you should be aware that there exists software that can reconstruct the outline shape of the face, similar to the picture shown on the right. Some facial features will be distorted and hair will be missing. Furthermore, similar to fingerprints, brain shape and anatomy are unique to each individual. While there is no current way of doing this, in the future technology may become available enabling one to recognize an individual from their brain structure.



Will my data be used for non-research purpose?

Your data may be also used for example for educational, teaching or media purposes.

What possible complications may arise during an MRI scan?

The enclosed space of the scanner can produce claustrophobia, so you should not volunteer if you have a history of claustrophobia. The scanner is a noisy environment. To counter this you will be given earplugs and headphones to wear. It is possible that lying motionless on your back in the scanner for some time might cause discomfort. This will be minimised by the use of comfortable padding and positioning. In rare cases it is also possible to experience mild tingling sensations. If you do experience any discomfort you should press the emergency call button. Should this happen, scanning will be stopped immediately and the scan operator will talk to you. If necessary, the scanning session will be ended and you will be brought out of the scanner. Any complaint about the way the project has been conducted or any possible harm you may have suffered will be addressed.

Detailed information on this can be found below. Normally there are no after-effects from the scan and you can return to your normal activities as soon as the scan is over.

Will my taking part in the project be kept confidential?
Yes. All the information about your participation in this project will be kept confidential. Further details regarding this can be found below and in the Data Privacy Statement.

What will happen if I do not want to carry on with the research project?
You are free to withdraw from participating in the project at any time. You are also free to withdraw your data from the study within two weeks of the last date when you participated in the research.

What if there is a problem?
The University of Birmingham has an insurance policy in place to cover claims arising from negligent harm. If you have any problems with the conduct of the project there are various people who you can contact:

(i) Anyone named below under "CHBH Personnel Contact Details".
(ii) The Research Governance Committee of the University of Birmingham (Tel: 0121 414 7618).

They can arrange for your concerns to be investigated.

Unexpected findings on your scan
The images obtained of your brain are for specific research purposes only and are generally not suitable for diagnostic medical opinions. They do not form any part of your medical records. However, although the pictures are not diagnostic scans, in the unlikely event that any unusual findings are noted incidentally by the scanner operator, further professional advice will be sought and you may be contacted at a later date to discuss any follow-up.

Will my taking part in this project be kept confidential?
Our procedures for handling, processing, storing and anonymising your data are all compliant with the Data Protection Act 2018. All information that is collected about you during the course of the research will be kept strictly confidential.

Who has reviewed the project?
This project was reviewed and approved by the Research Ethics Committee, University of Birmingham.

Who is conducting the research?
The research is conducted by the people below If you have any questions or require further details please contact these people.

PI: osiufisdjfoiosdjfijsouhh

Research Associate: duihfsodkjhlhlkjlkjlkjlluhfio

For enquiries not specific to study please contact the CHBH personnel below.

CHBH Personnel Contact Details

Prof Ole Jensen, CHBH Co-Director ,

School of Psychology, University of Birmingham

Dr Andrew Bagshaw, CHBH Co-Director

School of Psychology, University of Birmingham

Dr Magda Chechlacz, CHBH MRI Coordinator

School of Psychology, University of Birmingham

Ms Nina Salman, CHBH Chief Radiographer,

CHBH, University of Birmingham

Thank you for considering taking part and for taking the time to read this information.

DATA PRIVACY STATEMENT

In order to carry out the research project described above, we will need to collect information about you, and some of this information will be your personal data. Personal data is information that relates to an identified or identifiable individual. Under data protection law, we have to provide you with very specific information about what we do with your data and about your rights. We have set out below the key information you need to know about how we will use your personal data. More information on how the University processes personal data can be found on the University's website on the page called 'Data Protection - How the University Uses Your Data': https://www.birmingham.ac.uk/privacy/index.aspx

Who is the Data Controller?

The University of Birmingham, Edgbaston, Birmingham B15 2TT is the data controller for the personal data that we process in relation to you.

What data are we processing and for what purpose will we use it?

We will collect and process your personal data to conduct the research project, as explained in the Participant Information Sheet. These data will not be used to make decisions about you.

What is our legal basis for processing your data?

The legal justification we have under data protection law for processing your personal data is that it is necessary for our research, which is a task we carry out in the public interest.

Who will my personal data be shared with?

For the purposes of the research project, we may need to share your personal data with collaborators of the project principal investigator and other researchers in the University of Birmingham so that they can verify your identity in order to re-use your data (for example to make use of a particular scan without needing to scan you again) or to ensure that data sets do not contain duplicate versions of your data. We may also need to share a version of your data with external third parties such as data repositories or journal web sites. In this case your data will be fully anonymized. Anonymized data is not considered to be personal data as defined under data protection law.

How will my personal data be kept secure?

The University takes great care to ensure that personal data is handled, stored and disposed of confidentially and securely. Our staff receive regular data protection training, and the University has put in place organisational and technical measures so that personal data is processed in accordance with the data protection principles set out in data protection law.

The University has an Information Security Management System based on ISO27001 with a range of controls covering the protection of personal information. Annual security awareness training is mandatory for staff and the University is accredited under the NHS Information Governance Toolkit, the Payment Card Industry Data Security Standard and is in the process of gaining Cyber Essentials Plus for defined services.

In relation to this project, all electronically recorded data will be kept on secure University of BirmIngham computer servers. These servers are located on a secure password protected private network behind multiple firewalls. This data is only accessible to a small number of authorised users who have been approved to have access, such as the project principal investigator and their named collaborators. These researchers have an individual responsibility to safeguard the data and to ensure that security of the data is maintained. This includes any transfer of data to other computer systems elsewhere for secondary processing. Secure encrypted USB devices and/or laptops with encrypted filing systems will be used for data transport in case of theft or accidental loss. All paper records will be kept in secure, locked filing cabinets. Access to these records will be limited to a small number of authorised users who have been approved to have access such as the CHBH Radiographer and/or other scan operators. All servers and filing cabinets will be kept in locked rooms behind multiple physical barriers including alarm system and video surveillance.

How long will my personal data be kept?

Your data will be retained for a minimum of 10 years following data acquisition. This is in order that your data can be re-used if needed by the project principal investigator, their collaborators and

other researchers in the University of Birmingham. If you withdraw from the project, we will keep the information we have already obtained but, to safeguard your rights, we will use the minimum personally-identifiable information possible.

Your rights in relation to your data

You may have the following rights in respect of your personal data:

- The right to access to your data (often referred to as a Subject Access Request).
- The right to rectification of inaccuracies in your data.
- The right to erasure of your data (in certain circumstances).
- The right to restrict processing of your data (in certain circumstances).
- The right to object to the processing of your data (in certain circumstances).
- The right to ask for your personal data to be transferred electronically to a third party.

However, your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the project, we will keep the information we have already obtained but, to safeguard your rights, we will use the minimum personally-identifiable information possible.

If you would like more information on your rights, would like to exercise any right or have any queries relating to our processing of your personal data, please contact:

> The Information Compliance Manager, Legal Services, The University of Birmingham, Edgbaston, Birmingham B15 2TT
>
> Email: dataprotection@contacts.bham.ac.uk Telephone: +44 (0)121 414 3916

If you wish to make a complaint about how your data is being or has been processed, please contact our Data Protection Officer.

> Mrs Carolyn Pike, OBE, The Data Protection Officer, Legal Services, The University of Birmingham, Edgbaston, Birmingham B15 2TT
>
> Email: dataprotection@contacts.bham.ac.uk Telephone: +44 (0)121 414 3916

You also have a right to complain to the Information Commissioner's Office (ICO) about the way in which we process your personal data. You can make a complaint using the ICO's website.

A-19 MRI Safety screening questionnaire for BioPoP Study

MRI SAFETY SCREENING QUESTIONNAIRE



EVERYONE must fill in this form BEFORE entering the MRI corridor

The MRI corridor houses a very powerful magnet that may be hazardous to those with metallic, electronic, magnetic or mechanical implants or devices.

All information will be kept strictly confidential.

Name:		**Date of Birth:**	

Section A – To be completed by EVERYONE entering the MRI restricted corridor

Please indicate if you have any of the following:	**YES**	**NO**	**If yes please explain**
Cardiac pacemaker, cardioverter defibrillator (ICD) or pacing wires			
Aneurysm clips (metal clips inserted during brain surgery)			
Electrical or magnetic stimulator for nerves, bone or brain			
Ear or Eye Implants or surgery (e.g. cochlear implant)			
Artificial heart valve, heart stent or heart loop recorder			
Any implanted devices such as implanted insulin, drug or infusion pump, surgical mesh			
Stent, shunt, graft, filter, clips or any vascular (blood vessel) implant			
Artificial joints, metal plates, screws, pins or wires			
Gun pellets, shrapnel, bullets or metal fragments or foreign body			
Any other type of prosthesis, implant, surgery or operation			

Section B – Complete ONLY if you are being scanned or intend to go in the MRI controlled area

Email:		**Weight (kg):**	
Tel No:		**Height (cm):**	

Please answer the following questions carefully	**YES**	**NO**	**Staff Notes**
Are you claustrophobic to any degree?			
Have you ever been a welder, machinist, grinder or worked with metal without using continuous eye protection?			

Have you ever had a fit, blackout, epilepsy, diabetes, asthma, angina, vertigo or tinnitus?			
Do you have any tattoos, permanent makeup, or body piercings? *If **yes** have you also read the Tattoo Information Sheet?*			
Are you wearing tinted or coloured contact lenses?			
Do you wear dentures, braces, dental plate or dental wires?			
Are you wearing a medication skin patch (e.g. nicotine patch) or silver wound dressing?			
Are you wearing any clothing that may contain metallic threads?			
Do you have any drains/catheters attached to or within your body?			
Do you have an implanted IUD or other contraceptive device?			
Are you or could you be pregnant?			
Other information for staff (e.g. spectacle prescription):			

Tick the boxes below before proceeding

I confirm that the above information is accurate to the best of my knowledge. ☐

I acknowledge that CHBH has taken reasonable precautions to screen for potential difficulties and is not liable for any event that might result from incorrect answers to the above. ☐

Please remove **all** metal items on your person and any mobile phones, keys, belts, watches, coins, credit cards, jewellery, body piercings, microdermal piercings, false teeth, hearing aids, hair pins, coloured contact lenses or clothing with metallic threads before entering the scanner room. Lockers are available in the waiting area.

Signed:		**Date:**	

Verified by:	***AUTHORISED PERSONNEL ONLY***				
Signed:		**Initials:**		**Date:**	

This form is only valid when signed by an Authorised Person in the presence of the participant being screened

To be completed by Authorised Personnel only:

ENTERING THE MRI RESTRICTED CORRIDOR ONLY: ☐

309 ☐

☐

Tick **one** of these only:

NON-RESEARCH VOLUNTEER MRI SCAN:
CHBH PROJECT MRI SCAN

:

(If CHBH MRI project) **CHBH PROJECT CODE:**	

A-20 Assessment checklist for BioPop Study

Assessment checklist

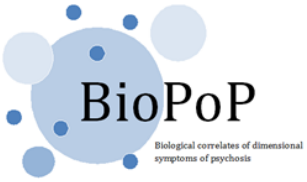
Participant ID	
Date of Visit	
Time of Visit	

Measure	Notes	Completed
Height	M.	
Weight	Kg.	
BMI	Calculated from height and weight	
Pregnancy screen		
Smoking status		
Occupation		
Handedness		
Education		
Ethnicity		

Consent form		
PANSS		
SBQ		
SANS		
CTQ		
CDSS		
MINI		
PSYRATS		
WHODAS		
Cognitive assessments	To be completed after the MRI scan or within 2 weeks of the MRI scan	
MRI scan	TO be completed within 2 weeks of assessment	
Bloods	If neuroleptic naive, take another sample	
YMRS		
ALS		

Details of history of physical health problems		

A –21 Personal Information Sheet for BioPoP study



Personal Information Sheet

Participant ID	
Date of Visit	
Time of Visit	

Name	
Address	
Phone number	
Date of Birth (and age)	
CPN	
CPN Phone number	
Consultant	
RIO number	
NHS Number	
GP name	
GP address	
Risk issues	

Neuroleptic naive	

M.I.N.I.

Mini International Neuropsychiatric Interview

English Version 5.0.0

DSM-IV

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hospitals, and government institutions) may make copies of a M.I.N.I. instrument for their own clinical and research use.

PATIENT'S NAME :	_____	*PROTOCOL NUMBER :*	_____
DATE OF BIRTH :	_____	*Time Interview Began :*	_____
INTERVIEWER'S NAME :	_____	*Time Interview Ended :*	_____
DATE OF INTERVIEW :	_____	*TOTAL TIME :*	_____

M.I.N.I. 5.0.0 / **English version / DSM-IV / current**

MODULES	TIME FRAME	
A. MAJOR DEPRESSIVE EPISODE	Current (past 2 weeks) + Lifetime	
A'. MDE with melancholic features	Current (past 2 weeks)	Optional
B. DYSTHYMIA	Current (past 2 years)	
C. SUICIDALITY	Current (past month)	
D. (HYPO) MANIC EPISODE	Current + Lifetime	
E. PANIC DISORDER	Lifetime + current (past month)	
F. AGORAPHOBIA	Current	
G. SOCIAL PHOBIA	Current (past month)	
H. OBSESSIVE-COMPULSIVE DISORDER	Current (past month)	
I. POSTTRAUMATIC STRESS DISORDER	Current (past month)	Optional
J. ALCOHOL DEPENDENCE / ABUSE	Current (past 12 months)	
K. DRUG DEPENDENCE / ABUSE (Non-alcohol)	Current (past 12 months)	
L. PSYCHOTIC DISODERS	Lifetime + Current	
M. ANOREXIA NERVOSA	Current (past 3 months)	
N. BULIMIA NERVOSA	Current (past 3 months)	
O. GENERALIZED ANXIETY DISORDER	Current (past 3 months)	
P. ANTISOCIAL PERSONALITY DISORDER	Lifetime	Optional

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P and the CIDI. The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 min., median 15 min.) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

- **Interview :**

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which requires a yes or no answer.

- **General format :**

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

- At the beginning of each module (except for psychotic disorders module), **screening question(s)** corresponding to the main criteria of the disorder are presented in a **gray box**.
- At the end of each module, **diagnostic box(es)** permit(s) the clinician to indicate whether the diagnostic criteria are met.

- **Conventions :**

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not to be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Sentences (in parentheses) are clinical examples of the symptom .These may be read to the patient to clarify the question.

Answers with an arrow above them (⃠) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, to circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)*, the interviewer should read only those symptoms known to be present in the patient (for example, question A3).

- **Rating instructions:**

All questions read must be rated. The rating is done at the right of each question by circling either YES or NO. The clinician should be sure that each dimension of the question is taken into account by the patient (i.e.: time frame, frequency, severity, « and/or » alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I.. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

A. MAJOR DEPRESSIVE EPISODE

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks ?	NO	YES	1
A2	In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time ?	NO	YES	2
	IS **A1** OR **A2** CODED **YES** ?	NO	YES	

A3 **Over the past two weeks, when you felt depressed and/or uninterested :**

a Was your appetite decreased or increased nearly every day or did your weight decrease or increase without trying intentionally ? (i.e., ± 5 % of body weight or ± 3,5 kg or ± 8 lbs., for a 70 kg / 120 lbs. person in a month) NO YES 3

IF **YES** TO EITHER, CODE **YES**

b Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening, or sleeping excessively) ? NO YES 4

c Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still, almost every day? NO YES 5

d Did you feel tired or without energy, almost every day? NO YES 6

e Did you feel worthless or guilty, almost every day? NO YES 7

f Did you have difficulty concentrating or making decisions, almost every NO YES 8 day?

g Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead ? NO YES 9

NO YES

A4 ARE **3** OR MORE **A3** ANSWERS CODED **YES** ?

(OR **4 A3** ANSWERS IF **A1** OR **A2** ARE CODED **NO**) ***MAJOR DEPRESSIVE EPISODE CURRENT***

IF PATIENT MEETS CRITERIA FOR MAJOR DEPRESSIVE EPISODE CURRENT : A5 a During your lifetime, did you have other periods of two weeks or more when you felt depressed or uninterested in most things, and had most of the

↯ MEANS : GO TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, CIRCLE NO IN ALL OF THEM AND MOVE TO THE NEXT MODULE

problems we just talked about ? NO YES 10

b Was there an interval of at least 2 months without depression and/or lost of interest between your current episode and your last episode of depression ? NO YES 11

NO YES

IS **A5b** CODED **YES** ?

MAJOR DEPRESSIVE EPISODE PAST

A'. MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

IF THE PATIENT CODES POSITIVE FOR A MAJOR DEPRESSIVE EPISODE (**A4** = **YES**), EXPLORE THE FOLLOWING :

A6 a IS **A2** CODED **YES** ? NO YES 12

b During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up?
IF NO : When something good happens does it fail to make you feel better, even temporarily ? NO YES 13

↯

IS EITHER **A6a** OR **A6b** CODED **YES** ? NO YES

Over the past two weeks period, when you felt depressed and uninterested :

A7 a Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies ?

ARE **3** OR MORE **A7** ANSWERS CODED **YES** ?

b Did you fell regularly worse in the morning, almost every day ?

c Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day ?

e IS **A3c** CODED **YES** ? d IS **A3a** CODED **YES** (ANOREXIA OR WEIGHT LOSS ONLY)?

f Did you feel excessive guilt or out of proportion to the reality of the situation ? NO YES 14

NO YES 15

MEANS : GO TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, CIRCLE NO IN ALL OF THEM AND MOVE TO THE NEXT MODULE

NO YES

MAJOR DEPRESSIVE EPISODE
With Melancholic Features
CURRENT

NO YES 16

NO YES 17

NO YES 18

NO YES 19

B. DYSTHYMIA

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE

B1	Have you felt sad, low or depressed most of the time for the last two years ?	NO	YES	20
B2	Was this period interrupted by your feeling OK for two months or more ?	NO	YES	21

B3 **During this period of feeling depressed most of the time :**

a Did your appetite change significantly ? NO YES 22

b Did you have trouble sleeping or sleep excessively ? NO YES 23

c Did you feel tired or without energy ? NO YES 24

d Did you lose your self-confidence ? NO YES 25

e Did you have trouble concentrating or making decisions ? NO YES 26

f Did you feel hopeless ? NO YES 27

ARE **2** OR MORE **B3** ANSWERS CODED **YES** ? NO YES

B4 Did the symptoms of depression cause you significant distress or impair your

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

ability to function at work, socially, or in some other important way ? NO YES 28

IS **B4** CODED **YES** ?

NO **YES**

DYSTHYMIA CURRENT

C. SUICIDALITY

In the past month did you :

C1	Think that you would be better off dead or wish you were dead ?	NO	YES	1
C2	Want to harm yourself ?	NO	YES	2
C3	Think about suicide ?	NO	YES	3
C4	Have a suicide plan ?	NO	YES	4
C5	Attempt suicide ?	NO	YES	5

In your lifetime

C6	Did you ever make a suicide attempt ?	NO	YES	6

IS AT LEAST **1** OF THE ABOVE CODED **YES** ? **NO** **YES**

IF YES, **SPECIFY** THE LEVEL OF SUICIDE RISK AS FOLLOWS :

C1 or C2 or C6 = YES : LOW

C3 or (C2 +C6) = YES : MODERATE

C4 or C5 or (C3 + C6) = YES : HIGH

SUICIDE RISK CURRENT

LOW

MODERATE

HIGH

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

D. (HYPO) MANIC EPISODE

D1 a	Have you **ever** had a period of time when you were feeling "up" or "high" or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self ? (Do not consider times when you were intoxicated on drugs or alcohol) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY "UP" OR "HIGH", CLARIFY AS FOLLOW : By "up" or "high" I mean : having elated mood, increased energy, needing less sleep, having rapid thoughts, being full of ideas, having an increase in productivity, creativity, motivation or impulsive behavior.	NO	YES	1
	IF YES :			
b	Are you currently feeling "up" or "high" or full of energy ?	NO	YES	2
	:			
D2 a	Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family ? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified ? (Do not consider times when you were intoxicated on drugs or alcohol)	NO	YES	3
	IF YES :			
b	Are you currently feeling persistently irritable ?	NO	YES	4
	ARE **D1a** OR **D2a** CODED **YES** ?	NO	YES	

D3 IF D1B OR D2B = YES : EXPLORE ONLY **CURRENT** EPISODE
IF D1B AND D2B = NO : EXPLORE **THE MOST SYMPTOMATIC** PAST EPISODE

During the time(s) when you felt "high", full of energy or irritable did you :

a	Feel that you could do things others couldn't do, or that you were an especially important person ?	NO	YES	5
b	Need less sleep (e.g., feel rested after only a few hours sleep) ?	NO	YES	6
c	Talk too much without stopping, or so fast that people had difficulty understanding ?	NO	YES	7

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

d Have thoughts racing? NO YES 8

e Become easily distracted so that any little interruption could distract you ? NO YES 9

f Become so active or physically restless that others were worried about you ? NO YES 10

g Want so much to engage in pleasurable activities that you ignored the risks or consequences (e.g., spending sprees, reckless driving, or sexual indiscretions) ? NO YES 11

ARE **3** OR MORE **D3** ANSWERS CODED **YES**

OR **4** IF **D1a = NO** (PAST EPISODE) OR **D1b = NO** (CURRENT EPISODE) ? NO YES

D4 Did these symptoms last at least a week **and** cause significant problems at home, at work, or at school,

or were you hospitalized for these problems? NO YES 12

IF YES TO EITHER, CODE YES

IS **D4** CODED **NO** ?

IF YES, SPECIFY IF THE EPISODE EXPLORED IS CURRENT OR PAST

NO **YES**

HYPOMANIC EPISODE

CURRENT
PAST

IS **D4** CODED **YES** ?

IF YES, SPECIFY IF THE EPISODE EXPLORED IS CURRENT OR PAST

NO **YES**

MANIC EPISODE

CURRENT
PAST

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

E. PANIC DISORDER

E1 Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way ? Did the spells peak within 10 minutes ?
CODE YES ONLY IF THE SPELLS PEAK WITHIN 10 MINUTES — NO YES 1

IF **E1** = **NO**, CIRCLE NO IN E5 AND SKIP TO F1

E2 At any time in the past, did any of those spells or attacks come on unexpectedly or spontaneously, or occur in an unpredictable or unprovoked manner ? — NO YES 2

IF **E2** = **NO**, CIRCLE NO IN E5 AND SKIP TO F1

E3 Have you ever had one such attack followed by a month or more of persistent fear of having another attack, or worries about the consequences of the attack ? — NO YES 3

IF **E3** = **NO**, CIRCLE NO IN E5 AND SKIP TO F1

E4 **During the worst spell that you can remember :**

a Did you have skipping, racing or pounding of your heart ? NO YES 4 b Did you have sweating or clammy hands ? NO YES 5 c Were you trembling or shaking ? NO YES 6 d Did you have shortness of breath or difficulty breathing ? NO YES 7 e Did you have a choking sensation or a lump in your throat ? NO YES 8 f Did you have chest pain, pressure or discomfort ? NO YES 9 g Did you have nausea, stomach problems or sudden diarrhea ? NO YES 10 h Did you feel dizzy, unsteady, lightheaded or faint ? NO YES 11 i Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from, part or all of your body ? NO YES 12 j Did you fear that you were losing control or going crazy ? NO YES 13 k Did you fear that you were dying ? NO YES 14 l Did you have tingling or numbness in parts of your body ? NO YES 15 m Did you have hot flashes or chills ? NO YES 16

E5 ARE **4** OR MORE **E4** ANSWERS CODED **YES** ? — NO YES

IF **E5** = **NO**, SKIP TO E7

Panic Disorder Life time

E6 In the past month, did you have such attacks repeatedly (2 or more) followed by persistant fear of having another attack ? — NO YES 17

IF **E6** = **YES**, SKIP TO F1

Panic Disorder Current

E7 ARE **1**, **2** OR **3** **E4** ANSWERS CODED **YES** ? — NO YES 18

Limited Symptom Attacks Lifetime

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

F. AGORAPHOBIA

F1 Do you feel anxious or particularly uneasy in places or situations from which escape might be difficult, and where help might not be available in case of panic attack, like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car ?

NO YES

19

IF **F1** = **NO**, CIRCLE NO IN F2

F2 Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them ?

NO YES

Agoraphobia Current

IS **F2** (CURRENT AGORAPHOBIA) CODED **NO** and IS **E6** (CURRENT PANIC DISORDER) CODED **YES** ?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES** and IS **E6** (CURRENT PANIC DISORDER) CODED **YES** ?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**
and
IS **E5** (PANIC DISORDER LIFETIME) CODED **NO** ?

NO **YES**

AGORAPHOBIA without history of Panic Disorder CURRENT

G. SOCIAL PHOBIA

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated ? This includes situations like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	NO	YES	1
G2	Is this fear excessive or unreasonable ?	NO	YES	2
G3	Do you fear these situations so much that you avoid them or suffer through them ?	NO	YES	3
G4	Does this fear disrupt your normal work or social functioning or cause you significant distress ?	NO	YES	4

IS **G4** CODED **YES** ? **NO** **YES**

SOCIAL PHOBIA CURRENT

H. OBSESSIVE-COMPULSIVE DISORDER

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

H1 In the past month, have you been bothered by recurrent thoughts, impulses or images that were unwanted, distasteful, inappropriate, intrusive or distressing ? (e.g., the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though you didn't want to, **or** fearing you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.)

NO YES

DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS.
DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.

1

IF **H1** = **NO**, SKIP TO H4

H2 Did they keep coming back into your mind even when you tried to ignore or get rid of them ?

NO YES 2

IF **H2** = **NO**, SKIP TO H4

H3 Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside ?

NO YES 3

H4 In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals ?

NO YES 4

ARE **H3** OR **H4** CODED **YES** ?

NO YES

H5 Did you recognize that either these obsessive thoughts and / or these compulsive behaviors you can not resist doing them, were excessive or unreasonable ?

NO YES 5

H6 Did these obsessive thoughts and / or compulsive behaviors significantly interfere with your normal routine, occupational functioning, usual social activities, or relationships, or did they take more than one hour a day ?

NO YES 6

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

NO **YES**

OBSESSIVE-COMPULSIVE DISORDER
CURRENT

IS **H6** CODED **YES** ?

I. POSTTRAUMATIC STRESS DISORDER (optional)

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else ? EX OF TRAUMATIC EVENTS : SERIOUS ACCIDENT, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, HOLD-UP, FIRE, DISCOVERNG A BODY, UNEXPECTED DEATH,, WAR, NATURAL DISASTER…	NO	YES	1
I2	During the past month, have you re-experienced the event in a distressing way (i.e., dreams, intense recollections, flashbacks or physical reactions) ?	NO	YES	2

I3 **In the past month :**

a Have you avoided thinking about the event, or have you avoided things that remind you the event ? NO YES 3

b Have you had trouble recalling some important part of what happened ? NO YES 4

c Have you become less interested in hobbies or social activities ? NO YES 5

d Have you felt detached or estranged from others ? NO YES 6

e Have you noticed that your feelings are numbed ? NO YES 7

f Have you felt that your life would be shortened because of this trauma ? NO YES 8

ARE **3** OR MORE **I3** ANSWERS CODED **YES** ? NO YES

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

I4 **In the past month :**

a Have you had difficulty sleeping ? NO YES 9 b Were you especially irritable or did you have outbursts of anger ? NO YES 10 c Have you had difficulty concentrating ? NO YES 11 d Were you nervous or constantly on your guard ? NO YES 12 e Were you easily startled ? NO YES 13

ARE **2** OR MORE **I4** ANSWERS CODED **YES** ? NO YES

I5 During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress ? NO YES 14

IS I5 CODED YES ? NO YES

POSTTRAUMATIC STRESS DISORDER CURRENT

J. ALCOHOL ABUSE AND DEPENDENCE

J1 In the past 12 months, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions ? NO YES 1

J2 **In the past 12 months :**

a Did you need to drink more in order to get the same effect that you did when you first started drinking ? NO YES 2

b When you cut down on drinking did your hands shake, did you sweat, or feel agitated ? Or, did you drink to avoid these symptoms or to avoid being hangover, e.g., "the shakes", sweating or agitation ? NO YES 3

IF YES TO EITHER, CODE YES

c During the times when you drank alcohol, did you end up drinking more than you planned when you started ? NO YES 4

d Have you tried to reduce or stop drinking alcohol but failed ? NO YES 5

e On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol ? NO YES 6

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

f Did you spend less time working, enjoying hobbies, or being with others because of your drinking ? NO YES 7

g Have you continued to drink even though you knew that the drinking caused you health or mental problems ? NO YES 8

ARE **3** OR MORE **J2** ANSWERS CODED **YES** ? **NO** **YES**

ALCOHOL DEPENDENCE
CURRENT

DOES THE PATIENT CODES POSITIVES FOR ALCOHOL DEPENDENCE ? NO YES

J3 **In the past 12 months :**

a Have you been intoxicated, high, or hangover more than once when you had other responsibilities at school, at work, or at home ? Did this cause any problems ? NO YES 9

CODE YES ONLY IF THIS CAUSED PROBLEMS

b Were you intoxicated in any situation where you were physically at risk, e.g., driving a car, riding a motor bike, using machinery, boating, etc. ? NO YES 10

c Did you have any legal problems because of your drinking, e.g., an arrest or disorderly conduct ? NO YES 11

d Did you continue to drink even though your drinking caused problems with your family or other people ? NO YES 12

ARE **1** OR MORE **J3** ANSWERS CODED **YES** ?

NO **YES**

ALCOHOL ABUSE
CURRENT

CARD OF SUBSTANCES

AMPHETAMINE

CANNABIS

COCAINE

CODEINE

CRACK

DICONAL

ECSTASY

ETHER

FREEBASE

GASOLINE

GLUE

GRASS

HASHISH

HEROIN

LSD

MARIJUANA

MESCALINE

METHADONE

MORPHINE

OPIUM

PALFIUM

PCP

RITALIN

TEMGESIC

THC

TOLUENE

TRICHLORETHYLENE

↯ MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

K1 Now I am going to show you (SHOW THE CARD OF SUBSTANCES) / to read to you a list (READ THE LIST BELOW) of street drugs or medicines. In the past 12 months, did you take any of these drugs, more than once, to get high, to feel better or to change your mood ?

↯ NO YES

CIRCLE EACH DRUG TAKEN :

Stimulants : amphetamines, « speed », crystal meth, « rush », Dexedrine, Ritalin, diet pills.

Cocaine : snorting, IV, freebase, crack, « speedball ».

Narcotics : heroin, morphine, dilaudid, opium, demerol, methadone, codeine, percodan, darvon.

Hallucinogens : LSD (« acid »), mescaline, peyote, PCP (« angel dust », « peace pill »), psilocybin, STP, « mushrooms », ecstasy, MDA, or MDMA.

Inhalants : « glue », ethyl chloride, nitrous oxide, (« laughing gas »), amyl or butyl nitrate (« poppers »).

Marijuana : hashish (« hash »), THC, « pot », « grass », « weed », « reefer ».

Tranquilizers : quaalude, Seconal (« reds »), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown.

Miscellaneous : steroids, nonprescription sleep or diet pills. Any others ?

SPECIFY MOST USED DRUG(S) : _____

SPECIFY WHICH WILL BE EXPLORED IN CRITERIA BELOW :

- IF CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE :

  EACH DRUG (OR DRUG CLASS) USED INDIVIDUALLY MOST USED DRUG (OR DRUG CLASS) ONLY

- IF ONE DRUG (OR DRUG CLASS) USED :

  SINGLE DRUG (OR DRUG CLASS) ONLY

K2 **Considering your use of [NAME THE SELECTED DRUG / DRUG CLASS] in the past 12 months :**

a Have you found that you needed to use more of [NAME OF SELECTED DRUG / DRUG CLASS] to get the same effect than you did when you first started NO YES 1 taking it ?

b When you reduced or stopped using [NAME OF SELECTED DRUG / DRUG CLASS] did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable or depressed) ?

Or did you use any drug(s) to keep yourself from getting sick (WITHDRAWAL SYMPTOMS) or so that you would feel better ?

IF **YES** TO EITHER, CODE **YES** NO YES 2

c Have you often found that when you used [NAME OF SELECTED DRUG / DRUG CLASS], you ended up taking more than you thought you would ? NO YES 3

d Have you tried to reduce or stop taking [NAME OF SELECTED DRUG / DRUG CLASS] but failed ? NO YES 4

MEANS : **GO** TO THE DIAGNOSTIC BOX(ES) OF THIS MODULE, **CIRCLE NO** IN ALL OF THEM AND **MOVE** TO THE NEXT MODULE

e On the days that you used [NAME OF SELECTED DRUG / DRUG CLASS], did you spend substantial time (>2 hours), obtaining, using or recovering from the effects, or thinking about it ? NO YES 5

f Did you spend less time working, enjoying hobbies, or being with family or friends, because of your drug use ? NO YES 6

g Have you continued to use [NAME OF SELECTED DRUG / DRUG CLASS] even though it caused you health or mental problems? NO YES 7

ARE **3** OR MORE **K2** ANSWERS CODED **YES** ? **NO** **YES**

SPECIFY DRUG(S) : _____ ***DRUG(S) DEPENDENCE***

CURRENT

DOES PATIENT CODES POSITIVE FOR DRUG DEPENDENCE ? NO YES

K3 **In the past 12 months :**

a Have you been intoxicated, high, or hangover from [NAME OF SELECTED DRUG / DRUG CLASS], more than once when you had other responsibilities at school, at work, or at home ? Did this cause any problem ? (CODE YES ONLY IF THIS CAUSED PROBLEMS) NO YES 8

b Have you been high or intoxicated from [NAME OF SELECTED DRUG / DRUG

CLASS] in any situation where you were physically at risk (e.g., driving a car, NO YES 9 or a motorbike, using machinery, boating, etc.) ? c Did you have any legal problems because of your [NAME OF SELECTED DRUG / DRUG CLASS] use, e.g., an arrest or disorderly conduct ? NO YES 10

d Did you continue to use [NAME OF SELECTED DRUG / DRUG CLASS] even though it caused problems with your family or other people ? NO YES 11

ARE **1** OR MORE **K3** ANSWERS CODED **YES** ? **NO** **YES**

SPECIFY DRUG(S) : _____ ***DRUG(S) ABUSE***

CURRENT

L. PSYCHOTIC DISORDERS

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS « BIZARRE ».

DELUSIONS ARE BIZARRE IF : CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE RATED BIZARRE IF : A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

Now I'm going to ask you about unusual experiences that some individuals may experience.

			BIZARRE	
L1 a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you ?	NO	YES	YES 1
b	**IF YES** : Do you currently believe these things ?	NO	YES ⊘ L6a	YES 2
L2 a	Have you ever believed that someone was reading your mind or could hear your thoughts or that you could actually read or hear what another person was thinking ?		YES	
			YES ⊘ L6a	NO 3
b	**IF YES** : Do you currently believe these things ?	NO		4
L3 a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self ?Have you ever felt that you were possessed	NO 5	YES	
			YES ⊘ L6a	
b	**IF YES** : Do you currently believe these things ?	NO		6
L4 a	Have you ever believed that you were being sent special messages through the TV, radio or newspaper, or that a person you did not personally know was particularly interested in you ?		YES	
			YES ⊘ L6a	
		NO		YES 7
b	**IF YES** : Do you currently believe these things ?	NO	YES	YES 8
L5 a	Have your relatives or friends ever considered any of your beliefs strange or out of reality ?		YES	
		NO	YES	YES 9
	ANY DELUSIONAL IDEAS NON EXPLORED IN QUESTIONS L1 TO L4, E.G., OF GRANDIOSITY, RUIN, GUILT, HYPOCONDRIASIS,...			
b	**IF YES** : Do they currently consider your beliefs strange ?	NO		ES 10
L6 a	Have you ever heard things other people couldn't hear, such as voices ?	NO	YES ⊘ L8b	ES 11

HALLUCINATIONS ARE CODED « BIZARRE » ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING :

Did you hear a voice commenting on your thoughts or behavior, or did you hear two or more voices talking to each other ?

b	**IF YES** : Have you heard these things in the past month ?	NO	YES 12

L7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see ? 13
CODE YES ONLY IF THE VISIONS ARE CULTURALLY INAPPROPRIATE.
NO YES

b **IF YES** : Have you seen these things in the past month? : NO YES 14

INTERVIEWER'S JUDGMENT :

L8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS ? 15
NO YES

L9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR ? NO YES 16

L10b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW ? 17
NO YES

L11 FROM L1 TO L10 : NO YES

- ARE **1 OR MORE** « **b** » QUESTIONS CODED **YES BIZARRE** ?

OR ***PSYCHOTIC SYNDROME***

- ARE **2** OR MORE « **b** » QUESTIONS CODED **YES** (RATHER THAN YES BIZARRE) ? ***CURRENT***

L12 FROM **L1 TO L7** :

- ARE **1** OR MORE « **a** » QUESTIONS CODED **YES BIZARRE** ? **NO** **YES**

OR

- ARE **2** OR MORE « **a** » QUESTIONS CODED **YES** (RATHER THAN YES BIZARRE**)** ? ***PSYCHOTIC SYNDROME***

(CHECK THAT THE 2 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD) ***LIFETIME*** **OR**

- IS **L11** CODED **YES** ?

L13a IF L12 IS CODED YES OR AT LEAST ONE YES FROM L1 TO L7 :

DOES THE PATIENT CODE POSITIVE FOR EITHER MAJOR DEPRESSIVE EPISODE (CURRENT OR PAST) **OR** MANIC EPISODE (CURRENT OR PAST) ?

NO YES

b You told me earlier that you had period(s) when you felt (depressed/ high/ persistently irritable).
Were the beliefs and experiences you just described (SYMPTOMS CODE YES FROM L1 TO L7) restricted exclusively to times when you were feeling depressed / high / irritable ?

NO YES 18

IS L13b CODED YES ? NO YES

MOOD DISORDER WITH PSYCHOTIC FEATURES CURRENT

M. ANOREXIA NERVOSA

M1 a	How tall are you ?	|__|__|__|		Ft Ins Cm	
b	What was your lowest weight in the past 3 months ?	|__|__|__|		Lbs. Kg	
c	IS PATIENT'S WEIGHT LOWER THAN THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT ? SEE TABLE BELOW	NO	YES		1

In the past 3 months :

M2	In spite of this low weight, have you tried not to gain weight ?	NO	YES	2
M3	Have you feared gaining weight or becoming fat, even though you were underweight ?	NO	YES	3
M4	Have you considered yourself fat or that part of your body was too fat ?	NO	YES	4
a				
b	Has your body weight or shape greatly influenced how you felt about yourself ?	NO	YES	5
c	Have you thought that your current low body weight was normal or excessive ?	NO	YES	6
M5	ARE **1** OR MORE **M4** ANSWERS CODED **YES** ?	NO	YES	
M6	FOR WOMEN ONLY : During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant) ?	NO	YES	7

FOR WOMEN : ARE **M5** AND **M6** CODED **YES** ?

FOR MEN : IS **M5** CODED **YES** ?

NO **YES**

ANOREXIA NERVOSA CURRENT

TABLE HEIGHT / WEIGHT THRESHOLD (HEIGHT-WITHOUT SHOES ; WEIGHT-WITHOUT CLOTHING)

HEIGHT(cm)	140	145	150	155	160	165	170	175	180	185	190
Females	37	38	39	41	43	45	47	50	52	54	57
WEIGHT (kg)											
Males	41	43	45	47	49	51	52	54	56	58	61

THE WEIGHT THRESHOLDS ABOVE ARE CALCULATED AS A 15% REDUCTION BELOW THE NORMAL RANGE FOR THE PATIENT'S HEIGHT AND GENDER AS REQUIRED BY DSM-IV.

N. BULIMIA NERVOSA

N1 In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period ? NO YES 8

N2 In the last three months, did you have eating binges as often as twice a week ? NO YES 9

IF **N6** = **NO**, SKIP TO **N8**

N3 During these binges, did you feel that your eating was out of control ?

N4 Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications ?

N5 Does your body weight or shape greatly influence how you feel about yourself ?

N6 DOES THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA ?

N7 Do these binges occur only

* TAKE THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE

IS **N5** CODED **YES** AND **N7** CODED **NO** (OR SKIPPED) ?

NO	YES
BULIMIA NERVOSA CURRENT	

IS **N7** CODED **YES** ?

NO	YES
ANOREXIA NERVOSA Binge-Eating/Purging Type CURRENT	

NO YES 10

NO YES 11

NO YES 12

NO YES 13

NO YES 14

O. GENERALIZED ANXIETY DISORDER

O1 a Have you worried excessively or been anxious about several things of day to day life, at work, at home, in your close circle over the past 6 months ? NO YES 1

DO NOT CODE YES IF THE FOCUS OF THE ANXIETY IS CONFINED TO ANOTHER DISORDER EXPLORED PRIOR TO THIS POINT SUCH AS HAVING A PANIC ATTACK (PANIC DISORDER), BEING EMBARRASSED IN PUBLIC (SOCIAL PHOBIA), BEING CONTAMINATED (OCD), GAINING WEIGHT (ANOREXIA NERVOSA)...

b Are these worries present most days ? NO YES 2

O2 Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing ? NO YES 2

FROM O3a TO O3f, CODE NO THE SYMPTOMS CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT

O3 When you were anxious over the past 6 months, did you, almost every day :

a Feel restless, keyed up or on edge ? NO YES 3

b Feel tense ? NO YES 4

c Feel tired, weak or exhausted easily ? NO YES 5

d Have difficulty concentrating or find your mind going blank ? NO YES 6

e Feel irritable ? NO YES 7

f Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively) ? NO YES 8

ARE **3** OR MORE **O3** ANSWERS CODED **YES** ?

NO **YES**

GENERALIZED ANXIETY DISORDER
CURRENT

P. ANTISOCIAL PERSONALITY DISORDER (optional)

P1 **Before you were 15 years old, did you :**

a Repeatedly skip school or run away from home overnight ?

b Repeatedly lie, cheat, « con » others, or steal ?

c Start fights or bully, threaten, or intimidate others ?

d Deliberately destroy things or start fires ?

e Deliberately hurt animals or people ?

f Force someone to have sex with you ?

ARE **2** OR MORE **P1** ANSWERS CODED **YES** ?

P2 DO NOT CODE YES THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED

Since you were 15 years old, have you :

a Repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself ?

b Done things that are illegal even if you didn't get caught (i.e., destroying property, shoplifting, stealing, selling drugs, or committing a felony) ?

c Been in physical fights repeatedly (including physical fights with your spouse or children) ?

d Often lied or « conned » other people to get money or pleasure, or lied just for fun ?

e Exposed others to danger without caring ?

f Felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property ?

ARE **3** OR MORE ITEMS FROM **P2** CODED **YES** ?

NO YES 10

NO YES 11

NO YES 12

NO YES 1

NO YES 2

NO YES 3

NO YES 4

NO YES 5

NO YES 6

NO YES

NO YES

ANTISOCIAL PERSONALITY DISORDER LIFETIME

NO YES 7

NO YES 8

NO YES 9

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Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D. DSM-III-R Psychotic disorders : procedural validity of the Mini International Neuropsychiatric Interview (M.I.N.I.). Concordance and causes for discordance with the CIDI. *European Psychiatry*, 1998 ; **13** : 26-34.

The M.I.N.I. was developed simultaneously into French and English. The French and English original versions of the M.I.N.I. for DSM-IV were translated and can be asked to the authors (see page 3). An ICD-10 version is also available into French, English and Danish.

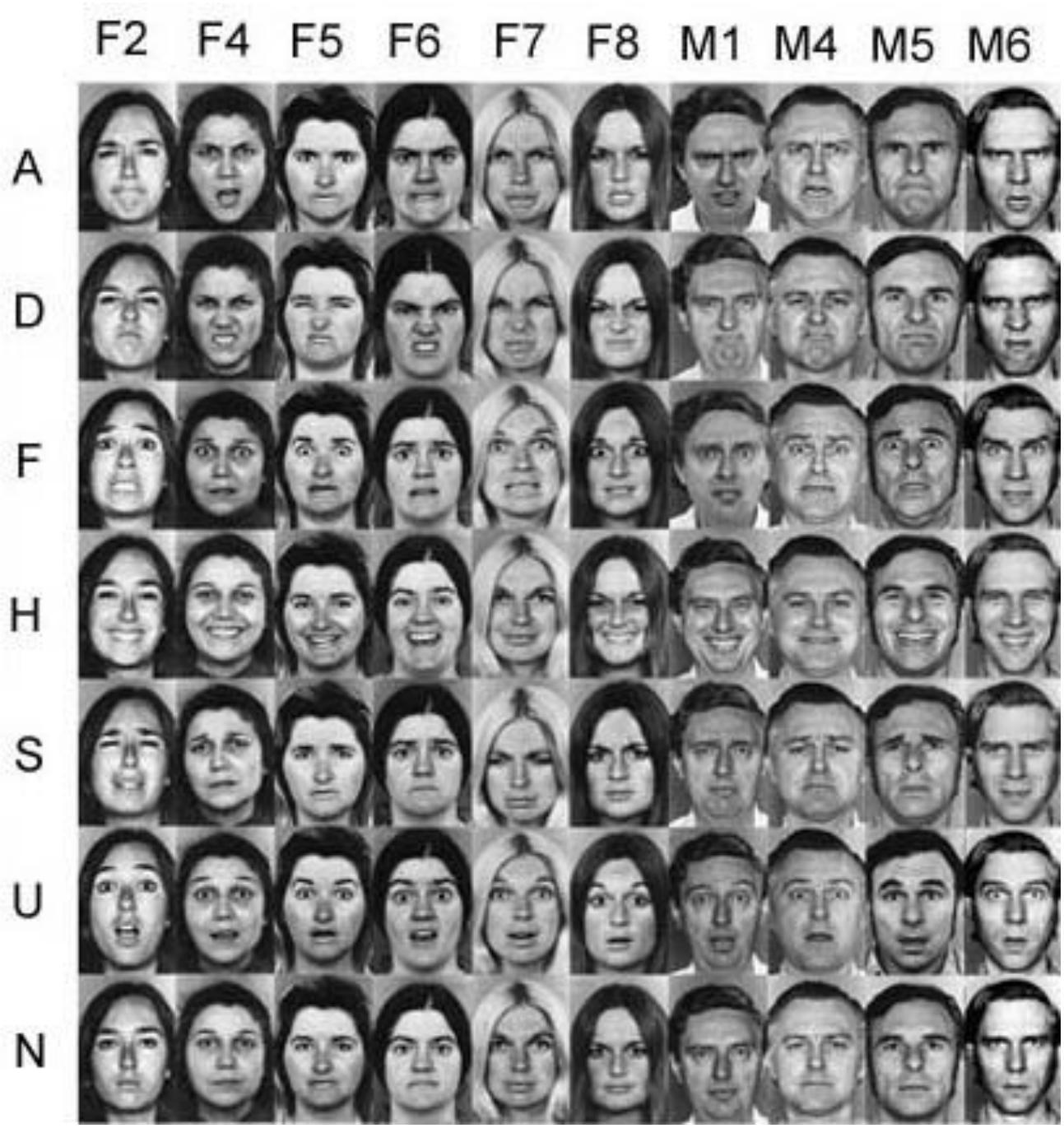
Translations	**M.I.N.I. 4.4 or earlier versions**	**M.I.N.I. 5.0, M.I.N.I. Plus 5.0, M.I.N.I. screen 5.0**
Afrikaans		R. Emsley
Arabic		O. Osman, E. Al-Radi
Basque		In preparation
Bengali		H. Banerjee, A. Banerjee
Brazilian	P. Amorim	In preparation
Bulgarian		L.G. Hranov
Catalan		In preparation
Czech	P. Zvolsky	P. Zvolsky
Chinese		L. Caroll
Croatian		In preparation
Danish	P. Bech	P. Bech, T. Scütze
Dutch/Flemish	E. Griez, K. Schruers, T. Overbeek, K. Demyttenaere	I. van Vliet, H. Leroy, H. van Megen
Farsi/Persian		K. Khooshabi, A. Zomorodi
Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	In preparation
German	I. van Denffer, M. Ackenheil, R. Dietz-Bauer	M. Ackenheil, G. Stotz, R. Dietz-Bauer
Gujarati		M. Patel, B. Patel
Greek	S. Beratis	T. Calligas, S. Beratis
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson
Hindi		K. Batra, S. Gambir
Hungarian	I. Bitter, J. Balazs	I. Bitter, J. Balazs
Italian	P. Donda, E. Weiller, I. Bonora	L. Conti, P. Donda, A. Rossi, M. Piccinelli, M. Tansella, G. Cassano
Japanese		H. Watanabe
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Norwegian	G. Pedersen, S. Blomhoff	K. Leiknes, U. Malt, E. Malt
Polish	M. Masiak, E. Jasiak	M. Masiak, E. Jasiak
Portuguese	P. Amorim	P. Amorim, T. Guterres
Punjabi		S. Gambir
Romanian		O. Driga
Russian		A. Bystitsky, E. Selivra, M. Bystitsky

Serbian	I. Timotijevic	I. Timotijevic
Setswana		K. Ketlogetswe
Slovenian	M. Kocmur	M. Kocmur
Spanish	L. Ferrando, J. Bobes-Garcia, J. Gibert-Rahola	L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes, O. Soto, L. Franco, J. Gibert
Swedish	M. Waern, S. Andersch, M. Humble	C. Allgulander, M. Waern, A. Brimse, M. Humble
Turkish	T. Örnek, A. Keskiner, I. Vahip	T. Örnek, A. Keskiner
Urdu		A. Taj, S. Gambir
Welsh		In preparation

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A-23 Ekman and Friesen Pictures of facial affect used in fMRI task in BioPop Study



A-24 Example of how Ekman and Friesen Pictures of facial affect used in fMRI task in BioPop Study



A-25 Scanning parameters for BioPoP study

SCANNING PARAMETERS	Bio-POP
	T1W
No. Slices	175
Slice thickness (mm)	1
Slice gap (mm)	
TR (ms)	8.4
TE (ms)	3.8
Flip angle (deg)	8
Reconstruction matrix	288
Field of View (FOV)	288 x 232 x 175
Voxel Size (acq)	1 x 1 x 2
Voxel Size (recon)	1 x 1 x 1
Direction of acquistion (slice orientation)	Sagittal
No. dynamics	
	Faces
No. Slices	36
Slice thickness (mm)	3
Slice gap (mm)	0
TR (ms)	2200
TE (ms)	39
Flip angle (deg)	79.1
Reconstruction matrix	80
Field of View (FOV)	240 x 240 x 108
Voxel Size (acq)	3 x 3 x 3
Voxel Size (recon)	3 x 3 x 3
Direction of acquistion (slice orientation)	Transverse
No. dynamics	235

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A-26 Participant's payment receipt for BioPop Study

UNIVERSITY OF BIRMINGHAM

Biological correlates of dimensional symptoms of psychosis (BioPoP)

Receipt £20 for time compensation

_____	_____	_____
Name of Participant (print)	Signed by Participant	Date

_____	_____	_____
Name of Researcher (print)	Signed by Researcher	Date

V1 02/12/15