RESILIENCE IN MENTAL HEALTH:

INVESTIGATING NEUROCOGNITION AS A PROTECTIVE FACTOR

by

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ABSTRACT

Individuals who are exposed to risk factors for psychiatric illness often demonstrate a diverse range of clinical and functional trajectories. One potential reason for this is that they have differing levels of *resilience*. The present thesis aimed to clearly define resilience, before investigating neurocognition as a potential protective factor. Resilience was defined as a dynamic process in which individuals utilise available protective factors in the face of risk or adversity, leading to better outcomes than might have been expected. After establishing that neurocognition is significantly impaired in people experiencing psychosis-spectrum disorders, this thesis demonstrated that neurocognitive performance is preserved in a transdiagnostic sample of people demonstrating resilience to the effects of psychopathology. Neurocognition was also associated with a measure of resilience to childhood trauma. Though neurocognitive performance was not associated with scores on a self-report measure of resilience in this sample, the findings of this thesis provide tentative evidence that neurocognition may exert a protective effect. Further longitudinal research which examines neurocognitive performance across the whole spectrum of mental health is required. Ultimately, high quality resilience research can inform new interventions which look to strengthen protective factors, and thus improve outcomes for individuals experiencing, or at-risk for, psychiatric illness.

For Mum and Dad

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LIST OF ABBREVIATIONS

ANOVA- Analysis of Variance

BD- Bipolar Disorder

BDI - Beck Depression Inventory

BDS- Backward Digit Span

BS- Basic Symptoms

CBT- Cognitive Behavioural Therapy

CD-RISC- Connor-Davidson Resilience Scale

COGDIS- Cognitive Disturbances

CPT- Continuous Performance Test

CRT- Cognitive Remediation Therapy

CTQ- Childhood Trauma Questionnaire

dACC- Dorsal Anterior Cingulate Cortex

DALYs- Disability-Adjusted Life Years

DANVA- Diagnostic Analysis of Non-Verbal Accuracy

DGPPN- German Association for Psychiatry, Psychotherapy, and Psychosomatics

DMN- Default Mode Network

DSM- Diagnostic and Statistical Manual for Mental Disorders

DSST- Digit Symbol Substitution Test

DUP- Duration of Untreated Psychosis

EI- Early Intervention

FDS- Forward Digit Span

FED- First Episode of Depression

FEP- First-Episode Psychosis

FHN- No Family History of Psychopathology

FHP- Positive Family History of Major Depressive Disorder

FHR- Familial High Risk

GAF- Global Assessment of Functioning

GF: Role- Global Functioning: Role Scale

GF: Social- Global Functioning: Social Scale

HC- Healthy Control

IQ- Intelligence Quotient

MAOA- Monoamine Oxidase A

MCCB- MATRICS Consensus Cognitive Battery

MDD- Major Depressive Disorder

NAPLS- North American Prodrome Longitudinal Study

NHS- National Health Service

NICE- National Institute for Health and Care Excellence

PRONIA- Personalised Prognostic Tools for Early Psychosis Management

PVF- Phonetic Verbal Fluency

QOL- Quality of Life

RAVLT- Rey Auditory Verbal Learning Test

RCT- Randomised Control Trial

ROCF- Rey Osterrieth Complex Figure

RSA- Resilience Scale for Adults

SD- Standard Deviation

SCID-IV- Structured Clinical Interview for DSM-IV Axis I Disorders

SOPT- Self-Ordered Pointing Task

SIPS- Structured Interview for Psychosis-Risk Syndromes

SPI-A- Schizophrenia Proneness Instrument, Adult Version

SVF- Semantic Verbal Fluency

TMT A- Trail Making Test Part A

TMT B- Trail Making Test Part B

UHR- Ultra-High Risk for Psychosis

UHR-NT- UHR Without Transition to Psychosis

UHR-T- UHR With Transition to Psychosis

WASI- Wechsler Abbreviated Scale of Intelligence

WHO- World Health Organisation

WHOQOL- World Health Organisation Quality of Life Scale

YLD- Years Lived with Disease

PUBLICATIONS AND PRESENTATIONS

PUBLISHED JOURNAL ARTICLES

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CONTRIBUTIONS

The PhD candidate was responsible for all aspects of experimental design, analytic strategy, interpretation of results, and preparation of this thesis. With regards to data collection, the data for this thesis was collected as part of a large, multi-site, EU-funded study. The data is pooled from all sites and is the result of years of hard work from the entire consortium. The PhD candidate spent over four years working on this project and was directly responsible for a significant proportion of the participant recruitment and data collection from the University of Birmingham site. The candidate was advised by her two named supervisors, and received feedback from secondary authors on any work which was published or presented at academic conferences.

CHAPTER ONE

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GENERAL INTRODUCTION

GENERAL INTRODUCTION

Mental illness is common, and one of the leading causes of disability globally. Surveys by the World Health Organisation (WHO) of twenty-eight participating countries have demonstrated lifetime prevalence rates for any mental disorder ranging from 18.1-36.1%. Anxiety disorders are the most common, followed by mood disorders (Kessler et al., 2009). A method commonly used to measure the impact of mental illness on an individual's wellbeing is to calculate Disability-Adjusted Life Years (DALYs), which combines years of life lost and Years Lived with Disease (YLDs). A recent investigation of published data suggested that mental illness accounts for 32.4% of YLDs and 13% of DALYs worldwide. These estimations would place mental illness as the leading cause of YLDs globally (Vigo, Thornicroft, & Atun, 2016). Insel (2008) estimated the overall cost of mental disorder in the United States as $317 billion annually. This figure incorporates the direct costs of medical care, and indirect costs such as the estimated $193.2 billion loss of earnings (Kessler et al., 2008), and the cost of disability benefits. However, additional factors such as incarceration and the presence of comorbidity, not accounted for in this figure, would greatly increase this economic burden of mental illness (Insel, 2008). These findings highlight the importance of identifying effective treatments, which would reduce the disability associated with mental illness, and prevent future relapse. While effective treatments are an important goal, researchers and clinicians are increasingly looking to *prevent* mental illness. By identifying risk factors to be reduced, and protective factors which could be strengthened, preventative interventions could be employed before an individual develops psychopathology and the associated disability. Such work will not only improve our understanding of mental illness, but will decrease these enormous personal and financial burdens.

Adolescence and early adulthood appear to be particularly important periods of life with regard to the onset of mental illness. Adult mental illness often has its onset prior to age 24 (Patel, Flisher, Hetrick, & McGorry, 2007), with 50% of all mental illness beginning before age 14 and 75% before age 24 (Kessler et al., 2005) Furthermore, it is common for mental illnesses which begin in adolescence to persist into adulthood. In a longitudinal study of a large cohort of Australian adolescents, Patton et al. (2014) identified that 60% of individuals who experienced mental illness in adolescence also experienced further psychopathology in adulthood. A longer duration of adolescent symptoms was the strongest predictor of mental disorder in adulthood (Patton et al., 2014). These findings further underscore the importance of a movement towards preventative intervention for mental health, with the implication being that intervening at an earlier stage of illness, often associated with earlier age, may prevent this persistence of illness to adulthood.

FIRST-EPISODE PSYCHOSIS

Psychosis is an episodic mental illness characterised by positive symptoms; new experiences of delusions (false beliefs) or hallucinations (perceptual abnormalities). It can also be accompanied by negative and disorganised symptoms (American Psychiatric Association, 2013). Negative symptoms refer to the absence or weakening of "healthy" processes such as speech, motivation, and affect. Disorganised symptoms can include behaviours which contradict the individual's social or cultural norms, as well as conceptual disorganisation. Psychosis is thought to lie at one end of a continuum of psychotic symptoms, and is differentiated from the rest of this psychosis spectrum by the intensity of the symptoms, and a characteristic lack of insight into the self-generated nature of the symptoms (McGlashan, Walsh, & Woods, 2001; Yung et al., 2005). Furthermore, the term "psychosis" does not only refer to schizophrenia; most research now focuses on the whole

spectrum of affective and non-affective psychoses. The term "First Episode Psychosis" (FEP) refers to the first time that an individual experiences an episode of psychosis. Following this, An individual may experience multiple episodes over the lifetime, interspersed with periods of remission or recovery (Henry et al., 2010; Larsen, McGlashan, & Moe, 1996). The illness may be long-term and have devastating effects on an individual's subjective quality of life (Browne et al., 2000; Malla & Payne, 2005). Suicidality (Clarke et al., 2006; Foley et al., 2008) and self-harm (Harvey et al., 2008; Patel & Upthegrove, 2009) may also be prominent in individuals with psychosis. The illness may also contribute to increased mortality through an increased risk of additional physical health concerns (Reininghaus et al., 2014).

In addition to clinical symptoms, there are a number of other markers of the illness. For example, FEP has been associated with significant neurocognitive impairment (discussed further in Chapter Three), as well as structural (Andreasen et al., 2011; Steen, Mull, McClure, Hamer, & Lieberman, 2006) and functional (Radua et al., 2012) brain alterations. Individuals with psychosis may also demonstrate significant functional impairments (Bellack, Morrison, Wixted, & Mueser, 1990; Henry et al., 2010). Such impairments can affect an individual's ability to retain a strong social network (Couture, Penn, & Roberts, 2006) and remain in education or employment (Hodgekins et al., 2015; Killackey, Jackson, Gleeson, Hickie, & McGorry, 2006), despite willingness or intent to do so (Rinaldi et al., 2010; Secker, Grove, & Seebohm, 2001).

Treatment for psychosis often involves a number of specialised strategies including Cognitive Behavioural Therapy (CBT; Bird et al., 2010; Tarrier et al., 2004) and antipsychotic medications which, though effective for treatment of psychotic symptoms (Kahn et al., 2008), are commonly associated with a number of unfavourable side effects

such as drowsiness and weight gain (McEvoy et al., 2007). While research is continually attempting to identify the most effective treatments for FEP, there is an increasing focus on *prevention.* Effective interventions employed before the onset of diagnosable illness would help to reduce the significant burden of psychosis for the individual and the community, as well as decreasing reliance on treatments such as antipsychotic medications which can be associated with negative side effects.

THE "ULTRA-HIGH RISK" CONCEPT

For more than twenty years, researchers have acknowledged that the onset of frank psychosis is often preceded by a period in which an individual begins to experience similar symptoms, at a lower level of intensity or frequency. While the concept of a psychosis "prodrome" is common, it can only be identified retrospectively following a diagnosis of FEP. Thus, work in this field has sought to identify specific criteria which would prospectively identify an individual who is at Ultra High Risk (UHR) for developing psychosis. Generally, three specific psychosis-risk groups are agreed upon. Firstly, the presence of attenuated psychotic symptoms at an intensity and frequency too low to be considered psychotic; secondly, the presence of symptoms of a psychotic intensity which are brief and resolve spontaneously; and finally, the presence of a genetic risk for psychosis, coupled with a significant decline in functioning (Miller et al., 2003; Yung & McGorry, 1996; Yung et al., 2005).

The number of individuals who "transition" (ultimately go on to experience frank psychosis) was initially estimated at approximately 40% within the first year of identification as UHR (Yung et al., 2003). Subsequent studies, however, have identified transition rates ranging from 4.5% at six months (Yung et al., 2006) to 50% after one year (Mason et al., 2004). In a longitudinal study which followed up over 400 individuals from a UHR service

in Melbourne, Australia, Nelson et al. (2013) identified that the highest risk for transition occurred within the first two years of identification. Transitions continued in their sample, however, over a 10-year follow-up period, with a total estimated 34.9% transition rate over the study period (Nelson et al., 2013). The results of this study are concordant with the general findings of the field, and one can accept that roughly one third of UHR individuals might be expected to transition to psychosis, however, a large degree of variation either side of this figure can be expected depending upon the sample and follow-up period.

Transition rates are likely to be highly variable due to a variety of factors. Firstly, UHR is a highly heterogeneous concept and will likely include individuals who will ultimately experience a wide range of clinical and functional outcomes. In addition to the "true prodromal" cases who ultimately transition to psychosis, individuals at UHR may also experience complete remittance of mental disorder, maintenance of attenuated symptoms, or may instead transition to a nonpsychotic disorder. In a sample of individuals who had not transitioned to psychosis, Addington et al. (2011) observed that 43% were still experiencing at least one attenuated psychotic symptom at one-year follow-up, and this remained true for 41% of the sample after two-years. Simon and Umbricht (2010) observed remittance from UHR status by one-year follow-up in 59.2% of their sample. Lin et al. (2015) studied a number of outcomes in individuals at UHR for up to fourteen years. They identified that 28% of the sample still experienced attenuated symptoms at follow-up. Furthermore, comorbidity was high in their sample, as 68% of individuals experienced another, nonpsychotic, mental disorder at some point during the course of follow-up (Lin et al., 2015). These results highlight the considerable variability in the outcomes one might expect to observe in individuals who are considered to be at UHR for psychosis. Further, research in this area is also likely to be influenced by the establishment of UHR clinics which has taken

place since the advent of the concept. With more individuals receiving treatment at this earlier stage of illness, it may be that for some individuals who would have been "true positive" cases, a transition to psychosis has been delayed or prevented due to such early intervention (Yung et al., 2007).

An alternative way to characterise people who are at high-risk for psychosis is to use the "Basic Symptom" concept. Basic Symptoms (BS) refer to subtle, self-reported changes in thinking and perception, which are also often observed in the years prior to a first-episode of psychosis. In particular, researchers have identified a particular subset of nine BS which appear to confer the highest risk for psychosis. These particular BS are referred to as "Cognitive Disturbances" (COGDIS), and involve a range of experiences including noticeable changes in concentration, pressured thought, and thought blockage (Schultze-Lutter, Klosterkötter, Picker, Steinmeyer, & Ruhrmann, 2007b). Although some studies have found no significant benefit of BS for predicting transition to psychosis (e.g. Hengartner et al., 2017) findings from several other studies have demonstrated the utility of COGDIS criteria. In their study, Schultze-Lutter et al. (2007b) observed that 23.9% of individuals fulfilling the COGDIS criteria transitioned to psychosis within one year of identification, and they continued to observe transitions occurring over more than three years. It is possible that combining the basic symptom and UHR criteria may confer the highest predictive value (Ruhrmann et al., 2010). In a naturalistic study observing transition rates over a 48-month period, individuals who fulfilled both COGDIS and UHR criteria were significantly more likely to transition to psychosis than individuals who fulfilled either one of those criteria alone (Schultze-Lutter, Klosterkotter, & Ruhrmann, 2014).

An array of factors which may be particularly predictive of a transition to psychosis from UHR has been identified. Many studies compare individuals identified as UHR who

do- or do not- go on to develop psychosis, and examine differing profiles in these groups on a number of test variables. Psychological factors such as depression, disorganisation, and schizotypal personality characteristics have all been associated with transition (Mason et al., 2004; Yung et al., 2003; Yung, Phillips, Yuen, & McGorry, 2004). In addition, individuals who have a longer period of untreated illness appear to be more likely to transition to psychosis (Yung et al., 2003; Yung et al., 2004). Individuals who do- or do not- transition also appear to significantly differ on a number of neurocognitive variables, including attention (Yung et al., 2004), working memory, verbal memory, Intelligence Quotient (IQ), and processing speed (Pukrop et al., 2007). Furthermore, using a multivariate pattern recognition technique, executive function and verbal learning have been found to predict transition (Koutsouleris et al., 2011). Finally, there is some evidence of structural and functional brain alterations which are predictive of transition. Wood, Reniers, and Heinze (2013) reviewed the literature in this area and found that activation of the stress system and increased striatal dopamine synthesis appear to be associated with transition to psychosis (Wood et al., 2013).

Researchers in this field quickly identified that transition to psychosis is not the only outcome of interest for individuals at UHR. Regardless of whether individuals develop psychosis, the UHR state impacts on an individual's wellbeing in a number of ways. Social and role functioning appear to be significantly impaired in individuals at UHR (Cornblatt et al., 2007), irrespective of transition (Addington et al., 2011). Additionally, functional disability in individuals at UHR has been identified as persistent and resistant to treatments (Cotter et al., 2014). These functional impairments are then also associated with lower subjective quality of life during this period (Domínguez-Martínez, Kwapil, & Barrantes-Vidal, 2015). Finally, individuals at UHR, even without transition, also demonstrate

significant neurocognitive impairment relative to Healthy Controls (HCs; de Paula, Hallak, Maia-de-Oliveira, Bressan, & Machado-de-Sousa, 2015), particularly on tasks of verbal and visual memory, executive function, and working memory (Fusar-Poli et al., 2012; Lencz et al., 2006).

The UHR concept has provided a valuable starting point for examining ways that we might understand the development of psychosis, and thus ultimately prevent it. The concept still has a number of limitations, including whether current conceptualisations of "transition" are truly valid (Yung, Nelson, Thompson, & Wood, 2010). Furthermore, there are several excellent reviews which highlight potential ethical issues of UHR research and intervention; It is important to consider the implications of applying treatment with such high "false positive" rates, in addition to potential issues arising from labelling individuals as "at-risk" (Corcoran, Malaspina, & Hercher, 2005; Cornblatt, Lencz, & Kane, 2001; Haroun, Dunn, Haroun, & Cadenhead, 2006). Moving forwards, the goal for researchers and clinicians will be to successfully navigate the balance between attempting to prevent the onset of psychosis and "over-treatment" of individuals who were never truly at-risk for psychosis. Studies continually aim to identify the most accurate methods of predicting psychosis (Riecher-Rössler & Studerus, 2017), to enable early intervention with a degree of certainty. Furthermore, it will be important to identify interventions which would reduce symptoms, distress, and risk of comorbidity which could be applied to a large proportion of individuals at UHR, with low risk of adverse effects in the event of a "false positive" case.

EARLY INTERVENTION FOR MENTAL ILLNESS

As discussed in the general introduction of this thesis, there is an increasing shift towards earlier intervention for mental health. Not only does mental illness often begin during adolescence and persist to adulthood (Patton et al., 2014), but there is also a wealth

of evidence which demonstrates that a longer period of untreated illness is associated with poorer outcomes. There is a well-established negative effect of a longer Duration of Untreated Psychosis (DUP). Longer DUP has been associated with poorer response to antipsychotic medication, positive and negative symptoms, depression and anxiety symptoms, and functional outcomes (Keshavan et al., 2003; Marshall et al., 2005; Perkins, Gu, Boteva, & Lieberman, 2005). Furthermore, in a study by Melle et al. (2004) which investigated the potential of an early detection programme for psychosis, they identified significant benefits of reducing the DUP. A shorter DUP was associated with fewer positive and negative symptoms at baseline, and lasting benefit for negative symptoms at three-month follow-up. The disadvantages of a prolonged duration of untreated illness are also observed in mood disorders. A longer duration of untreated Major Depressive Disorder (MDD) has been associated with significantly poorer response to treatment, and a higher likelihood of relapse (Altamura, Dell'Osso, Mundo, & Dell'Osso, 2007; Bukh, Bock, Vinberg, & Kessing, 2013; Ghio, Gotelli, Marcenaro, Amore, & Natta, 2014) as well as significantly poorer functioning (Ghio et al., 2015). It is possible that if reducing the duration of illness without treatment is effective, earlier intervention which prevents any period of illness would be even more beneficial.

Early Intervention (EI) services now exist all over the globe which attempt to identify and treat individuals experiencing a FEP, thus reducing the DUP and improving long-term outcomes. Such services are crucial, as the first years after a FEP would not only otherwise represent an elongated DUP, but also confer the highest risk for relapse and suicide (McGorry, Killackey, & Yung, 2008). EI may refer to a number of specialised treatment strategies including the use of antipsychotic medication, cognitive behavioural therapy, and cognitive remediation (McGorry et al., 2008). Several Randomised Control Trials (RCT)

which examine the efficacy of EI services for individuals experiencing a FEP have identified several significant benefits of this specialised care. These benefits include improved compliance with treatment (Marshall & Rathbone, 2011), fewer hospital readmissions (Craig et al., 2004), better functional outcomes and quality of life (QOL; Garety et al., 2006). A RCT of a specialised EI service in America identified that at two-year follow-up, participants who had received this treatment showed significantly greater improvements in clinical symptoms, functioning, and quality of life compared to individuals who received community care (Kane et al., 2015). Conversely, a number of studies have found mixed or negative findings regarding the benefits of EI. Garety et al. (2006), while identifying benefit for functional outcomes, found no impact of specialised care on symptom levels at 18-month follow-up. The OPUS trial in Denmark (Jørgensen et al., 2000) identified significantly greater improvement in positive and negative symptoms in individuals who had received specialised EI care when compared to standard treatment at two-year follow-up. However, these benefits for clinical symptoms were no longer present at five- (Bertelsen et al., 2008) or ten-year (Secher et al., 2014) follow-up. Aside from clinical symptoms, there were some other significant benefits for participants receiving the OPUS EI service after five and ten years. At five-year follow-up the EI group had spent significantly fewer days in psychiatric hospital (Bertelsen et al., 2008), and at both of these follow-up visits the EI group had spent significantly fewer days in supported housing (Bertelsen et al., 2008; Secher et al., 2014). A systematic review of RCTs by Marshall and Rathbone (2011) found no significant benefit of EI on suicidality, relapse, or independent living. Furthermore, a smaller RCT by Kuipers, Holloway, Rabe-Hesketh, and Tennakoon (2004) found no benefit of EI over treatment as usual in a sample of patients with psychosis from South London. In summary, EI services are still *relatively* new and therefore evidence relating to its long-term efficacy is sparse.

However, at present findings are generally promising with regard to the benefit of EI for individuals with a FEP on a number of clinical and functional outcomes. Of course, further longitudinal studies will help to confirm the most effective treatment strategies for FEP.

While the years following a FEP are thought to be crucial for an individual's long-term outcome, some of the negative outcomes such as functional impairment may have already begun during the UHR period (McGorry et al., 2008). Therefore, early intervention may be required before a transition to psychosis occurs, not only to prevent or delay more severe psychotic symptoms, but also to improve associated factors which are important for an individual's wellbeing. The establishment of several specialised prodromal services, such as the 'OASIS' service in London (Broome et al., 2005) and the 'PACE' clinic in Melbourne (Yung, McGorry, McFarlane, & Patton, 1995) illustrate that such services are a feasible addition to the clinical network. Evidence as to the efficacy of preventing transition to psychosis and other unfavourable outcomes during this period is mixed. Several RCTs have identified a significant benefit of CBT for preventing a transition to psychosis. Morrison et al. (2004) identified significantly lower transition rates following cognitive therapy, which were maintained for 6-months post-treatment. A study by van der Gaag et al. (2012) found similar benefits, with the incidence of psychosis at 18-month follow-up being halved in a group receiving CBT. The significant effect of CBT in this sample was also retained at four-year follow-up (Ising et al., 2016). In their RCT, Bechdolf et al. (2012) examined the effect of Integrated Psychological Intervention, a technique which combined individual CBT, group skills training, cognitive remediation and multifamily psychoeducation. They found that this intervention was associated with a significant benefit for preventing psychosis at 12- and 24-month follow-up when compared to supportive counselling. Some studies also demonstrated promising results for the use of low-dose antipsychotic medication to reduce

symptom levels in individuals at UHR (Woods et al., 2003; Woods et al., 2007), however, some RCTs do not demonstrate a treatment-effect beyond the trend-level (McGlashan et al., 2006). A recent meta-analysis by Davies et al. (2018) did not identify a significant benefit of any one intervention over other interventions. However, the trials included in this meta-analysis were often comparing two types of intervention as opposed to a "treatment as usual" condition. Thus, this study still supports the notion that intervention may be effective during the UHR period. One RCT which compared multiple intervention strategies including low-dose risperidone, CBT plus a placebo, and supportive therapy plus a placebo did not find any significant difference in transition rates between these groups after six (Yung et al., 2011) or twelve (McGorry et al., 2013) months. However, as in the previous study all three groups demonstrated significant improvements at follow-up. On balance, there are several findings which provide evidence that intervention, especially CBT, may significantly reduce the likelihood of transition to psychosis. Additionally, Ising et al. (2015) identified that CBT employed during the UHR period was a cost effective intervention. However, as of yet no specific therapy has been identified which can reliably prevent psychosis. Of course, research in this area is hindered by our understanding of UHR at present as outlined already. Therefore, any potential benefit of intervention in UHR is currently balanced with risks. Clinicians must be cautious of potential downsides to the identification and treatment of individuals at UHR such as self or externally generated stigma, and the risk of side effects from medication in individuals who are in fact "false positives". However, there is still a need for care during this period, as individuals may still experience significant distress or comorbid psychiatric symptoms. Research which improves our ability to predict psychosis with more accuracy will reduce the heterogeneity of the group, and thus also improve our understanding of EI for these individuals.

TRANSDIAGNOSTIC APPROACHES

There is growing discontent with the current diagnostic system. Such tools as the Diagnostic and Statistical Manual for Mental Disorders (DSM; American Psychiatric Association, 2013) and the WHO's International Classification of Diseases (World Health Organization, 1992) aim to categorise patterns of psychopathology into distinct disorders, which, theoretically, should not overlap or be associated with one another. This does not fit with common observation in clinical practice, in which presentations are often complex, comorbid, and changeable. Furthermore, even one particular diagnosis according to the current systems can in fact represent a highly heterogeneous group. A diagnosis of MDD, for example, is based upon a presentation of any five out of nine possible symptoms according to the DSM. This allows many different presentations within the same diagnosis, and yet it is assumed that the course, outcome, and treatment of two individuals with entirely different experiences should be similar. A further observation which contradicts this categorical approach is that of significant comorbidity in mental disorder. In fact, approximately 50% of individuals presenting with one mental disorder will also present with another, then 50% of those individuals will present with a third disorder, and so on (Caspi et al., 2014). A recent study by Plana-Ripoll et al. (2019) investigated comorbidity using Danish health registers which included 5,940,778 individuals born in Denmark over a 25-year-period. The authors identified that the presence of one mental disorder was associated with significantly higher risks of developing any other disorder. Risk of developing another disorder was highest during the six months prior to first diagnosis, but remained to a lesser extent for the entire duration of follow-up. Furthermore, several relationships between different disorders, such as mood and neurotic disorders, were bi-directional and independent of temporal sequence; regardless of which disorder occurred first, an individual

would still be at significantly higher risk of experiencing the second disorder (Plana-Ripoll et al., 2019). Such observations have caused a movement in both clinicians and researchers towards a more transdiagnostic approach towards the understanding and treatment of mental disorder.

Intervention trials have demonstrated that such a transdiagnostic approach may have validity. For example, a trial of internet based CBT demonstrated that this intervention was successful in reducing both anxiety and depressive symptoms in a transdiagnostic sample (Titov et al., 2011). Similarly, a randomised control trial comparing CBT to a "waitlist control" condition demonstrated that the treatment had significant positive effects on both primary anxiety diagnoses *and* comorbid depression, and that these gains were retained over six-month follow-up (Farchione et al., 2012). Taken together, these results suggest underlying commonalities between diagnoses, due to the success of employing transdiagnostic treatment strategies. However, McEvoy, Nathan, and Norton (2009) remind us to consider the potential downsides of such treatments. For example, group cohesion in therapy settings, which impacts upon treatment adherence, may be affected if a group consists of a highly heterogeneous cohort with very differing presentations.

Researchers now widely accept the existence of theoretical and biological similarities between diagnoses. Several theories have been put forward to explain the overlap between diagnoses. Some research has suggested that comorbidity might be better explained by the existence of "dimensions" of psychopathology. For example, some researchers have suggested that all disorders can be categorised into three broader dimensions: internalising, externalising, and thought disorder (Achenbach & Edelbrock, 1981; Caspi et al., 2014; Krueger & Eaton, 2015). There is evidence that in addition to these dimensions, there may be one underlying factor which reflects a propensity towards the development of any type of

psychopathology, which is further related to more life impairment, poorer developmental history, and significant early functional brain alterations (Caspi et al., 2014). Transdiagnostic research has also adopted approaches from other medical fields such as oncology. McGorry, Hickie, Yung, Pantelis, and Jackson (2006) discussed the potential benefit of adopting a Clinical Staging Model, which, as opposed to classifying mental disorders into specific diagnoses, focuses on the *intensity*, or stage, of illness. According to this model, individuals could be classified as any one of eight possible stages ranging from the presence of increased risk in the absence of symptoms (Stage 0) to chronic and unremitting illness (Stage 4). The model represents a logical response to the issues with the current understanding of UHR to psychosis, in which a number of outcomes are possible. Early data has suggested that approximately 19-30% of individuals will progress from the attenuated to discrete disorder stage within 12 months (Hickie et al., 2013; McGorry, Hartmann, Spooner, & Nelson, 2018). The Research Domain Criteria also proposes an alternative strategy, supporting the movement of psychiatry towards a more transdiagnostic approach. This initiative, launched by the National Institute of Mental Health in the United States, seeks to identify the underlying neural circuitry of mental illness, and use genetic and neurological data to supplement clinical opinion (Insel et al., 2010). As such, studies adopting this approach would group participants based upon particular patterns of neural circuitry, as opposed to using diagnoses based upon current nosological systems. Thus far, empirical research adopting this approach is still in its infancy. However, authors have suggested that this approach may have merit for the understanding and assessment of psychopathologies such as anxiety (Bauer et al., 2013; Hamm et al., 2016; Insel, 2014) and hallucinations (Badcock & Hugdahl, 2014).

To summarise, the theories discussed here suggest that the future of psychiatry is transdiagnostic. There is a growing acceptance that the current diagnostic system does not go far enough to explain real presentations of mental illness, which are often complex and comorbid in nature. Research which adopts a transdiagnostic approach can further our understanding of the biological and behavioural mechanisms which are common to multiple mental illnesses. Identifying successful transdiagnostic treatments which target multiple types of symptoms, or in fact an underlying propensity to psychopathology itself, may be more cost effective, and also be beneficial for clinician training and treatment waiting times (McEvoy et al., 2009). In addition, such strategies may be more appropriate for intervention at an earlier stage of illness, with less repercussions for potential "false positive" cases than current diagnosis-specific treatments.

CHAPTER TWO

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RESILIENCE AS A MULTIMODAL DYNAMIC PROCESS

INTRODUCTION

Not all individuals exposed to the same risk factors for psychiatric illness have identical subsequent trajectories. One potential reason for this is that they have differing levels of *resilience*, or varied ways in which they are able to utilise personal or environmental resources to their benefit. Understanding the basis of resilience will inform new strategies to promote and strengthen those factors in others who are at risk of experiencing a first-episode of psychiatric illness. Evidence suggests that resilience is higher in healthy individuals when compared to patients. For example, individuals identified as being at UHR for psychosis (Marulanda & Addington, 2016) and individuals with a schizophrenia-spectrum disorder (Bozikas et al., 2016) scored significantly lower on self-report measures of resilience than healthy controls. However, studies which compare resilience in patients and healthy controls often do not account for exposure to risk, an important consideration for resilience research. Other studies, therefore, have examined levels of resilience within patient groups. Kim et al. (2013) identified that resilience was lower in individuals at UHR who ultimately made a transition to frank psychosis than those who did not. Furthermore, in their sample of patients with schizophrenia-spectrum disorder, Bozikas et al. (2016) identified that patients with higher resilience also presented with better functioning. Together, findings like these indicate that higher resilience may have a protective effect against the development, or long-term effects, of mental illnesses.

While the current evidence clearly demonstrates the value of the resilience concept in mental health research, the field is still hindered by a number of theoretical and methodological issues. As such, the aims for the present review are as follows:

1. To discuss a consensus definition of resilience and attempt to define related terminology.

2. To provide evidence that resilience is a dynamic process.
3. To provide an updated examination of the literature which examines the specific, multimodal protective factors involved in resilience to mental illness.
4. To identify the mechanisms which support engagement in the resilience process.
5. Finally, to discuss further limitations and future directions for the field.

DEFINITIONS OF RESILIENCE

Previously, resilience has not been well defined, which has affected the validity and progression of research within the topic (Davydov, Stewart, Ritchie, & Chaudieu, 2010). More recently, several extensive reviews have attempted to provide a definition which encapsulates all aspects of the resilience concept (see Table 2.1). Despite this, the idea that resilience remains an undefined concept still influences the narrative of resilience research.

Many of the recent definitions listed in Table 2.1, however, appear to be fundamentally similar, something that has been recognised for a number of years (Herrman et al., 2011). Present definitions converge around three main factors: first, the presence of an adversity or specific risk for the development of mental illness; second, the influence of protective factors which supersede this risk; and finally, a more positive outcome than might be expected in the context of such a risk (Fletcher & Sarkar, 2013; Windle, 2011). While authors differ slightly in their wording of this definition, there is a fundamental agreement as to the core components of resilience. Importantly, these definitions also move away from the idea that resilience is merely the opposite of risk, or the absence of symptoms (Bonanno, 2004). Instead, resilience is an additional, active process which is distinctive from risk. This definition of resilience allows the identification of factors which can be strengthened to improve long term outcomes for “at-risk” individuals. While it is difficult to reduce resilience to one simple operationalisation, moving forwards it is essential that researchers

conceptualise resilience using these three core features, and do not conflate resilience with the opposite of risk. Not only will this strengthen the validity of the concept, but it also makes studies more comparable, providing a more solid base of knowledge to inform clinicians. It would now be more beneficial to the resilience field for researchers to move their focus from defining the concept to alternative issues which remain.

Table 2.1
Definitions of Resilience

"Resilience is the process of effectively negotiating, ***adapting*** *to, or managing significant sources of stress or trauma."* (Windle, 2011)
"Healthy, ***adaptive****, or integrated positive functioning over the passage of time in the aftermath of adversity."* (Southwick, Bonanno, Masten, Panter-Brick, & Yehuda, 2014)
"Most definitions are based around the two core concepts of adversity and positive ***adaptation****"* (Fletcher & Sarkar, 2013)
"In the context of exposure to significant adversity, resilience is both the capacity of individuals to ***navigate*** *their way to the psychological, social, cultural, and physical resources that sustain their wellbeing, and their capacity individually and collectively to* ***negotiate*** *for these resources to be provided and experienced in culturally meaningful ways"* (Ungar, 2011)
"Resilience is a ***dynamic*** *capability which can allow people to thrive on challenges given appropriate social and personal contexts."* (Howe, Smajdor, & Stockl, 2012)
"The term resilience is used in the literature for different phenomena ranging from prevention of mental health disturbance to successful ***adaptation*** *and swift recovery after experiencing life adversities, and may also include post-traumatic psychological growth."* (Rutten et al., 2013)
"Resilience is an ***interactive*** *concept that is concerned with the combination of serious risk experiences and a relatively positive psychological outcome despite those experiences."* (Rutter, 2006)
"Resilience appears to be a common phenomenon that results in most cases from the operation of basic human ***adaptational systems****. If those systems are protected and in good working order, development is robust even in the face of severe adversity." (Masten, 2001)*

There are several related concepts involved in resilience which are also important to define. The present review, informed by the definitions of Table 2.1, identifies resilience as

a dynamic process. The process of resilience is characterised by utilising the protective factors available to one's advantage, thus leading to better outcomes than would be expected within the context of a specific risk for mental illness. This review conceptualises "protective factors" as any personal or environmental factors which are of benefit to the individual's mental health or long-term functioning. Protective factors represent more than simply a lack of risk factors. Furthermore, they are not static. Analogous to the concept of 'fluid risk' (Bell, 1992), an individual's access to, or the strength of, these protective factors may fluctuate throughout their lifetime, further underscoring the dynamic aspect of the resilience process. This review also explores the "mechanisms' involved in the resilience process. Mechanisms refer to the underlying process by which a protective factor exerts a positive effect on an individual's mental health or long-term functioning. Mechanisms may function by moderating a risk factor, or mediating the effect of the risk factor on a long-term outcome. These concepts will be explored in further detail throughout this review.

RESILIENCE AS A DYNAMIC PROCESS

One debate in the field has been whether resilience should be considered a 'trait' phenomenon, which is stable and enduring across all risks, or a 'state' phenomenon which is dynamic and changeable (Hu, Zhang, & Wang, 2015; Rutter, 2012). The first investigations of resilience focused on "ego resilience", identifying resilient individuals, who had comparatively improved outcomes in the face of risks or adversities (Block & Block, 1980). The suggested "ego-resilient" person is already resourceful before they encounter an adversity, and their resilient characteristics can be observed even in childhood. Such definitions of resilience as a stable and enduring construct have begun to explain individual differences in response to risk.

It is noteworthy that recent definitions (Table 2.1) extend this concept of an a priori given resilience and focus on the dynamic aspects of the concept. They highlight resilience as a process, as opposed to a static or stable trait. These definitions conceptualise resilience as the process by which individuals adapt to unfavourable circumstances, as opposed to the characteristics of the individual themselves (Luthar & Cicchetti, 2000). Fergus and Zimmerman (2005) separated the components of resilience into 'assets' and 'resources'. Assets refer to the personality characteristics discussed in earlier definitions such as competence or coping skills (which may or may not be static traits). Resources consider protective factors which are external to the individual, such as family support or community organisations. The *process* of resilience refers to the utilisation of both assets and resources for a favourable outcome (Fergus & Zimmerman, 2005). It is also important to consider the physical state as an additional factor which influences one's ability to utilise these assets and resources. For example, changes to physical health may affect and individual's ability to understand and engage with these elements. This further underscores the dynamic aspect of the resilience process, which results from a complex interaction between personal and environmental factors which are always subject to change.

Moreover, resilience may be dynamic within a single individual, fluctuating across circumstances and as a function of time. For example, an individual may be proficient in one area of life such as academic skills, but struggle with social skills. Luthar, Cicchetti, and Becker (2000) highlight this idea as a fundamental principle of the concept. They state that, while we may expect to see similar levels of resilience in similar domains, we cannot expect one individual to demonstrate resilient outcomes in all areas, and at all times, of their life. Arguably, it is important to encourage the idea that resilience will fluctuate. As an individual navigates their life, not all assets or strategies will be useful in every circumstance (Rutter,

2012). If individuals are encouraged to utilise a range of strategies for different problems across their lifespan, they will be more equipped to deal with new problems, and changes they face due to ageing or circumstance. It is also important to remember that resilience is not impenetrable. If the presence of risk factors increases to an overwhelming level, any individual may experience the onset, or detrimental effects, of disorder. The purpose of resilience research is not to stigmatise, but to provide a new perspective on the highly variable trajectories of mental health and wellbeing.

The conception of resilience as a process suggests that it is possible for anyone to be taught to engage in this process, by utilising whichever protective factors may be available to them. This outlook informs intervention strategies in two ways: firstly, that protective factors associated with more favourable outcomes should be strengthened individuals experiencing, or at risk for, mental illness. In the long-term, it would also be these specific factors which could be transformed into larger public health interventions, with the aim of reducing the global burden of mental illness. Secondly, that it is important to understand the way individuals may engage with these resources to their benefit.

Due to the presence of many extensive, high quality reviews in the field, the core components of resilience are now largely agreed upon. Future research should now focus on identifying the specific, multimodal, protective factors involved in resilience. It is critical that these protective factors are conceptualised from a multimodal perspective. Mental health has numerous influences including the psychological, biological/neurobiological, genetic, and neurocognitive. Resilience research, therefore, should reflect the dynamic nature of mental health and illness. The examination of resilience in other domains can only strengthen the validity of the concept. Importantly, research should also attempt to understand the mechanisms which underlie people's engagement in this process. It is not enough that people

possess protective factors, they must also understand how to utilise them to their benefit, and in which circumstances this will be most appropriate.

PSYCHOLOGICAL AND SOCIAL PROTECTIVE FACTORS

The majority of research examining protective factors in resilience focuses on possible psychological or social factors. Various potential psychological factors have been identified in the literature, with reviews highlighting factors such as hardiness (Bonanno, 2004) and optimism (Fletcher & Sarkar, 2013; Lee et al., 2013a). Southwick et al. (2016) stressed the importance of social support as a protective factor, identifying the various beneficial aspects such as the size and quality of an individual's social network, and the frequency of social interactions. Southwick et al. (2016) suggest that social support may be related to resilience through a number of intermediary mechanisms, such as the motivation to reduce risky behaviours. In a qualitative study examining individuals' experience of FEP, Henderson (2015) identified two types of resilience: "Tenacity", which involved the input of effort over time, and "Rebounding", meaning springing back or continuing with life. Self-esteem, quality of life, and spirituality also positively correlated with higher scores on a self-report scale of psychological resilience in patients with schizophrenia and bipolar disorder (BD; Mizuno et al., 2016a).

Empirical methods have also been used to determine the psychological factors involved in resilience. In an observation of individuals who retained healthy functioning despite exposure to trauma, 'purpose in life' significantly predicted 'resilient' versus 'currently ill' status (Alim et al., 2008). Additionally, Harris, Brett, Starr, Deary, and McIntosh (2016) examined protective factors, evident in early life, which predicted adult resilience. In this birth cohort study, an array of risk and protective factors were assessed in early life, with self-report resilience subsequently assessed after approximately 66 years.

Interestingly, they found that adolescent dependability (higher teacher ratings on personality characteristics such as 'conscientiousness' and 'desire to excel) and childhood illness (number of serious illnesses during childhood) significantly predicted lower adult resilience scores. A higher number of stressors (such as house moves or parent separation or death) in early life predicted higher adult resilience. The authors suggest that developing a healthy stress reaction requires an initial exposure to stress, which has an inoculating effect. In turn, higher resilience scores were related to higher scores on measures of physical health, mental health, and wellbeing (Harris et al., 2016). Collishaw et al. (2016) studied mental health outcomes in the adolescent offspring of parents with depression over a period of four years. Approximately 20% of their sample retained good long term mental health, despite their established genetic risk for depression. Factors such as support from co-parents, good quality social relationships, and self-efficacy all predicted better sustained mental health. They also identified that the presence of multiple protective factors was required to sustain good mental health over time. This may be particularly informative if effective intervention requires the strengthening of a protective network.

Using these results, researchers have also attempted to build a model of psychological resilience. It is often suggested that resilience occurs across three distinctive domains, characterised by Windle (2011) as Individual, Social, and Cultural. Friborg, Hjemdal, Rosenvinge, and Martinussen (2003) further divided resilience into five reliable subdomains. The broader 'individual' domain includes 'personal competence' factors, such as self-esteem and determination, 'social competence' factors, including extraversion and social adeptness, and 'personal structure', including ability to uphold routines and organisation. The broader 'family' domain referred to 'family coherence', the amount of family conflict or co-operation, support, and stability. Finally, the 'external support systems' domain referred to

access to external support from friends and family. Much of this research into psychological and social protective factors is similar to the approach of Fergus and Zimmerman (2005), highlighting specific resources which are available to be utilised in the resilience process.

NEUROBIOLOGICAL PROTECTIVE FACTORS

In order to understand how resilience might function across domains, we can consider possible neurobiological differences between individuals with differing mental health outcomes. This approach enables the identification of structural differences, or potentially compensatory brain changes in response to risk, and would further our understanding of the variable outcomes in at-risk populations. Amico et al. (2011) compared individuals with MDD, healthy controls with no family history of psychopathology (FHN), and healthy controls with a positive family history of MDD (FHP). The FHP group was considered resilient as despite their relatively high genetic risk, they had not developed the disorder, and displayed significantly larger volumes of the dorsomedial prefrontal cortex compared to both other groups. This could suggest that increased volumes of this particular area are associated with resilience.

In a similar design, Frangou (2011) identified increased volumes of the vermis, and increased connectivity between the ventral and dorsal prefrontal cortex, as markers of resilience to BD. These structural and connective patterns were distinct to first-degree relatives of BD patients when compared to their family members with BD and healthy controls. The family members without psychopathology did express neurological markers of their genetic risk for BD; however, they also demonstrated these additional changes which to the authors hypothesised helped overcome that risk. In another study of resilience to BD, Dima (2016) presented BD patients, asymptomatic first-degree relatives of BD patients, and healthy controls, with a task to measure facial affect processing. They identified that

frontolimbic dysfunction characterised risk for BD and diffuse hypoconnectivity of the working memory network was related to disease expression. Asymptomatic relatives, however, evidenced an additional hyperconnectivity within the ventral visual stream, which the authors conclude to represent a marker of resilience to BD. Finally, Peterson et al. (2014) sought to identify specific endophenotypes of risk and resilience for MDD. The risk endophenotype was characterised by greater activation of cortical attention circuits, whereas resilience was characterised by greater activation of the dorsal anterior cingulate cortex (dACC). Activation of the dACC has also been found to correlate with increased self-report psychological resilience in healthy adults (Kong, Wang, Hu, & Liu, 2015). Additionally, increased volumes of the anterior cingulate cortex have also been related to increased optimism in health older adults (Chowdhury, Sharot, Wolfe, Duzel, & Dolan, 2014). These results provide an initial understanding of the potential biological protective factors involved in resilience to mental illnesses.

GENETIC PROTECTIVE FACTORS

Evidence also suggests a genetic component to the resilience process. In a study of boys who had experienced maltreatment, Caspi et al. (2002) identified that resilience may result from genes which indicate higher Monoamine Oxidase A (MAOA) expression. Compared to those who had the lower activity version of the same gene, high MAOA expression was related to significantly lower levels of antisocial behaviour, a common outcome following childhood maltreatment. In two independent samples, specific polymorphisms of the Corticotropin-Releasing Hormone Receptor 1 gene were found to moderate the effect of child abuse on adult depression with a protective effect (Bradley et al., 2008). In the Dunedin Birth Cohort, a polymorphism of the 5-HTT gene conferred resilience to depression (Caspi et al., 2003). In their sample, carrying two long ('l') alleles

of the gene reduced the effect of life events upon depressive symptoms when compared to individuals carrying at least one short ('s') allele of the gene. The same effect was observed for increases in depressive symptoms, suicide ideation/ attempts, and for the effect of childhood maltreatment on depression. These results could indicate that while carrying the s allele of the 5-HTT gene confers a risk for depression, carrying the l allele could indicate resilience to depression. Additionally, the long allele of 5-HTTLPR polymorphism has been associated with increased emotional resilience in college students (Stein, Campbell-Sills, & Gelernter, 2009).

It is important to note, however, that these are not simple cause and effect relationships between the gene and a resilient outcome. It is highly unlikely that one gene alone will underlie resilience. More likely, a cluster of genes will interact to produce such an outcome. Additionally, there is likely a highly complex relationship between genetics, environment, and life experience which altogether predicts an individual's trajectory or outcome.

NEUROCOGNITIVE PROTECTIVE FACTORS

There is also evidence that neurocognitive ability could be an important consideration when studying resilience. Neurocognitive deficits appear to be marked and longstanding in many mental illnesses such as depression (Marazziti, Consoli, Picchetti, Carlini, & Faravelli, 2010; Veiel, 1997) and psychosis (Fioravanti, Bianchi, & Cinti, 2012; O'Carroll, 2000). However, at present it is difficult to isolate neurocognitive protective factors, due to the current sparsity of research in this area. There have been some investigations of this relationship, with tentative suggestions of a positive correlation between cognitive ability and resilience. Results presented here are intended to highlight the potential benefit of investigating neurocognition as a protective factor, however, further empirical evidence is

required in order to form conclusions regarding the role of neurocognition in the resilience process.

There are several studies which demonstrate this link. For example, in the Dunedin Birth Cohort, neurocognitive performance at the age of seven was found to prospectively differentiate individuals who would develop a schizophrenia spectrum disorder in adulthood (Koenen et al., 2009). For each standard deviation (SD) increase in childhood IQ, the individual was found to have a 42% reduction in the odds of receiving a lifetime schizophrenia spectrum diagnosis. Such a differentiation was also seen for individuals who would receive a diagnosis of adult depression or anxiety disorders, and was associated with persistence of depression and likelihood of comorbidity (Koenen et al., 2009). In this study, odds of receiving an adult diagnosis continued to reduce along the whole range of IQ scores. It is possible, therefore, that one could consider a continuum by which deficits in IQ relate to risk, but *above average* IQ score adds additional protection. These results demonstrate that individuals with better performance on neurocognitive measures are less likely to receive diagnoses of mental illness in adulthood. In addition, better neurocognitive performance is consistently linked with improved social and role functioning (Lee et al., 2013b; Lin et al., 2011; Meyer et al., 2014) independent of clinical symptoms (Carrión et al., 2011; Lee et al., 2015). As such, these results indicate that neurocognition warrants further investigation in terms of its potential as a protective mechanism which may be utilised in the resilience process.

Wingo, Fani, Bradley, and Ressler (2010) investigated resilience to traumatic life events, in a sample of 226 traumatised individuals. They compared neuropsychological performance in individuals who had, or had not, developed psychopathology following exposure to trauma. They identified comparable performance between the two groups on

measures of verbal reasoning, nonverbal reasoning, and verbal memory. However, individuals classified as resilient exhibited better baseline performance on tests of nonverbal memory than those classified as non-resilient, an effect which remained after adjustment for severity of childhood abuse, exposure to other trauma, gender, and race. Furthermore, Genet and Siemer (2011) found that cognitive flexibility, the ability to inhibit or switch attention, and flexible processing of affective stimuli predicted higher scores on two scales of trait resilience. In their sample of undergraduate students, higher scores of trait resilience were associated with better performance on tasks of cognitive flexibility involving both neutral and emotionally weighted stimuli. Finally, in a cohort study of male soldiers, higher trait resilience was linked to higher scores on measures of attentional control (Schafer et al., 2015). Again, these results all demonstrate patterns of neurocognitive performance which are distinct to individuals who are thought to be engaging the resilience process. At present, we cannot be certain of the role that neurocognition plays in the resilience process as investigations have been hindered by methodological limitations such as a lack of control group. Therefore, further research in this area will be essential moving forwards.

MECHANISMS OF THE RESILIENCE PROCESS

It is crucial that research explores the mechanisms which underlie the resilience process and develops an understanding of how individuals engage with protective factors and utilise them to overcome a risk or adversity. In relation to resilience, a mechanism may refer to the process by which a protective factor either mediates or moderates the effect of risk on long-term outcomes. Positive appraisal style has been proposed as one such cognitive mechanism. Kalisch, Muller, and Tuscher (2015) propose that by classifying situations positively, reappraising where necessary, and avoiding interference by negative stimuli,

individuals may overcome the effects of stress. As such, a positive appraisal style may mediate the effect of stress on long-term mental health and wellbeing.

Additionally, there may be genetic mechanisms underlying the resilience process. The Differential-Susceptibility Hypothesis suggests that individuals who carry the "vulnerability" allele of a gene may in fact react better to positive child rearing than those carrying the "protective" allele. This "vulnerability" allele may in fact mean that they are more sensitive to the effects of their environment, whether positive *or* negative (Bowes & Jaffee, 2013; Davydov et al., 2010). Intervention for such individuals may be more effective, informing clinicians that "high-risk" cases should be the primary target for intervention. Such results provide an indication of how genetic mechanisms may influence resilience.

It has also been hypothesised that resilience may result from the experience of prior stresses or adversities. Circumstances which are stressful enough to challenge, but not overwhelm, the individual, can provide the opportunity to learn skills or identify attributes which can help the individual to overcome future risks (Harris et al., 2016). Often termed an "inoculating" or "steeling" effect, this means that when faced with future risks or adversities, the individual can draw on their prior experience and employ strategies which assisted them with past stresses (Southwick et al., 2016). In a study of monkeys, Katz et al. (2009) identified that those who had experienced the stress of intermittent separation from their natal group had larger prefrontal cortical volumes than those who had experienced no stress. As such, they suggested that this inoculation is exerted through the mediating effect of increased myelination of white matter in the prefrontal cortex (Katz et al., 2009; Lyons, Parker, Katz, & Schatzberg, 2009), which then promote enduring adaptations to behaviour (Lyons et al., 2009).

This research provides us with some ideas about the potential mechanisms underlying resilience. Ultimately, it reinforces resilience as a highly dynamic process which may vary according to time and circumstance. In addition, as suggested by Fergus and Zimmerman (2005), protective factors may vary in their usefulness in relation to particular risk circumstances, meaning the individual must decide how and when to utilise these resources. Further research in this area is required for us to truly understand how resilience works.

LIMITATIONS AND DIRECTIONS FOR FUTURE RESEARCH

There are a number of methodological limitations in the resilience field which limit ability to draw conclusions. Firstly, studies which have aimed to identify the protective factors involved in the resilience process have been largely cross-sectional. These studies have provided us with an insight into the potential protective factors involved in the resilience process; however, longitudinal follow-up and prospective reports are vital to understanding the full potential of the resilience concept.

Researchers have argued that the present resilience literature is highly heterogeneous (Mizuno, Wartelsteiner, & Frajo-Apor, 2016b) and thus resists comparison. For example, Bozikas et al. (2016) operationalised resilience as higher scores on a self-report scale of the construct. Frangou (2011), however, operationalised resilience as applying to individuals who had a genetic risk for BD who had not developed the disorder. Both approaches have merit, and use the definition of resilience outlined in this review; however, their outcome measures are very different which limits comparability. A clear statement regarding the type of resilience which is being examined (for example "self-report psychological resilience", or "observed resilience to genetic risk") should be made, allowing for more direct comparisons between studies using similar methodologies. This would make the resilience field more transparent, and thus informative for intervention strategies.

While definitions of resilience appear to have reached some stability, this is not to suggest that remaining debate around this concept would be obsolete. For example, as noted by Windle (2011), there is not yet a consensus on what would constitute a 'positive' outcome in resilience. Some authors would argue that the individual would need to 'flourish' after adversity, reaching levels of functioning which are superior to their premorbid state (Joseph & Linley, 2006). However, other researchers would argue that resilience is better reflected by generally stable functioning despite risk or adversity (Bonanno, 2004).

There are a number of ways in which the methodology of future research could improve the validity of the field. One suggestion would be to examine "observable" resilience. Studies already mentioned including those of Collishaw et al. (2016), Wingo et al. (2010), and Frangou (2011) examined their protective factors of interest by comparing individuals with, or without, good functioning in the context of risk. Additionally, the use of a control group by researchers such as Frangou (2011), allows for the identification of protective factors which are distinctive to individuals who are functioning well in the face of adversity, as opposed individuals who have low exposure to risk factors. In addition, birth cohort studies such as those of Koenen et al. (2009) and Harris et al. (2016) allow for the assessment of the same individuals at multiple time points longitudinally. Protective factors can then be prospectively identified by examining the baseline characteristics of the same individuals who ultimately exhibit good or poor functional outcomes in the long-term. Use of these methodologies would aid the field in its progression towards the identification of specific protective factors involved in resilience.

Transdiagnostic research is also important in the resilience field. Resilience research has tended to focus on identifying protective factors in relation to specific diagnoses. Future research should focus on factors which are present across, as well as within, diagnoses, to

identify variables which are protective against the development of psychopathology more generally. This would be useful for a number of reasons. Certain experiences may be a risk factor for multiple mental illnesses, such as experience of violence which may increase the likelihood of developing post-traumatic stress disorder, depression, or substance abuse/ dependence (Kilpatrick et al., 2003). The identification of cross-diagnostic protective factors would allow the promotion of these in instances where a non-specific risk has been experienced by an individual. Similarly, while fulfilling the operationalised Ultra-High Risk criteria predicts an increased risk of transition to psychosis (Yung, 2003), individuals in this group can also experience a number of other mental illnesses (Haroun et al., 2006; Lin, 2014). Identifying protective factors which function across diagnoses could be promoted in this group to reduce the chances of developing other psychopathologies. There is also increasing dissatisfaction with the current diagnostic system which categorises individuals with highly heterogeneous experiences into the same disorder (Kalisch et al., 2015). Therefore, further work identifying resilience which is not disorder-specific will help to identify how individuals are protected from particular outcomes, without reliance on the current system. Such "general" resilience mechanisms may also represent a more efficient intervention strategy (Kalisch et al., 2015). Additionally, this type of research could be used to form the basis of larger public health interventions to reduce the global burden of mental illness more generally.

Finally, the goal for future research should be to create a model of resilience which functions across modalities, and identifies how different protective factors interact to predict better outcomes in the context of risk. This would be done by building an extensive base of empirical studies which operationalise resilience in the same way; as a dynamic process by which individuals utilise protective factors to overcome risk for mental illness.

CONCLUSION

Research into the resilience process provides an exciting opportunity to highlight protective factors, which could be strengthened to provide better long-term outcomes for individuals at risk of mental illness. The definition of resilience is widely accepted as representing the presence of additional protective factors which counteract this risk, ultimately leading to more positive long-term outcomes; however, the idea that resilience is a poorly defined concept is still present in the field. Remaining debates do surround resilience; however, the core concepts are now largely agreed upon. Future research should focus on empirical studies which examine the long-term effects of multimodal protective factors, and the mechanisms which underlie them. This growing, more homogeneous, evidence base could then be used to trial new intervention strategies targeted at individuals who are identified as being at-risk for mental illness. In the long-term, resilience could also prove useful in large scale public health interventions which attempt to improve mental health outcomes more globally.

CHAPTER THREE

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NEUROCOGNITIVE DEFICITS IN PSYCHOSIS, ULTRA-HIGH RISK, AND MAJOR DEPRESSIVE DISORDER

INTRODUCTION

The goal for the present chapter is to provide an overview of the literature examining neurocognitive performance in the disorders of interest for this thesis: FEP, UHR, and MDD. The evidence regarding neurocognition in mental illness, which will be further explored below, suggests that deficits in these domains are a core symptom of mental illness (Fioravanti et al., 2012; Fusar-Poli et al., 2012; Lee, Hermens, Porter, & Redoblado-Hodge, 2012), and inhibit an individual's everyday functioning (Meier et al., 2014). Additionally, a significant proportion of the global economic burden of mental illness is related to the indirect effects of illness such as loss of work productivity or unemployment (Kessler et al., 2008; Wu et al., 2005). Neurocognition has direct links to work and educational outcomes in mental illness (Bowie et al., 2008; Lee et al., 2015; Lee et al., 2017), and therefore represents an important target for both individual and societal gain. There is evidence that neurocognitive deficits may be modifiable (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011) and that targeted interventions can also lead to subsequent improvements in other areas of everyday functioning (Lee et al., 2013c; McGurk et al., 2015). While deficits are established, there is tentative evidence to suggest that above average neurocognitive performance may exert a protective effect in mental illness. Above expected performance may reduce the chances of experiencing diagnosable mental illness (Koenen et al., 2009), improve the likelihood of positive functional outcomes (Niendam et al., 2007), and may be related to higher levels of psychological resilience (Genet & Siemer, 2011).

NEUROCOGNITIVE DEFICITS IN PSYCHOSIS

Deficits in neurocognitive performance are a common characteristic of psychotic disorders, with some studies suggesting that they are present in approximately 70-80% of individuals with schizophrenia (Keefe, 2008; Shmukler, Gurovich, Agius, & Zaytseva,

2015). Individuals with psychosis often evidence widespread impairments in all neurocognitive domains measured. A meta-analysis by Fioravanti et al. (2012) synthesised the findings of 240 studies of cognition in schizophrenia with comparison to healthy controls. These studies represented over 18,000 participants and demonstrated that the schizophrenia group was significantly impaired relative to controls in all cognitive domains, including memory, attention, executive function, language, and a composite cognitive score. Although this is one of the largest meta-analyses of cognitive performance in psychosis, this study only focuses on individuals with a schizophrenia diagnosis, and the authors note that their sample may include individuals in the acute, chronic, and remitted phase of the illness (Fioravanti et al., 2012). While this particular meta-analysis focuses on the cognitive performance of individuals with schizophrenia, significant deficits have also been identified in individuals with other psychotic diagnoses. For example, an older study by Addington, Brooks, and Addington (2003) studied the cognitive performance of 312 individuals with FEP when compared with healthy controls. The individuals with FEP were impaired on every task of a comprehensive battery, irrespective of psychotic diagnosis. Similarly, Carlsson, Nyman, Ganse, and Cullberg (2006) saw significant deficits in 120 individuals with FEP across a range of cognitive tasks relative to healthy controls. In their sample, impairments were significantly more pronounced in the schizophrenia-spectrum (schizophrenia, schizophreniform, and schizoaffective disorder) than non-schizophrenia spectrum (delusional disorder, brief psychotic disorder, affective psychosis, and psychotic disorder not otherwise specified) diagnoses (Carlsson et al., 2006). Performance of individuals with psychosis is, on average, between one and two SDs below that of healthy controls (Bilder et al., 2000), with one SD translating to 15 IQ points. Additionally, research has revealed significant impairments in the social cognition of psychosis patients. Savla,

Vella, Armstrong, Penn, and Twamley (2013) conducted a meta-analysis of studies involving 3908 participants with schizophrenia and 3570 healthy controls. In this meta-analysis, the schizophrenia group were significantly impaired on all social cognitive domains measured, comprising of Theory of Mind, Social Perception, Social Knowledge, Attributional Bias, Emotion Perception, and Emotion Processing. It must be noted that the studies included were heterogeneous and included samples with wide ranging ages and duration of illness, as well as having a lack of standardisation in the measurement scales used. However, the study provides convincing evidence that a range of social cognitive processes are impaired in psychotic illnesses, with medium to large effect sizes (Savla et al., 2013). The observed neurocognitive deficits in psychosis are shown to be more severe than in other mental illnesses such as major depression or bipolar disorder (Lee et al., 2015). Taken together, the findings of a wealth of research demonstrate that cognitive impairment is a core feature of psychotic illness. Though the research may be heterogeneous, it appears that these deficits are consistent irrespective of psychotic diagnosis (Carlsson et al., 2006; Zanelli et al., 2009), antipsychotic medication exposure (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014), or stage of illness (Addington et al., 2003; Sponheim et al., 2010; Zhang et al., 2015).

Following the onset of first-episode psychosis, research has largely indicated that cognitive performance remains stable over time (Addington, Saeedi, & Addington, 2005; Bozikas & Andreou, 2011; Sponheim et al., 2010). For example, work from the Early Treatment and Intervention in Psychosis Study (TIPS) examined cognitive performance in varying proportions of their total sample of 301 patients with psychosis, and observed relative stability at 2- (Rund et al., 2007), 5- (Barder et al., 2013b), and 10-year (Barder et al., 2013a; Barder et al., 2015) follow-up. However, the sample of these studies has a wide

age range of 18-65 and an average age of 28 at the baseline assessment. Therefore, these works are not necessarily documenting the trajectory of cognitive performance in the ten years following a *first* episode of psychosis. More recently, evidence is suggesting that different cognitive domains may follow differing trajectories in the years following illness onset. For example, a study by Wannan et al. (2018) recruited 95 individuals within weeks of transition to psychosis, and saw significant deterioration in visuospatial associative memory in the decade following FEP. A systematic review by Bozikas and Andreou (2011) examined studies of cognition in FEP with follow-up periods of at least one year. They identified that for most cognitive domains there were no significant changes after follow-up. However, verbal memory may be subject to further declines in the long-term. A recent study by Zanelli et al. (2019) tested the cognitive performance of 106 individuals with psychosis at the first presentation and after ten years. They observed stable deficits in processing speed and executive function, but progressive declines in IQ, verbal knowledge, and memory. However, in this study the researchers converted raw cognitive scores into z-scores which are standardised against the means and standard deviations of the healthy control group. Though this is a widely used procedure in cross-sectional studies of cognition, this standardisation in longitudinal studies may mask the true trajectory of performance over time. For example, it may be that the individuals with psychosis are failing to make the same developmentally appropriate gains as the healthy controls, as opposed to an absolute decline in performance (Panayiotou et al., 2020). In summary, it is likely that cognitive deficits are established by the first episode of illness and largely remain stable in the years following. However, particular cognitive domains may follow different trajectories, either deteriorating further or failing to improve to the extent that might be seen in the healthy population.

Neurocognitive deficits might also be one of the earliest appearing signs of abnormal development in psychotic illness. Cohort studies, in which large population samples are followed up longitudinally, are a robust method for examining this hypothesis. For example, the Dunedin Birth Cohort Study followed a cohort of 1037 children born in Dunedin, New Zealand, during a one-year period from 1972-3. The sample were followed up at several time points until adulthood, with current studies reporting adult follow-up data for 96% of the living participants. In this sample, poorer childhood performance on measures of IQ, receptive language, executive function, attention, and motor skills significantly predicted a diagnosis of schizophreniform disorder in adulthood (Cannon et al., 2002; Cannon et al., 2006). This effect was not seen for adult depression/anxiety or mania diagnoses, suggesting that these neurocognitive indicators might be specific to schizophrenia-spectrum disorders. In a review of birth cohort studies, (Welham, Isohanni, Jones, & McGrath, 2009) deficits in intellectual function were identified as a key theme, appearing in all studies which measured this domain. Children who later develop adult psychosis showed consistent deficits in intellectual functioning compared to peers who do not develop adult psychopathology. These deficits may have already emerged by seven years of age (Seidman, Buka, Goldstein, & Tsuang, 2006a). Similarly, Zammit et al. (2004) replicated this result in their cohort study of adult Swedish conscripts. They identified that lower premorbid IQ was associated with the development of schizophrenia, schizoaffective disorder, other non-affective psychoses, and severe depression over a 27-year follow-up period. Interestingly, average premorbid IQ conferred a higher risk than high IQ, indicating that this effect was spread across the whole range of IQ scores (Zammit et al., 2004). It must be noted that this study only included male subjects, and relied on hospital admissions as their outcome measure, therefore possibly missing episodes of mental illness which did not require admission. However, this is a large

cohort of over 50,000 Swedish males which provides valuable insight into the relationship between premorbid cognitive functioning and later mental health outcomes.

Neurocognitive deficits are central to the experience of psychotic disorders, and such impairments may be present long before the onset of diagnosable clinical symptoms. This early onset of cognitive impairments highlights the significant potential for early intervention. Although neurocognitive performance alone may not specifically predict whether an individual will develop psychosis, the research summarised suggests that neurocognitive interventions during childhood may have the potential to improve long-term outcomes.

NEUROCOGNITIVE DEFICITS IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS

The neurocognitive deficits observed in psychosis are also present in individuals at UHR for psychosis. "At-risk" individuals appear to demonstrate a similar pattern of performance to that of psychosis, however impairments are less pronounced at this stage (de Paula et al., 2015). Lencz et al. (2006) identified that a small sample of individuals at UHR (N=38) performed significantly poorer than HCs (N=39) in both estimated premorbid and current IQ. However, the mean IQ of the UHR sample was in the typical range for both estimates. The authors identified a generalised deficit across the neuropsychological domains, which averaged 1.24 SDs relative to control subjects. Beyond this generalised deficit, performance in verbal memory and executive function/working memory domains was significantly more impaired than other neurocognitive domains in UHR subjects (Lencz et al., 2006). Results from the North American Prodrome Longitudinal Study (NAPLS) also suggest significant impairments in the UHR population. In their study, Seidman et al. (2010) observed significantly poorer performance of 304 individuals at UHR than HCs in tests of

processing speed, verbal fluency, verbal memory, sustained attention, and a composite score of cognition. Kelleher et al. (2013b) also investigated this concept in a non-help seeking sample of 212 adolescents from the general population in Ireland. 8% (N=19) of their population sample met UHR criteria, and these individuals demonstrated significantly poorer performance than the rest of the sample on tests of processing speed and working memory. This demonstrates that such neurocognitive deficits are also evident in individuals who may not yet have engaged with clinical services (Kelleher et al., 2013b). There is also a suggestion that neurocognitive deficits may vary with the severity of UHR status. Frommann et al. (2010) grouped 205 individuals into Early Stage UHR (BS: subtle, self-reported changes in thought and sensory experience) and Late Stage UHR (the presence of attenuated psychotic symptoms). Those in the late stage of UHR were impaired in all neurocognitive domains measured, with the most pronounced impairment in memory. Those in early stage UHR, however, demonstrated less pronounced deficits, with particular severity in executive control/ processing speed (Frommann et al., 2010). However, there is not yet the evidence to suggest that these two groups represent meaningful, consecutive stages of the illness trajectory.

Some studies also report significant deficits in social cognition during the UHR stage. For example, participants from the NAPLS consortium fulfilling UHR criteria performed significantly poorer than HCs on all tests of social cognition, at all time-points of the longitudinal study (Piskulic et al., 2016). In addition, Davidson et al. (2018) tested the social cognition of 675 individuals at UHR and compared to that of HCs. In this study, there were no significant differences in the age-related trajectory of development for emotion perception, but the authors did identify a different trajectory for the development of theory of mind for individuals at UHR. This difference between UHR and HCs, driven by the

perception of sarcasm, reached statistical significance at age 17.4 and continued to grow until age 34 (Davidson et al., 2018). However, other recent studies have found no evidence of significant differences in social cognition between individuals at UHR and HCs. Glenthøj et al. (2018) saw no significant differences between their UHR and HC samples, however their main outcome measure was the *latency* of responses to a facial emotion processing task. Zheng et al. (2018) conducted a meta-analysis of studies testing performance of individuals at UHR on the MATRICS Consensus Cognitive Battery (MCCB). In this analysis comprising 396 individuals at UHR, they saw no significant social cognitive impairments relative to HCs. However, the MCCB measure of social cognition is a task which measures the individual's own ability to manage emotions, very different to some of the other social cognitive tasks mentioned previously. As such, it is possible that individuals at UHR for psychosis may demonstrate significant deficits in social cognition. However, at present this is not an established characteristic of this group and research in this area varies greatly in the type of social cognitive processes being measured.

In comprehensive reviews and meta-analyses of neurocognitive functioning during the prodromal phase, overall findings appear to suggest significant impairments relative to HCs during the UHR period in all domains measured, with large effect sizes for the domains of processing speed, attention, verbal and visual memory (Fusar-Poli et al., 2012; Pukrop & Klosterkötter, 2010; Zheng et al., 2018).

Neurocognitive impairments also appear to be more pronounced in individuals at UHR who make a transition to psychosis (UHR-T) when compared with those who do not transition (UHR-NT; Bora et al., 2014; Brewer et al., 2005; Carrión et al., 2015; Eastvold, Heaton, & Cadenhead, 2007; Fusar-Poli et al., 2012; Seidman et al., 2016). However, evidence on which specific neurocognitive domains which may be more predictive of

transition is mixed (Addington & Barbato, 2012). In one of the largest meta-analyses of cognitive functioning in UHR to date, Fusar-Poli et al. (2012) synthesised the findings of 19 studies including 1188 participants. They identified poorer performance in verbal fluency, verbal and visual memory, and working memory in UHR-T compared to UHR-NT. Keefe et al. (2006) also found that composite cognitive scores were significantly lower in the subset of individuals who transitioned to psychosis, and that impairment on the Continuous Performance Test, combined with better WAIS-R digit symbol performance predicted progression to psychosis. However, these results are based on the very small number (N=11) of their sample who transitioned to psychosis within one-year of the baseline assessment. De Herdt et al. (2013) conducted a meta-analysis of nine studies investigating neurocognition in relation to transition (n=583). They identified the performance of individuals who transition was significantly poorer than individuals who do not transition in the domains of working memory and visual learning (De Herdt et al., 2013). Lin et al. (2013a) found that risk of transition was significantly associated with poorer performance on visual reproduction and matrix reasoning. In this sample, however, neurocognitive variables were not strong predictors of transition to psychosis (Lin et al., 2013a). Additionally, a recent study by Mourik et al. (2017) identified significantly poorer performance of UHR individuals compared to controls in all measured domains. However, in this sample there were no significant differences between those who did or did not transition to psychosis. Again, these findings are based on a small number (N=14) of individuals who transitioned within their two-year follow-up period. Overall, these results suggest that neurocognitive impairments may be more severe in individuals at UHR who ultimately go on to transition to psychosis than those who do not. However, the literature regarding which domains may specifically predict transition varies greatly.

Similar deficits are observed when considering individuals who may be at Familial High Risk (FHR). Such individuals have a first-degree relative with a history of psychosis, and thus an increased genetic risk for psychosis (Sullivan, Kendler, & Neale, 2003), but have not necessarily developed symptoms themselves. Bora et al. (2014) conducted a meta-analysis which included 929 individuals at FHR, 1184 individuals at UHR, and 1140 HCs. They identified modest, but significant, deficits in the neurocognitive performance of both UHR and FHR individuals across every cognitive domain and individual test measured. The most severe impairment observed in those who had both attenuated psychotic symptoms and a genetic risk for psychosis (Bora et al., 2014). Seidman et al. (2006b) observed significant impairments in executive function/working memory and verbal ability in their sample of individual at FHR for schizophrenia-spectrum disorders with medium and large effect sizes, respectively. Only scores on the coding task were significantly impaired in their subsample of individual at FHR for affective psychoses, however this represented a small number of participants (N=18), and requires further investigation. The impairments seen in individuals at FHR may also be evident in childhood. After accounting for potential confounders such as socio-economic status, psychopathology, and IQ, de la Serna et al. (2017) saw specific deficits in visual memory, verbal learning, and working memory in their sample of children aged 6-17 at FHR. Finally, Eack et al. (2009) examined the social cognition of individuals at FHR. While they did not see a significant difference in the overall accuracy of the FHR group on a facial emotion recognition task, this group was significantly more likely to misattribute neutral faces as negative, and took longer to complete the task. The literature discussed here illustrates that even a genetic risk for psychosis alone, without accompanying symptom expression, is detrimental to an individual's neurocognitive performance.

In summary, these results suggest a significant global impairment in the neurocognitive performance of UHR individuals, but must be interpreted within the context of overall mixed findings in the literature. Neurocognitive impairment appears to be common in the "at-risk mental state", but at this stage cannot be thought of as a reliable predictor of transition. Research in the area is hindered by relatively low transition rates and the heterogeneity of the UHR concept. Further longitudinal studies examining the predictors of transition will help to clarify the role of neurocognition.

DOES NEUROCOGNITIVE PERFORMANCE DECLINE FROM THE UHR TO FEP PERIOD?

Generally, research indicates that individuals at UHR for psychosis demonstrate neurocognitive performance which is at an intermediate level; poorer than HCs, but not as impaired as those experiencing FEP (Sawada et al., 2017; Simon et al., 2007). This led researchers to question whether there is a decline in neurocognitive performance prior to, or following the onset, of psychotic disorder. Research which compares the effect sizes of impairments in individuals at UHR or FEP assumes that these samples represent the same populations at a different stage of illness. However, this is unlikely to be the case due to the heterogeneity of the UHR concept (discussed in Chapter One). An interesting study by Carrión et al. (2018) compared the neurocognitive performance of HCs, help-seeking controls, individuals at UHR, and individuals with FEP. The authors observed significant group differences in processing speed, verbal learning, and a composite neurocognitive score. In subsequent analysis, the authors examined retrospective baseline neurocognitive performance of individuals who later transitioned to psychosis. This subset of the UHR sample already evidenced large impairments at baseline, which were comparable to the FEP sample, in processing speed, working memory, attention, and verbal learning.

Neurocognitive performance of the individuals who did not transition, however, resembled that of the help-seeking controls (Carrión et al., 2018). These findings support those of an earlier study by Lee et al. (2014), in which individuals who remitted from the UHR state at follow-up demonstrated comparable neurocognitive performance to HCs at baseline, and the individuals who did transition performed significantly poorer than both groups (Lee et al., 2014).

Birth cohort studies can also be used to overcome the methodological limitation of comparing two, possibly distinct, samples. In such studies, a general population sample is assessed at several time points longitudinally. Cognitive development can be tracked over time, and the presence of risk or protective factors can be established by retrospectively analysing differences between individuals who ultimately developed mental illness and those who did not. Several large birth cohort studies have provided evidence of varying cognitive trajectories in individuals who later develop psychosis.

For example, some cognitive domains such as verbal and visual skills, deficits emerge many years before the onset of psychotic illness, and remain stable over time. In the Dunedin Birth Cohort, such deficits were already observable by age seven in the future psychosis sample (Meier et al., 2014; Reichenberg et al., 2010). Mollon, David, Zammit, Lewis, and Reichenberg (2018) conducted analysis on individuals recruited into the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study and attempted to map cognitive performance from age 18 months to 20 years. They compared the performance of individuals with differing mental health diagnoses at age 20 (psychotic disorder, psychosis with depression, psychotic experiences, depression, and controls) and saw that individuals with adult psychotic disorder demonstrated deficits in verbal IQ which were already present at eight years of age and remained stable until age 20. While this study is a valuable insight

into the trajectory of cognitive performance from childhood to adulthood, the findings are based on small numbers (e.g. 19 individuals with adult psychotic disorder diagnoses from a total sample of 4724 individuals). Further, there may be some diagnostic overlap between their groups, in that some individuals with previous psychotic experiences were assigned to the depression group.

Alternatively, 'developmental lags' may be observed in other domains, in which future psychosis subjects do improve throughout childhood, but do not make the same developmental gains as those made by healthy controls. In their examination of individuals from the Dunedin Birth Cohort, Meier et al. (2014), identified that children (age 7-13) who would later develop adult schizophrenia evidenced a significant decline in IQ from childhood to adulthood. In childhood, the schizophrenia group showed a 9-point deficit compared to controls, however, by the time they reached adulthood this deficit had increased to 15-points. Thus, although the scores of the schizophrenia group were improving from childhood to adulthood, they were not improving at the same rate as the controls. This developmental lag was not affected by use of antipsychotic medications, and was not observed in individuals who developed adult depression (Meier et al., 2014). Similarly, developmental lags in both full-scale and nonverbal IQ were observed by Mollon et al. (2018) in their cohort of individuals who developed adult psychotic disorder. In this sample, full-scale and nonverbal IQ declines were specific to the group who developed psychosis (Mollon et al., 2018). Again, the authors identify that the raw scores of all participants were increasing throughout the study period, and thus IQ development was "lagging" in the group who would eventually develop psychosis. Such developmental lags also appear to be prevalent in domains of processing speed, working memory, and attention (Mollon et al., 2018; Reichenberg et al., 2010). In the ALSPAC cohort, a developmental lag of eight years

was observed in the processing speed domain. Performance in this domain by psychotic individuals aged 20 was comparable to that of healthy controls aged 12 (Mollon et al., 2018).

A recent study by Allott et al. (2018) measured the cognitive performance of the same 268 individuals ten years after being identified as at UHR for psychosis. The results from this study demonstrated significant improvements in all tasks, other than verbal learning which significantly declined, over the ten-year period. Transition to psychosis was not associated with change in cognitive performance, however individuals who transitioned within one-year of the baseline assessment did show significant decline in the digit-symbol coding task. Although change in cognitive performance was not related to transition, the subset of this UHR sample who did ultimately transition to psychosis were clearly demonstrating lower cognitive performance at baseline compared to those who did not transition (Allott et al., 2018).

Longitudinal studies which test the same individuals pre- and post-onset of psychotic illness suggest that during childhood, some neurocognitive deficits may emerge early and remain stable, while others show a 'developmental lag', failing to make the expected improvements with age. As such, cognitive deficits may represent one of the earliest appearing signs of abnormal development related to psychosis. By the time that "true prodromal" individuals reach the UHR stage, they are likely already exhibiting the neurocognitive deficits that we observe in FEP (e.g. Allott et al., 2018; Carrión et al., 2018). If not, the onset of frank psychotic illness may bring a slight deterioration in cognitive performance after years of impairment, followed by a relative stability, or further decline in specific domains, thereafter. This may mirror the structural and functional brain alterations which occur predominantly around the onset of illness (Shmukler et al., 2015).

NEUROCOGNITIVE DEFICITS IN MAJOR DEPRESSIVE DISORDER

While neurocognitive deficits appear to be most pronounced in psychotic disorders, they are also a core, and debilitating, feature of mood disorders such as MDD. Lee et al. (2012) conducted a meta-analysis examining 15 studies (N=644) of neurocognition in First Episode Depression (FED). They identified that patients with a FED performed significantly worse than HCs (with small to moderate effect size) in a range of cognitive domains including psychomotor speed, attention, visual learning and memory, attentional switching, verbal fluency, and cognitive flexibility. Subsequent analysis identified that performance in these domains was significantly, negatively, impacted by other demographic and clinical variables such as older age, less education, current depressive symptoms, and inpatient status (Lee et al., 2012). Rock, Roiser, Riedel, and Blackwell (2014) also conducted a meta-analysis of 24 studies of neurocognition in both current and remitted MDD. In this study, individuals with depression evidenced significant deficits of moderate effect size in executive function, memory, and attention, relative to HCs. However, this was not a sample of individuals with FED and may have included individuals with multiple episodes of MDD. Another comprehensive review of the area by Ahern and Semkovska (2017) identified a range of cognitive impairments in 994 individuals with FED, the largest of which were in Stroop colour naming and word reading speed, visuospatial WM errors, and shifting correct responses. The most recent meta-analysis in this area also identified significantly poorer neurocognitive performance of young, depressed, people. After excluding low quality studies which were at risk of bias, the authors saw significant impairment on tasks of attention, verbal reasoning/ knowledge, verbal memory, visual memory, and IQ, when compared to controls (Goodall et al., 2018). Hermens et al. (2011) instead sought to identify specific *profiles* of neurocognitive performance in MDD. In their sample, three distinct

profiles emerged which were characterised as follows: Impairments in memory but preserved attention; reduced performance in all cognitive domains with marked impairments in both mental flexibility and memory; and finally, impairment in mental flexibility, with intact memory and verbal measures. These findings suggest that even within the diagnosis of MDD there may be considerable variation in the pattern of neuropsychological impairments.

There are also several theories as to the underlying mechanisms of neurocognitive deficits in MDD; deficits may result from a state, trait, or scarring effect. If neurocognitive deficits were a state phenomenon, they should follow the course of mood symptoms, present during episodes of illness and reduced during periods of remission. The trait theory would suggest that instead, deficits are independent of mood state, and would thus be present during remission. Finally, the scarring hypothesis would suggest that the presence of mood symptoms add to the severity of the deficit, and thus, neurocognitive performance would worsen with multiple episodes of illness. Attentional and executive function deficits appear to be a trait marker of neuropsychological performance in MDD, persisting even during periods of remission from mood symptoms (Lee et al., 2012; Paelecke-Habermann, Pohl, & Leplow, 2005; Rock et al., 2014). Alternatively, deficits in psychomotor speed and visual learning and memory may represent a state marker of illness. In the sample from Lee et al. (2012) inpatient status significantly accounted for performance in these domains, suggesting that these deficits may relate to mood symptoms as inpatients tend to have more severe symptomatic presentations. In their sample of depressed patients, however, Paelecke-Habermann et al. (2005) also observed greater deficits in individuals who had experienced three or more depressive episodes than in those who had one or two episodes. This

observation also hints at a 'scarring' effect of mood symptoms on attention and executive functions.

HOW MIGHT NEUROCOGNITION RELATE TO RESILIENCE?

The evidence reviewed thus far indicates that neurocognitive deficits are pervasive in mental illness, and are considered to be core symptoms of psychotic and mood disorders. However, it is possible that neurocognition may also exert a protective effect, or support other protective factors in the resilience process. As reviewed in Chapter Two, higher childhood IQ may reduce the risk of adult psychopathology (Koenen et al., 2009), and domains such as nonverbal memory (Wingo et al., 2010), and cognitive flexibility (Genet & Siemer, 2011) may be associated with higher trait resilience. Furthermore, several other studies have identified a possible role of cognitive processes in resilience. For example, Southwick and Charney (2012) highlight the importance of cognitive reappraisal, which they define as "the ability to cognitively reframe adverse and negative events in a positive light" in the resilience process. Boyes, Hasking, and Martin (2016) conducted a study of 2637 Australian high school students and observed that cognitive reappraisal was associated with significantly less psychological distress, and mediated the relationship between childhood adversity and psychological distress in adolescence (Boyes et al., 2016). However, this is of course a general population study and the sample may not be demonstrating clinically significant levels of distress. These findings may be relevant for experiences at the less intense end of the mental health continuum, and further investigation may be required to understand the role of cognitive appraisal in individuals with clinically significant mental illnesses. Hoorelbeke, Marchetti, De Schryver, and Koster (2016) conducted a network analysis of risk and resilience factors in individuals who had remitted from depression. Resilience, as measured by a self-report scale, emerged as a core component of the network,

and was associated with significantly fewer perceived working memory complaints. However, a behavioural task of cognitive control did not significantly contribute to the network (Hoorelbeke et al., 2016). Together, these findings suggest a possible role of neurocognitive performance in the resilience process. However, examinations of this possible protective factor are in their infancy, and further work is required to reliably identify such a role.

Neurocognition may also predict long-term functional outcomes, which are inherently related to resilience (see definitions in Table 2.1). As mentioned in Chapter Two, definitions of resilience refer to the achievement of more positive outcomes than might be expected in the context of risk. Clinical outcomes such as a reduction or remission of symptoms are undoubtedly important, and are often the primary target of current intervention strategies. However, functional outcomes, such as an individual's ability to maintain their social life and engage in work or study, will also be important determinants of long-term quality of life (Lee et al., 2013b). Furthermore, functional outcomes are often independent of clinical symptoms. For example, in a sample of individuals at UHR, up to 45% of individuals who did not develop psychosis were still displaying poor functioning at follow-up (Carrión et al., 2013). This demonstrates that, in addition to interventions which target clinical symptoms, functioning should also be a target for treatment. It is important that resilience research considers factors which may be protective against adverse clinical *and* functional outcomes.

Neurocognitive performance is a strong predictor of long-term functional outcomes following an episode of psychosis. In a sample of 120 patients with FEP, poorer baseline IQ scores significantly predicted lower functioning scores at 3-year follow-up (Carlsson et al., 2006). Lee et al. (2017) examined employment and educational outcomes in a

transdiagnostic sample of 163 psychiatric outpatients, including individuals with psychosis. In this sample, baseline neurocognitive performance was the only factor which significantly predicted whether an individual was engaged in education, employment, or training at 24-month follow-up. The evidence as to which specific domains of neurocognition might predict long-term functioning after an episode of psychosis is mixed. However, implicated domains have included verbal learning and memory (Allott, Liu, Proffitt, & Killackey, 2011; Green, 1996; Lee et al., 2013b), working memory (Lee et al., 2013b; Torgalsboen, Mohn, & Rishovd Rund, 2014), and attention (Nuechterlein et al., 2011; Torgalsboen, Mohn, Czajkowski, & Rund, 2015; Torgalsboen et al., 2014). Allott et al. (2011) systematically reviewed 22 studies of neurocognition and functional outcomes. After ranking the studies based on methodological sophistication (e.g. controlling for other predictors, having adequate power, and low attrition rates), they identified that reasoning and problem solving were the most consistent predictors of functional outcome in psychosis. Other domains which ranked highly in their prediction of functional outcomes were global cognition, verbal and language skills, and verbal learning and memory (Allott et al., 2011). The authors do emphasise, however, the heterogeneity of the research in this area. Studies varied in their measures of cognitive performance, and the number of tests used, as well as varying greatly in sample size and statistical approach. Therefore, the findings of these studies must be interpreted with caution until more homogeneity is achieved in the field. Nuechterlein et al. (2011) used principal component analysis to identify three factors which predicted a return to work or education in 47 schizophrenia patients. In their sample, working memory, attention and early perceptual processing, and verbal memory and processing speed significantly predicted long-term functioning, explaining 52% of the variance in return to work or education after nine months.

There is also evidence which suggests that performance in specific neurocognitive domains predicts specific functional outcomes. Fujii, Wylie, and Nathan (2004) conducted a 15-year follow-up of their sample of 30 patients with severe and persistent mental illness (N=24 psychotic diagnoses, N=6 BD) and identified that baseline memory performance predicted income, satisfaction with daily activities, and general health at follow-up. Additionally, baseline motor skills predicted subsequent satisfaction with family contact, and baseline working memory predicted victimization and satisfaction with social contacts (Fujii et al., 2004). These findings indicate that neurocognitive performance is predictive of long-term functional outcomes. However, even at baseline the sample was not necessarily a first-episode sample, meaning that cognitive and functional deficits may have been well-established already. Further, the sample also included a small subset of individuals with BD and so the findings are not limited to psychosis-spectrum disorders. Bowie et al. (2008) also identified relationships between neurocognitive performance and specific aspects of real-world functioning in their sample of 222 older outpatients with schizophrenia. They observed that attention/ working memory had a direct link with current work skills, executive functions predicted interpersonal behaviours, and processing speed predicted the aforementioned factors in addition to community functioning. These results suggest that neurocognitive performance may be used as a predictor, or possibly a target to improve, specific aspects of functional performance.

Functional outcomes are also an important consideration for UHR individuals, as social and role functioning is often impaired during this period (Carrión et al., 2011; Cornblatt et al., 2007). Similar to results observed in psychosis samples, neurocognition may also have value for the prediction of functioning in UHR. Several large studies of UHR populations suggest that baseline cognitive performance is able to predict levels of

functioning both cross-sectionally (Carrión et al., 2011; Cotter et al., 2014) and longitudinally (Carrión et al., 2013; Cotter et al., 2014; Lin et al., 2011). Alternatively, in their study, Niendam et al. (2007) suggest that it is in fact the *course* of cognitive performance which provides information about long term functional outcomes. Approximately 50% of their UHR sample (N=35) showed functional improvements at an eight-month follow-up. This group was characterised by concurrent improvements in processing speed and visual memory (Niendam et al., 2007). These findings would suggest a possible protective effect of these neurocognitive domains but require replication with larger sample sizes and a longer follow-up period. There is not yet a consensus as to which specific neurocognitive domains best predict functional outcomes in UHR. However, several domains including verbal learning and memory (Cotter et al., 2014; Lin et al., 2011), processing speed (Carrión et al., 2011; Carrión et al., 2013; Meyer et al., 2014), and verbal fluency (Lin et al., 2011; Shin et al., 2016) are highlighted in the literature. As in psychotic populations, these neurocognitive domains appear to predict functional outcomes in UHR irrespective of clinical symptoms (Cotter et al., 2014; Lin et al., 2011).

Though less widely studied, neurocognitive performance also appears to be associated with functional outcomes in individuals experiencing MDD. A systematic review by McIntyre et al. (2013) identified significant neurocognitive deficits in MDD with small to medium effect sizes, and that these deficits are significantly associated with functioning, particularly performance at work. These findings were also replicated by a later systematic review of 10 studies examining the relationship between cognition and functioning in MDD. However, the authors of this review again note that the literature in this area is highly heterogeneous in the measurement of both cognition and functioning, often has small sample sizes, and employs a range of study designs. Therefore, findings here are promising but must

be interpreted with caution (Evans, Iverson, Yatham, & Lam, 2014). Jaeger, Berns, Uzelac, and Davis-Conway (2006) tested the same sample of 48 individuals with MDD at baseline and at six-month follow-up. They observed that follow-up neurocognitive performance was significantly associated with follow-up functional outcomes. Furthermore, baseline visuo-spatial skills, visual and verbal learning, and motor skills significantly predicted six-month functional outcomes in this sample (Jaeger et al., 2006). More recently, Knight, Air, and Baune (2018) also observed that executive function also significantly predicted cross-sectional psychosocial functioning in a sample of 182 individuals who had remitted from MDD. Taken together, these findings suggest that neurocognition, though significantly impaired in mental illness, may also exert a protective effect if performance is preserved or above average. Better cognitive performance is associated with higher scores on resilience scales, and may predict of improved functional outcomes which are inherent in the resilience process.

The hypothesis that neurocognitive performance could be one of the protective factors involved in the resilience process may prove particularly useful for potential therapeutic intervention if neurocognition can be modified. Theoretically, if an individual can be taught to better utilise cognitive skills, this may aid them in the resilience processes mentioned in Chapter Two such as developing and utilising social connections, flexibility and development of new strategies to overcome risk or adversity. This would hopefully lead to the individual experiencing more positive long-term outcomes. There is already a large body of work which has investigated whether cognitive performance can be modified, using a technique known as Cognitive Remediation Therapy (CRT). CRT can be broadly defined as any intervention technique which uses training strategies to improve neurocognitive performance, with the ultimate goal that these improvements would generalise to other areas

of daily life and functioning (Wykes et al., 2011). At present, this intervention has largely been trialled in individuals with psychosis. CRT has been effectively delivered using computerised programmes (d'Amato et al., 2011; Dang et al., 2014; Dickinson et al., 2009) and with therapist guidance (Kambeitz-Ilankovic et al., 2019), in both individual and small group settings (Cella, Reeder, & Wykes, 2016; Tan et al., 2016), and may involve techniques such as "drill and practice" or may involve the translation of training to everyday circumstances (Medalia & Choi, 2009). Evidence has also suggested that CRT can be incorporated into standard clinical care for psychosis (Dark, Harris, Gore-Jones, Newman, & Whiteford, 2018; Østergaard Christensen et al., 2014). Furthermore, several studies have reported on the cost-effectiveness of the intervention (Patel et al., 2010; Reeder et al., 2014). Two RCTs identified that this cost-effectiveness was achieved through significant reductions in the requirement for acute psychiatric care for individuals with psychosis who complete CRT when compared to an active control condition (Garrido et al., 2017) and treatment as usual (Vita et al., 2016), respectively. Another RCT by Wykes et al. (2003) also identified changes in the usage, and subsequent costs, of services following CRT. In a relatively small trial comparing CRT to occupational therapy, the authors found that the overall treatment costs were reduced for both groups. However, the CRT group showed a significant increase in the costs related to day-care, possibly reflecting an increased capacity to engage in outpatient services and, hopefully, subsequent benefits for the individual's functioning (Wykes et al., 2003). Overall, these studies demonstrate that CRT is a feasible, and cost-effective treatment which can be employed with individuals with psychosis.

The results from trials which have investigated the efficacy of CRT are varied. Some studies have found no significant benefit for the training. For example, a RCT by Dickinson et al. (2009) found that while those who received CRT performed significantly better than

those in an active control group on the tests that they were trained on, these improvements did not generalise to other neuropsychological tests, or to measures of functioning (Dickinson, Bellack, & Gold, 2006). The distinction between improvement on training tasks versus transfer to other neuropsychological measures is crucial for research in this area. If improvement is only seen on the tasks that participants were trained in, as in this particular study, this would suggest a low utility for CRT making meaningful changes for individuals experiencing cognitive deficit. However, further evidence presented shortly does suggest transfer of improvements to other, untrained, cognitive tasks. Ueland and Rund (2004) saw no significant differences in the cognitive improvement of their participants who were randomised to CRT or a psychoeducation programme. However, this study included just 26 young people with psychosis, and therefore may have been underpowered to detect meaningful differences between the groups. Another RCT investigated cognitive performance following CRT compared with both an active control condition and Treatment as Usual (TAU). In this study, the CRT group improved on the training tasks, but did not improve on other cognitive tasks or in their post-treatment functioning (Gomar et al., 2015). This was a large, multi-site trial involving 130 participants with chronic schizophrenia. It is possible that the chronicity of this sample, who had an average length of illness of 23.6-24.3 years, may explain these results. If the cognitive deficits associated with schizophrenia have been left untreated for a longer period, they may be more ingrained and thus harder to ameliorate. This interpretation is supported by a study by Kontis, Huddy, Reeder, Landau, and Wykes (2013) which saw significant improvements on untrained tasks measuring working memory, cognitive flexibility, and planning following CRT in their participants who were younger than 40 (mean age 30.27 years), but not in those who were older than 40 (mean age 47.75 years). This would again suggest that cognitive deficits, while still a valid

target for treatment in chronic samples, may be *more* amenable to change earlier in the course of illness. A larger RCT of 131 individuals with schizophrenia-spectrum disorders by Lystad et al. (2017) found no significant benefit of CRT over CBT when both were combined with vocational rehabilitation. However, both groups significantly improved on the outcome measures of occupational status and number of hours spent in work (Lystad et al., 2016). Although some studies do not find evidence to support a significant benefit of CRT specifically, these studies often have relatively small sample sizes (e.g. Dickinson et al., 2009; Ueland & Rund, 2004) and often find that both experimental groups make subsequent improvements in their cognitive performance, thus underscoring the notion that cognition can be improved, and could therefore serve as a target for resilience interventions.

The small amount of evidence suggesting no significant benefit of CRT is far outweighed by that demonstrating the efficacy of the intervention. RCTs which examine the efficacy of CRT compared with wait-list control conditions or TAU have reported significantly more improvement in cognitive performance following CRT (d'Amato et al., 2011; Hodge et al., 2010; O'Reilly et al., 2019; Østergaard Christensen et al., 2014; Puig et al., 2014; Sartory, Zorn, Groetzinger, & Windgassen, 2005; Twamley, Vella, Burton, Heaton, & Jeste, 2012; Wykes et al., 2007). Of course, it is possible that this study design may lead to biased results, as there might be other indirect effects of CRT, such as time socialising, engaging in an activity, or therapist involvement, which may impact on the outcomes of these studies. Other studies however, have used an active control condition, such as computer games or other types of training, and have also reported significant cognitive improvement which is specific to the CRT groups (Ahmed et al., 2015; Bell, Bryson, & Wexler, 2003; Bell, Choi, Dyer, & Wexler, 2014; Bowie, McGurk, Mausbach,

Patterson, & Harvey, 2012; Donohoe et al., 2018; Garrido et al., 2013; Holzer et al., 2014; Trapp et al., 2013; Ueland & Rund, 2005).

The largest investigations of the effects of CRT are the meta-analyses that have been carried out thus far. Wykes et al. (2011) analysed the data from 40 studies which included 2104 individuals with psychosis. All studies included in this meta-analysis had to adhere to a standardised definition of CRT, have a control group (which may have been active or passive), and an allocation procedure. Crucially, as mentioned previously, the cognitive and functional outcome measures used by included studies had to be distinct from the tests upon which participants were trained. The analysis found that CRT significantly improved global cognition and functional outcomes with small to moderate effect sizes. This benefit was seen at post-treatment and remained at follow-up. CRT was also associated with a significant reduction in clinical symptoms post-treatment; however, this effect was no longer present at follow-up. In subsequent analysis, the authors were able to determine that the observed benefit of CRT was present regardless of delivery method (e.g. individual, group, computerised etc.), trial quality, clinical symptoms, or duration of treatment (which ranged from 3-130 hours in the included studies). Finally, the effect of CRT on functional outcomes was increased when the treatment was combined with other forms of rehabilitation (Wykes et al., 2011). The results of this meta-analysis suggest a small to moderate benefit of CRT on improving cognitive performance and functioning, and have been supported by subsequent meta-analyses (Kambeitz-Ilankovic et al., 2019; Revell, Neill, Harte, Khan, & Drake, 2015).

It appears likely therefore, that cognition is modifiable, and that deficits can be improved in individuals with psychosis. This effect has been found in samples of varying ages, ethnicities, chronicity. Though the effects are moderate at best, they appear consistent

and durable. Targeting cognition may also lead to a number of subsequent benefits for an individual's functioning, such as improving real-world skills (Bowie, Grossman, Gupta, Oyewumi, & Harvey, 2014), and increasing the amount of time spent in work (Lindenmayer et al., 2008), especially when combined with other forms of rehabilitation (Wykes et al., 2011). While there are several remaining questions about CRT (discussed further in Chapter Nine) the current body of evidence suggests strongly that cognitive performance is modifiable. It could therefore be targeted for direct improvement, and for additional benefits in everyday functioning. It is possible that the improvement of cognitive performance in vulnerable individuals would facilitate the use of protective, or resilience, strategies in the face of risk or adversity, ultimately leading to improved long-term outcomes.

CONCLUSION

In summary, the literature suggests that cognitive deficits are pervasive in mental illness, with significant implications for long-term clinical and functional outcomes. Current evidence suggests that deficits are most pronounced in FEP, with milder patterns of deficit in UHR. Neurocognitive deficits also extend beyond the psychosis-spectrum, and appear in individuals with MDD. There are, however, a number of crucial areas for improvement in the cognitive literature. For example, cognitive research often uses a wide-ranging methodology for the measurement of cognitive performance. Some research only reports composite scores which are the average of several tests, while others report individual test or domain scores. While specific, separable cognitive domains have been identified in illnesses such as psychosis, there is still a wide variety in the type and number of tests which are used to assess performance in these domains. Another potential issue with the wider cognitive literature is that at present, some longitudinal studies which are interested in tracking the long-term trajectory of cognitive performance use standardised scores. While

the use of standardised cognitive scores is appropriate for cross-sectional studies, using this method longitudinally may mask the real trajectory of performance. For example, whether an individual is showing an absolute decline in cognitive performance over time as opposed to a "lag", in which they are not making the same appropriate gains as healthy controls. A more homogeneous evidence base will help to provide a clearer picture of the nature, and trajectory, of cognitive performance in mental illness. While the evidence reviewed highlights the dominance of neurocognitive impairments in mental illness, it also highlights the possibility of a protective effect. Individuals with better neurocognitive performance may be less likely to develop psychopathology, and may experience improved functional outcomes in the long-term. It is important that future research attempts to identify the specific protective factors which are involved in resilience, and the evidence presented in this chapter highlights the potential that neurocognition may have as such a protective factor. As such, this thesis will investigate whether neurocognitive performance is associated with resilience in a sample of individuals experiencing, or at-risk for, a first-episode of mental illness.

GENERAL SUMMARY AND RESEARCH AIMS

So far, research into the concept of resilience has begun to explain why not all individuals exposed to the same risk factor for mental illness experience the same trajectory of long-term psychiatric symptoms or wellbeing. While some people may not experience any symptoms of mental illness following exposure to a risk factor, some may have brief episodes of illness followed by functional recovery, and others may experience a chronic and disabling trajectory of illness. It is important that we understand the resilience process because it has potential for the development of new interventions which could strengthen protective factors. This would result in individuals being better equipped to navigate risk or

adversity in their life, thus lowering the chance of developing mental illness or improving the chance of quick and sustained recovery after a period of illness. This would be hugely beneficial at an individual level but could also lessen the global economic burden of mental illness.

Within the resilience literature, several potential frameworks for the concept have been proposed, including resilience as nodes within a network of psychiatric disorder (Kalisch et al., 2019), a harm-reduction or health promotion strategy (Davydov et al., 2010) and one core appraisal mechanism (Kalisch et al., 2015). In a relatively emerging field, these frameworks have provided detailed and valuable insights into how resilience might function and lead to better long-term outcomes. A full exploration and evaluation of the various frameworks of resilience, or the development of a new framework, is beyond the scope of this thesis. However, Chapter Two of this thesis reviewed the resilience literature and summarised the pre-existing literature in a model of resilience as a process including three core components: first, the presence of a risk or adversity; second, the utilisation of protective factors to offset the negative effect of the risk; and third, a better outcome for the individual than might have been expected given their exposure to said risk. An individual may have a range of protective factors available to them which can be used during this second step of the resilience process. As highlighted by previous literature, some protective factors might include assets or resources such as social skills or family cohesion (Fergus & Zimmerman, 2005; Friborg et al., 2003) which can be consciously accessed by the individual. There may also be protective factors which cannot be immediately accessed by the individual, but still may impact on the individual's outcome following exposure to risk. These unconscious protective factors might include genetic susceptibility, geographical and political climate, and social norms (Davydov et al., 2010).

Although a range of protective factors may be available to the individual, the resilience process is highly dynamic with regard to time, circumstance, and the type of risk or adversity. As such, the individual must also utilise a "filtering" process in which they decide whether they can influence the impact of the current risk, and if so, which protective factors would be the most appropriate. This filtering would be based on factors such as previous experience (for example, whether the strategy worked previously) and access (for example, an individual having moved away from family who would usually support them). Following this, the most appropriate protective factors would be chosen and utilised, subsequently leading to a more positive outcome for the individual than would have been expected given the exposure to risk. This aspect of the resilience process is similar to the framework of Kalisch et al. (2015), who have proposed that appraisal is the most important mechanism underlying resilience. They argue that in order for an individual to navigate adversity, they must be able to appraise the situation in terms of its potential threat to their functioning. A more positive appraisal style (e.g. perceiving the threat as manageable) and being able to inhibit negative emotional responses, will lead to a more positive outcome for the individual. This filtering process can also be linked with the theory of "stress inoculation", outlined in Chapter Two. If an individual encounters stressors which are enough to challenge, but not overwhelm, them, this may provide the opportunity to identify successful strategies which can be utilised against future stressors (Harris et al., 2016; Southwick et al., 2016). In summary, the second component of the resilience process may include both conscious and unconscious protective factors, as well as a mechanism in which the individual decides *how* to adequately utilise those factors in their current circumstance.

In this thesis, neurocognition is investigated as a potential protective factor involved within the resilience process. At present, it is unknown exactly how neurocognitive

performance may function within the resilience process. It is possible that neurocognition may underlie or contribute to other specific protective factors which have been identified by previous resilience frameworks. For example, protective factors such as social skills are likely to require good memory, attention, processing speed and social cognition. Neurocognition may also strengthen the "filtering" process; given that a large part of the dynamic process of resilience is the requirement to be flexible, to build new strategies, to evaluate strategies used previously and the similarity of the circumstance to the present risk, this is also likely to require a number of cognitive skills which, if impaired, would also impair an individual's current resilience. Investigating neurocognition in particular is also beneficial due to the fact that it is modifiable (as outlined earlier in this chapter). By investigating protective factors which are modifiable, this work is adding to a base of knowledge which can inform future intervention strategies.

In summary, the existing literature has provided a rich and detailed conceptualisation of resilience, which is now established. It is crucial that resilience research moves away from conceptual work and instead focuses on identifying the specific protective factors which are involved in the process; it is these protective factors which would be incorporated into resilience interventions. The current gaps in the literature are as follows: So far, resilience research has focused on defining the concept. There is less work which uses empirical methods that fit with the, now established, definition of the concept. In addition, the smaller amount of empirical work which has investigated protective factors has focused on the psychological and social factors, such as optimism, social skills, and family cohesion. While these are important findings, it is also important that research looks to identify protective factors in *other* domains.

This thesis will address important gaps in the resilience literature by examining the neurocognitive performance, observed and self-reported resilience, clinical symptoms, and functioning of a sample of adults with FEP, UHR, and FED, as well as HCs. The thesis will:

1. Investigate the potential of neurocognition as a protective factor supporting the resilience process. This is important to broaden the resilience literature beyond investigations of psychological or social protective factors.

2. Use empirical methods which fit with the established definition of resilience. There has been an abundance of theoretical work in the resilience field, but less so which attempts to empirically investigate resilience and isolate the specific protective factors involved in the process.

3. Test and evaluate multiple methods of empirically testing the efficacy of a particular protective factor. This is important given the limited number of empirical investigations of resilience at present. Work such as this will help researchers to identify the best methods of investigating resilience which are in accordance with the established definition of the concept. The methods used in this thesis to investigate the relationship between neurocognition and resilience are informed by previous literature and fit with the established conceptualisation of resilience. The thesis will examine resilience as an "observable" retention of good functioning in the context of psychopathology, as higher scores on a self-report measure of resilience, and as the extent to which an individual is functioning well given their level of exposure to childhood trauma.

The overarching hypothesis tested by this thesis is that neurocognition will serve as a protective factor involved in the resilience process. This relationship will be tested in a number of ways and the specific hypotheses for these methods are as follows:

1. Individuals who retained higher functioning in the context of psychopathology will also have higher scores on tasks in a comprehensive neurocognitive test battery.
2. Higher neurocognitive test scores will be associated with higher scores on measures of self-reported resilience.
3. Neurocognitive test scores will be associated with the extent to which an individual is functioning well in the context of childhood trauma. Higher neurocognitive performance will be associated with better functioning than would be predicted, given the level of exposure to childhood trauma.

At first, a traditional approach will be used in which the participants are grouped by diagnosis. This approach will be used first to provide context of this sample and their cognitive performance in relation to previous samples. As diagnosis is used by most previous literature this is the best approach for comparison. The thesis will then move to using a transdiagnostic approach to the investigation of resilience, so that protective factors can be identified which are beneficial for long-term functional outcome, regardless of diagnosis. A transdiagnostic approach is important for resilience research given the previously discussed high prevalence of comorbidity, and the risk for impaired functioning and wellbeing which is associated with many different mental illnesses. Identifying protective factors which are present irrespective of traditional diagnosis could be used to inform novel intervention strategies and would be a more applicable and cost-effective method than focusing on protective factors to specific diagnoses.

CHAPTER FOUR

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GENERAL METHODOLOGY

INTRODUCTION TO THE PRONIA STUDY

The present research was conducted in conjunction with an international, EU-funded project, which focuses on early intervention in emerging mental illness. Primarily, the goal of the PRONIA study ('Personalised Prognostic Tools for Early Psychosis Management') is to improve the prediction of long-term outcomes in emerging mental illness, particularly FEP. The multimodal data collected from this project will contribute to the creation of a commercial tool, which will use machine learning techniques to provide more reliable prognostic evaluations, specific to the individual. Recommendations for treatments could then be based upon these personalised prognoses, with the goal that tailored treatment strategies could be more effective. PRONIA collects data across a range of domains, including clinical, neuropsychological, neuroimaging, hormonal, and genetic. The collection of such a wide range of data, using multiple assessment tools, also means that this will add to the base of knowledge as to which of these factors, and which specific measures, provide the most important and reliable information about developing mental illness and subsequent long-term outcomes. Data used in this thesis is taken from the baseline assessment, and was collected at six partner sites (Birmingham, Munich, Cologne, Basel, Udine, Turku) over a two-year period from 2014 to 2016. Following their baseline assessment, participants in the study went on to complete six further assessments over an 18-month period.

This project was chosen to address the proposed research questions for a number of reasons. Firstly, the PRONIA study enables the investigation of protective factors in a transdiagnostic group of individuals who are early in the course of psychiatric illness. Individuals recruited into the study are experiencing their first episode of psychiatric illness, or are within their first year of meeting UHR criteria, and have not been exposed to more than 12 weeks of antipsychotic medication. This is crucial for resilience research as

protective factors can be isolated which are present at the onset of illness and will be protective against the negative long-term effects of illness. Future interventions can thus attempt to strengthen these protective factors as early as possible and prevent chronic or disabling trajectories of illness. Furthermore, the PRONIA study provides a large, rich dataset with clinical, functional, and resilience measures, as well as a full neurocognitive test battery which captures a wide spectrum of cognitive domains. Given the thesis' focus on the potential of neurocognitive performance supporting the resilience process, this large cognitive battery will also help with the understanding of whether global cognition as a whole, or specific cognitive domains, are associated with resilience to the detrimental effects of mental illness. Finally, though unavailable for the present thesis, the PRONIA study will have data available examining clinical, functional, and resilience outcomes 18-months after baseline assessment. Future analysis will be able to examine whether any baseline protective factors presently are also associated with improved wellbeing after 18-months. Although the data for the present thesis are cross-sectional, this method is valuable for the investigation of neurocognition within the resilience process. There is very little in the resilience literature thus far which includes neurocognition. Therefore, this thesis will serve as an initial investigation regarding the possible protective effect of neurocognition, and will form the basis for future longitudinal studies.

PARTICIPANTS

Individuals participating in the study comprised four sample groups: FEP, FED, UHR, and HCs. Participants were categorised as UHR by fulfilling at least one of the previously determined criteria set out in Table 4.1. Inclusion into the UHR study group had to be agreed by team experts during a monthly, multi-site teleconference.

Table 4.1
Operationalised Criteria Representing Ultra-High Risk for Psychosis

Measure	Description
Structured Interview for Psychosis-Risk Syndromes (SIPS)	**Brief Intermittent Psychotic Syndrome** Symptoms of psychotic intensity which resolve within seven days without the intervention of antipsychotic medication. Must have an intensity score of 6, and be present for at least a few minutes per day. Onset of symptoms must be within 3 months prior to assessment.
	Attenuated Positive Symptom Syndrome The presence of positive symptoms which are a subthreshold intensity than would be considered psychotic. Intensity scores are between 3-5. Symptoms must have begun, or worsened by at least one scale point, within the past year, and must occur for at least a few minutes, at least one day per week in the past month.
	Genetic Risk and Deterioration Syndrome Participants must have a genetic risk for psychosis by either having a first-degree relative with a diagnosis of any affective or non-affective psychosis or by personally meeting criteria for DSM-IV schizotypal personality disorder. *Additionally*, the participant must have experienced at least a 30% drop in their Global Assessment of Functioning score within the year prior to assessment.
Basic Symptoms; (COGDIS)	Participants must have experienced at least two of the following nine symptoms: • **Inability to Divide Attention** • **Thought Interference** • **Thought Pressure** • **Thought Blockages** • **Disturbance of Receptive Speech** • **Disturbance of Expressive Speech** • **Unstable Ideas of Reference** • **Disturbances of Abstract thinking** • **Captivation of Attention by Details of the Visual Field** The experience must be novel, having a noticeable onset at some point during the participant's lifetime, and must still be occurring within 3 months prior to assessment. The experiences must be occurring at least weekly within that period.

All participants were subject to stringent inclusion and exclusion criteria. Appendix A provides a full description of the inclusion and exclusion criteria which are applied in the PRONIA study, briefly comprised in Table 4.2.

Table 4.2
A table briefly comprising the full inclusion and exclusion criteria for the PRONIA study

Study Group	Inclusion Criteria	Exclusion Criteria
All Groups	Age 15-40	Current or past head trauma
	Capacity to consent	Current or past neurological illness
	Sufficient proficiency in the native language of the site	Current or lifetime alcohol dependence
FEP	DSM-IV affective or non-affective psychotic episode within 3 months of baseline assessment	Antipsychotic medication at or above the German Association for Psychiatry, Psychotherapy, and Psychosomatics (DGPPN) S3 guidelines (Appendix A) for more than 90 days
	Onset of psychotic episode within 24 months prior to baseline assessment	Onset of psychotic episode longer than 24 months prior to baseline assessment.
FED	DSM-IV major depressive episode within 3 months of baseline assessment	Meeting criteria for FEP or UHR
	Onset of depressive episode no longer than 24 months before baseline	Any intake of antipsychotic medication within 3 months of baseline assessment at or above DGPPN S3 guidelines
UHR	Meeting any of the SIPS psychosis-risk syndromes *AND/OR* meeting COGDIS criteria	Antipsychotic medication at or above DGPPN S3 guidelines for more than 30 days
		Any intake of antipsychotic medication at or above DGPPN S3 guidelines within the month prior to baseline assessment
		Meeting FEP criteria

Participants were recruited through a variety of means at all sites. Clinical participants were recruited through early intervention and primary care services, posters, and online advertisements. Healthy controls were recruited using a range of methods, including online advertisements, posters, and word-of-mouth. From the outset of the study, controls

were recruited to match the clinical group as closely as possible in terms of their demographic variables such as age, gender, and education level.

PROCEDURE

Data collection for the present thesis followed the protocols and procedures the PRONIA study. All aspects of the research received full ethical approval from the University of Birmingham Research Governance, and the Coventry and Warwickshire National Health Service (NHS) Research Ethics Committee, as well as the relevant ethics committees at each site. Funding for the PRONIA project was provided by the European Union under the 7th Framework Programme under grant agreement n° 602152.

All participants underwent the same assessment schedule. Initially, participants were seen at a baseline assessment which included all study measures outlined below. Participants received financial reimbursement in respect of their time.

All interviewers involved in data collection received full training to conduct the clinical interviews and neurocognitive testing required for this study. To ensure that inter-rater reliability of the measures was as high as possible, all interviewers attended regular training conferences and received feedback on their scoring of test vignettes.

MEASURES

The present study gathered demographic information from participants which included: age, gender, ethnicity, education, and occupation. The following measures were utilised to assess clinical symptoms, psychological resilience, functioning, quality of life, childhood trauma, and neuropsychological performance. The measures are described here as they are pertinent to all empirical chapters.

Clinical Symptoms

The Structured Interview for Psychosis-Risk Syndromes (SIPS; Miller et al., 2003) is a semi-structured interview which assesses the positive, negative, disorganised, and general symptoms of psychosis. The goal of the instrument is to be able to categorise individuals as psychotic, or at UHR for psychosis based on positive symptoms, which are further divided into the following subdomains: Unusual Thought Content, Suspiciousness/ Persecutory Ideas, Grandiose Ideas, Perceptual Abnormalities, and Disorganised Communication. Qualitative interview answers are transformed to intensity scores from '0' (absent) to '6' (severe and psychotic). Inter-rater reliability has been reported as 0.95 for the total score, with all subdomains in the excellent range, higher than 0.75 (Miller et al., 2003).

The Schizophrenia Proneness Instrument, Adult Version (SPI-A;Schultze-Lutter, Addington, Ruhrmann, & Klosterkotter, 2007a) assesses BS of schizophrenia. BS (as introduced in Chapter One) represent subtle, self-reported, subclinical disturbances, which the individual identifies as significantly different from their usual mental state (Schultze-Lutter, 2009). In particular, the nine COGDIS items (see Table 4.1) were used in the present research to determine UHR status. The COGDIS items have been used to predict psychosis, with transition rates of 25% within 12 months (Schultze-Lutter et al., 2007b).

Presence of psychosis and major depression were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002). Individuals were included in the FEP group if they met criteria for any affective or non-affective psychotic disorder. Major depression was defined by the SCID-IV as the presence of any five symptoms occurring for a significant portion of a two-week period. At least one symptom had to be low mood or loss of enjoyment in usually pleasurable

activities. Inter-rater reliability for diagnosis of all 12 Axis I disorders has been found to range from fair to excellent, with kappa values of 0.61-0.83 (Lobbestael, Leurgans, & Arntz, 2011).

The second version of the Beck Depression Inventory (BDI) is a 21-item self-report questionnaire used to measure the experience of depressive symptoms within the past two weeks (Beck, Steer, & Brown, 1996). Nineteen items are rated on a four-point Likert scale with '0' indicating no symptoms of depression and '3' indicating the highest severity. Two of the items relating to changes in sleep pattern and appetite have two additional possible responses to enable the participant to indicate both increases and decreases in these factors. High Cronbach's Alphas of 0.91-0.93 and test-retest reliability of 0.93 (Beck et al., 1996; Dozois, Dobson, & Ahnberg, 1998) indicate good psychometric properties of the measure.

Resilience

The Resilience Scale for Adults (RSA) is a 33-item self-report questionnaire which assesses psychological resilience (Friborg et al., 2003). The items capture the following six aspects of psychological resilience: Perception of Self, e.g. "I know how to solve my personal problems", Social Resources, e.g. "I can discuss personal issues with friends/ family members", Family Cohesion, e.g. "I feel very happy with my family", Social Competence, e.g. "I enjoy being together with other people", Planned Future, e.g. "My plans for the future are possible to accomplish", and Structured Style e.g. "I am at my best when I have a goal to strive for". Participants score each item on a seven-point scale, however anchor points are only provided for the two extreme scores. Items are reverse scored so that higher scores always indicate higher resilience. Internal consistency of the scale has been found to be satisfactory, with Cronbach's alphas for the subscales ranging from 0.67-0.90,

as has the test-retest reliability, ranging from 0.69-0.84 (Friborg, Barlaug, Martinussen, Rosenvinge, & Hjemdal, 2005).

Functioning

Social and role functioning were measured using the Global Functioning: Social (GF: Social) and Global Functioning: Role (GF: Role) scales (Cornblatt et al., 2007). These seven-item semi-structured interviews assess various aspects of an individual's functioning and are rated on a 10-item scale ranging from *1-Extreme Dysfunction* to *10-Superior Functioning* in both domains. Role functioning is tailored to the individual's efficacy in their role as a student, worker, or homemaker. The social functioning scale examined both the quality and quantity of relationships with friends and family members. For the present analysis, "current" functioning on both scales was assessed using the individual's highest functioning in the past month. Inter-rater reliability of both scales is high with coefficients ranging from 0.78-0.96 (Cornblatt et al., 2007).

The Global Assessment of Functioning (GAF) was also used to measure disability and functioning in this sample. Interviewer scores range from zero to 100. GAF scores can be split into two separate scales of clinical symptoms and disability/impairment. In order to avoid a circular definition of functioning based on the severity of symptoms, only the disability/impairment subscale was used presently. Reliability coefficients for this subscale have been reported at 0.58-0.70 (Jones, Thornicroft, Coffey, & Dunn, 1995), indicating acceptable reliability.

Quality of Life

QOL was assessed using an abbreviated version of the WHO's QOL scale (WHOQOL). This 26-item self-report scale assesses physical, psychological, social, and

environmental factors associated with an individual's wellbeing. Participants were instructed to rate their QOL in the past four weeks on a five-point Likert scale which was worded to suit each item. However, scores of one consistently indicated poorer QOL while scores of five indicated higher QOL. Scores on the brief version of this scale have been found to highly correlate with the original 100-item scale, and have high test-retest reliability with correlations of 0.56-0.84 on individual items (Whoqol Group, 1998).

Childhood Trauma

The Childhood Trauma Questionnaire (CTQ) measures the extent to which the participant experienced adverse events during childhood. This study employed a 28-item version of the scale which assessed five subtypes of childhood trauma: physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect (Bernstein et al., 2003). Participants are instructed to respond using a five-point Likert scale from *0-Never True* to *4-Very Often True*. Following the reverse scoring of nine items such as "I felt loved", higher scores always indicated more trauma. Test-retest reliability of the CTQ total score has been reported as 0.85, indicating good reliability (Paivio & Cramer, 2004).

General Neurocognitive Testing Procedures

Neurocognitive testing was completed on a computer or tablet device. Participants were seated at a comfortable distance from the screen in a quiet room. Standardised instructions were read verbatim by the interviewer from a script. Participants completed the tasks in the native language of the site. Where possible, the neuropsychological test battery was conducted in one sitting, in a standardised order so that tasks with delayed memory aspects always had the same amount of time between the first and subsequent parts of that task. Testing was broadly counterbalanced in relation to time of day.

IQ

IQ estimates were gathered using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2011) two-subtest abbreviated version including Vocabulary and Matrix Reasoning. In the Vocabulary subscale, participants are shown a list of up to 31 words and asked to describe their meaning. Scores vary from 0-2 which indicate an incorrect answer, a fair synonym, and a good synonym, respectively. In the Matrix Reasoning subtest, participants are required to complete a pattern by selecting a component from 5 different options. Testing is stopped following three consecutive incorrect responses. For both subscales, age-related T-scores were computed from raw scores. These t-scores were then converted to an estimate full-scale IQ score for each participant. Both the Vocabulary and Matrix Reasoning subtests of the WASI have high inter-rater reliability, 0.94 and 0.99 respectively, and internal consistency, 0.95 and 0.94 respectively (McCrimmon & Smith, 2013).

Executive Functioning

The Trail Making Test A&B (TMT; Army Individual Test Battery, 1944) is a paper-based task in which participants are required to connect numbered circles in chronological order (TMT A) and then alternate between chronological letters and numbers (TMT B). For both parts, participants are instructed to complete the task as quickly but accurately as possible, without lifting their pen from the page. If errors are made, participants are instructed to return to the last correct response and re-start the task from there, meaning that poorer performance is reflected in longer completion times. Subtracting completion time of Part A from Part B is used as an indicator of executing functioning abilities (Sanchez-Cubillo et al., 2009). Inter-rater reliability has been reported as 0.94 for Part A and 0.9 for Part B, indicating high reliability (Fals-Stewart, 1992).

Verbal Fluency was assessed using a modified version of the Controlled Oral Word Association Test from the Benton, Hamsher, and Sivan (1994) Multilingual Aphasia Examination. Two subtests assessed Phonetic Verbal Fluency (PVF) and Semantic Verbal Fluency (SVF). In each task, the participant is provided 60-seconds to generate as many novel words as they can which either all begin with the letter 'F' (phonetic), or are all examples of real animals (semantic). The measure has high internal consistency of 0.83 and a test-retest reliability of 0.74 (Ruff, Light, Parker, & Levin, 1996).

Sustained Attention

In the Continuous Performance Task, Independent Pairs Version (CPT; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988), participants are presented with three- or four-digit numbers which are presented at one-second intervals in the centre of the screen. Participants are instructed to respond when two consecutive numbers are entirely identical. The main outcome measure for this test is "d prime", a sensitivity index used to indicate a participant's ability to discriminate a target from distractors. Test-retest reliability for the primary outcome index was significant at 0.73 (Cornblatt et al., 1988).

Verbal Learning & Memory

The Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) was used to assess verbal learning and memory, according to the well standardised procedure described by Lezak (2004). Over five trials, the participant must repeat as many words as they recall from a list of 15. After five trials, an interference list of 15 new words is read and the participant must recall as many of these new words as they are able to. Memory of the first list is then tested post-interference. After a 30-minute delay, participants must recall the words from List A. Finally, in a recognition trial, participants must identify words from List A among a selection also including List B and entirely new words. A sum score of the trials one to five

was used to indicate verbal learning, and the 30-minute delayed score was used to measure verbal memory. Test-retest reliability using an alternative form has been reported as high, with coefficients ranging from 0.6-0.77 (Ryan, Geisser, Randall, & Georgemiller, 1986).

Visual Memory

The Rey-Osterrieth Complex Figure (ROCF; Osterrieth, 1944; Rey, 1941) assesses immediate and delayed visual memory. The established procedure described by Lezak (2004) was used in which participants are presented with the figure and must copy it to the best of their ability with no time limit. The figure is then removed from screen and the individual must draw as much as they remember of the image. After a 30-minute delay, the participant must again draw everything they remember of the figure. Performance is scored based on the accuracy and placement of each element of the figure. A high inter-rater reliability of 0.91 has been reported for this measure (Delaney, Prevey, Cramer, Mattson, & Group, 1992).

Working Memory

In the Self-Ordered Pointing Task (SOPT; Petrides & Milner, 1982), participants are shown a set of abstract shapes on-screen and must select each shape within the set after the shapes are rearranged following each selection. The participant must inhibit their prior selections within the set and only choose the shapes they have yet to select. The number of shapes on screen at any one time starts at four and progresses to ten. The task has a high test-retest reliability of 0.82 (Ross, Hanouskova, Giarla, Calhoun, & Tucker, 2007).

The Auditory Digit Span task, originally developed by Wechsler (1939), has two subtests to assess both ‘Forward’ and ‘Backward’ digit span. In the forward subtest, participants must recall a list of digits in the exact order that they were read. In the second

subtest, participants must again repeat the numbers, this time reversing the order that they were read. In both tasks, participants start with a list of two digits which progressively increases until three consecutive errors are provided.

Processing Speed

The Digit-Symbol Substitution Test (DSST; Copyright free version) is a component of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), used to assess processing speed. In this task, the participant is shown a key demonstrating that the numbers one to nine all correspond to a distinct geometric symbol. After a short practice session, the participant must use the key to complete the empty boxes with the correct number corresponding to each geometric symbol. The participant is given 90 seconds to complete as many symbols as they are able to. Final scores subtract the number of incorrect responses from the number of correct responses. Test-retest reliability of this measure is high with reported coefficients of 0.81-0.88, and the measure is thought to be particularly sensitive to cognitive impairment (Lezak, 2004).

Social Cognition

Social cognition was assessed using the Diagnostic Analysis of Non-Verbal Accuracy (DANVA; Nowicki & Duke, 1994). Participants completed the receptive facial expression subtest of this measure. Images of adult faces were presented on-screen, each expressing one of four emotions. Participants had the four possible responses (happy, sad, angry, or fearful) presented on screen. The image of the face remained on screen until they selected their response. Both the internal consistency and the test-retest reliability of this task have been found to be acceptable, with values of 0.88 and 0.84, respectively.

Aberrant Salience

Aberrant salience was assessed using the Salience Attribution Task (SAT; Roiser et al., 2009), in which participants must assess the relationship between categorised images and their likelihood of receiving points on a target-response task. Participants must respond with a finger press every time they see a black box appear in the centre of the screen. The black boxes are preceded by pictures which appear on screen and are categorised as either: red animals, blue animals, red household objects, or blue household objects. On some goes they are awarded points, the amount of which increases with a quicker response time. There is a relationship between the type of picture which precedes the black box, and the participant's likelihood of receiving points for their response. At the end of the session, they must provide a percentage estimation of their likelihood of receiving points in relation to each category of image. One dimension (e.g. blue colour) was task relevant, and was therefore rewarded on 87.5% of trials. The other dimension (e.g. type of object) was task irrelevant, and was rewarded on 50% of trials. Aberrant salience was measured as any difference in implicit (reaction time) and explicit (likelihood ratings) responses to trials which had equal chance of reward (e.g. blue animals versus blue objects).

DATA PREPARATION

The data from each site was compiled. The neurocognitive data was prepared as follows: Firstly, the primary outcome scores for each test were chosen, with any 'reaction time' or 'error' scores reversed to ensure that higher scores always indicated better performance. As the PRONIA study is a consortium project, the data was then checked for significant site effects. Table 4.4 highlights the significant effects of centre on demographic variables. As such, a regression model including Age, Sex, IQ, Education (by qualification) and First Language was developed using the HC sample, in line with previous research

which has also used such models to correct neurocognitive scores (e.g. Zanelli et al., 2009). Each neurocognitive test score was examined using this regression model. If there was a significant effect of the covariates on the test score, the raw score was then corrected for these variables using the model residuals. If this regression was non-significant, the variable was left as the raw score. Following this, z-scores were created from the corrected scores using the mean and SD of the HC study group.

Missing values in the measures of interest were then assessed. Missing data values were small in this dataset, particularly in the neurocognitive data (exact values presented in Table 4.3). More data was missing in the neurocognitive tests of verbal learning and memory as an alternative measure was used by the Finnish site. As such, no responses from Turku were available for these tests and it is possible that interpretation of this domain may require more caution than that of the other domains. Little's Missing Completely at Random (MCAR) test was significant, indicating that the data were not MCAR, and were more likely Missing At Random. Expectation-Maximization (EM) methods were used to impute missing values in the data. EM is an iterative procedure by which missing values are first estimated from the existing data and current parameter estimates. In the second step, the complete dataset is used to calculate a new mean vector and covariance matrix, which is then used again in the first step. The process repeats until stable parameter estimates are reached (Enders, 2001). Evidence has shown that all imputation methods are valid when missing values are very small (Scheffer, 2002; Shrive, Stuart, Quan, & Ghali, 2006) as in this dataset. However, EM often emerges as a particularly effective method when several imputation methods are compared (Musil, Warner, Yobas, & Jones, 2002; Scheffer, 2002), and can be a more efficient method than multiple imputation (Dong & Peng, 2013). EM is also appropriate when the data are MAR (Enders, 2001, 2010), as in this dataset. Furthermore,

multiple imputation is not compatible with the planned MANOVAs conducted later in this thesis in most statistical packages, and therefore single imputation was more appropriate. As such, EM was used to impute missing values in the data prior to the construction of domain scores, given that item-level imputation (as opposed to domain-level) has been found to increase power and reduce potential bias (Mazza, Enders, & Ruehlman, 2015).

Table 4.3
A table illustrating the exact missing data values for the neurocognitive and clinical data

Neurocognitive Data		
Domain	**Task**	**Missing Data (%)**
Executive Function	TMT (Part B-Part A)	3.1
	PVF (Number of Words)	1.2
	SVF (Number of Words)	0.9
Sustained Attention	CPT (*d'* for commission errors)	1.2
	CPT (*d'* for random errors)	1.2
Verbal Learning & Memory	RAVLT (Sum of Trials 1-5)	11.0
	RAVLT (Delayed Memory)	11.1
Working Memory	Forward Digit Span	1.1
	Backward Digit Span	1.1
	SOPT (Total Span)	1.4
	SOPT (Total Errors)	1.4
Visual Memory	ROCF (Immediate Memory)	0.9
	ROCF (Delayed Memory)	1.1
Processing Speed	DSST (Total Score)	0.2
	TMT (Part A)	2.8
Social Cognition	DANVA (Total Score)	0.9
Aberrant Salience	SAT (Implicit)	2.2
	SAT (Explicit)	1.5
Clinical Data		
Measure	**Missing Data (%)**	
GAF	1.2	
GF: Social	1.4	
GF: Role	1.4	
	Missing Data Range (Item-level, %)	
RSA	7.9-9.1	
BDI	6.6-7.4	
WHOQOL	7.7-10	
CTQ	8.5-9.7	
SIPS	1.2-1.7	
SPI-A	1.5	

Finally, domain scores were calculated for each participant. Neurocognitive domain scores were calculated as the average of z-scores which had been identified in the literature as assessing that domain. Previous research supports the existence of separate and specific neurocognitive domain impairment in psychosis (Nuechterlein et al., 2004), and the use of similarly established domains was intended to facilitate comparison to previous literature. Table 4.5 provides a full description of the neurocognitive domains assessed in the present study, and the previous literature which informed domain construction. Clinical measures used total scores by summing all responses to the items in that particular measure.

Table 4.4

A table demonstrating the effects of site on demographic variables in the HC sample used to create normative data for neurocognitive variables.

	Birmingham	Munich	Cologne	Basel	Turku	Udine	Statistic	*p-value*
Gender								
Male %	53.6	37.3	47.9	37.5	35	37.8	χ^2=3.795	0.579
Age								
Mean	20.7	26.5	25.7	26	29.6	27.2	F=5.922	<0.001*
(SD)	(5.7)	(6.5)	(5.8)	(5.5)	(6.2)	(6.8)		
IQ								
Mean	104.4	111.9	111.3	110.3	115.2	116.5	F=2.821	0.017*
(SD)	(13.6)	(15.2)	(17.4)	(13.1)	(13.7)	(20.3)		
Education Years								
Mean	15.3	15	14.2	15.3	15.1	15.2	F=0.695	0.628
(SD)	(3)	(3.1)	(3.3)	(3.3)	(2.2)	(3.5)		
Qualification								
N (%)							χ^2=50.38	<0.001*
No Graduation	6 (21.4)	2 (3.4)	0	0	0	0		
Middle School	7 (25)	11 (18.6)	5 (10.4)	6 (15)	2 (10)	5 (11.1)		
High School	14 (50)	31 (52.5)	24 (50)	21 (52.5)	13 (65)	19 (42.2)		
Degree	1 (3.6)	15 (25.4)	19 (39.6)	13 (32.5)	5 (25)	21 (46.7)		
First Language								
N (%)							χ^2=672.5	<0.001*
English	24 (85.7)	1 (1.7)	0	0	0	0		
German	1 (3.6)	55 (93.2)	46 (95.8)	35 (87.5)	0	0		
Italian	0	0	0	1 (2.5)	0	45 (100)		
Finnish	0	0	0	0	20 (100)	0		
Other	3 (10.7)	3 (5.1)	2 (4.2)	4 (10)	0	0		

χ^2= Chi-Squared. F=One-Way Analysis of Variance. *=Statistically significant at a level of $p \leq 0.05$

Table 4.5

A table demonstrating the test scores contributing to neurocognitive domain scores and the literature informing this selection

Neurocognitive Domain	**Test Scores**	**Literature**
Executive Function	Trail Making Test (Part B-Part A)	(Sanchez-Cubillo et al., 2009)
	Phonetic Verbal Fluency (Number of Words) Semantic Verbal Fluency (Number of Words)	(Joyce, Collinson, & Crichton, 1996)
Sustained Attention	Continuous Performance Task (*d'* for commission errors) Continuous Performance Task (*d'* for random errors)	(Cornblatt et al., 1988; Nuechterlein et al., 2008)
Verbal Learning & Memory	Rey Auditory Verbal Learning Test (Sum of Trials 1-5) Rey Auditory Verbal Learning Test (Delayed Memory)	(Lezak, 2004; Rey, 1964)
Working Memory	Auditory Digit Span Task (Forward Digit Span) Auditory Digit Span Task (Backward Digit Span)	(Conklin, Curtis, Katsanis, & Iacono, 2000)
	Self-Ordered Pointing Task (Total Span) Self-Ordered Pointing Task (Total Errors)	(Cragg & Nation, 2007; Petrides & Milner, 1982; Ross et al., 2007)
Visual Memory	Rey-Osterrieth Complex Figure (Immediate Memory) Rey-Osterrieth Complex Figure (Delayed Memory)	(Lezak, 2004; Osterrieth, 1944; Rey, 1941)
Processing Speed	Digit Symbol Substitution Test (Total Score)	(Nuechterlein et al., 2008)
	Trail Making Test (Part A)	(Nuechterlein et al., 2008)
Social Cognition	Diagnostic Analysis of Non-Verbal Accuracy (Total Score)	(Nowicki & Duke, 1994)
Aberrant Salience	Salience Attribution Test (Implicit: Reaction Time) Salience Attribution Test (Explicit: Visual Analogue Scale)	(Roiser et al., 2009)

CHAPTER FIVE

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NEUROCOGNITIVE PERFORMANCE IN A TRANSDIAGNOSTIC SAMPLE: A COMPARISON OF INDIVIDUALS WITH FIRST-EPISODE PSYCHOSIS, FIRST-EPISODE DEPRESSION, AT ULTRA-HIGH RISK FOR PSYCHOSIS, AND HEALTHY CONTROLS

INTRODUCTION

As discussed in Chapter Three, neurocognitive impairments are pervasive in mental illness and have significant impact at an individual and societal level. While there is a wealth of evidence regarding neurocognitive deficit in specific mental disorders, there is less literature which investigates this area in transdiagnostic samples. Studies like these provide the opportunity to examine neurocognition in individuals with mental illness and identify whether profiles of neurocognitive performance are specific to particular disorders, or whether there is an overlap between what are considered to be distinct illnesses. Some studies which have examined neurocognitive performance in both psychosis and depression have reported differing patterns of impairment in the two disorders. Individuals with psychotic disorders demonstrate impairments which are widespread and more severe than those seen in MDD (Lee et al., 2015; Rund et al., 2006). Liang et al. (2018) used machine-learning to examine neurocognitive performance in individuals with FEP and MDD. In their study, participants with FEP demonstrated larger impairments in IQ, memory, attention, processing speed, and learning than in MDD (Liang et al., 2018).

Comparisons of individuals pre- and post-onset of psychosis can also give an insight into the trajectories of neurocognitive performance in mental disorder. Zhang et al. (2015) investigated neurocognition in UHR, FEP, and chronic psychosis, and compared their performance to that of HCs. They identified that individuals at UHR did not differ significantly from HCs on any measure other than visuospatial skills, whereas individuals in both post-onset groups were significantly impaired in all measures. In their study, impairment in delayed memory emerged as a factor which significantly predicted transition from UHR to FEP, and was the only measure correlated with the later stage of psychosis. Simon et al. (2007) compared the performance of both early (BS) and late (psychosis-risk

syndromes) stage UHR to that of FEP. The groups demonstrated increasing levels of impairment from the early-stage UHR to the FEP, with both UHR groups performing at a level that was intermediate to control subjects, and the FEP group. However, as discussed in the introduction to this thesis, studies such as these must be interpreted with caution as these samples may not truly reflect groups which are at differing stages of the same illness process.

Some studies have used a clinical staging approach (McGorry et al., 2006), in which participants are divided into two groups: the experience of attenuated symptoms of mental disorder (clinical stage 1b), and the experience of discrete or persistent mental disorder (stages two and three). These groups are formed irrespective of traditional diagnoses. In a study by Hermens et al. (2013), these two groups differed significantly on all domains except for verbal fluency. The group with discrete and persistent disorder demonstrated the largest impairments in verbal memory and executive function (Hermens et al., 2013). A later study by the same group replicated these results. However, in this larger sample, the two groups differed on measures of verbal learning, verbal memory, visual memory, and set shifting, with poorer performance by participants in stages two and three (Tickell, Lee, Hickie, & Hermens, 2017).

In summary, results from studies with transdiagnostic samples do indicate differing neurocognitive profiles according to disorder. However, similarities between neurocognition in UHR and FEP might suggest that neurocognitive profiles are specific to the *type* of disorder, e.g. mood versus psychosis-spectrum. Neurocognitive impairments appear to be more severe, and more widespread in psychosis than in depression. Studies which compare samples of UHR versus FEP subjects can give an indication of the trajectory of neurocognitive development in psychosis-spectrum disorders. These results must be

interpreted with caution, however, as we cannot ultimately assume that these two samples represent an identical population at different stages of illness. As discussed in Chapter Three, the most effective method for studying this trajectory would be to use large birth cohort methodologies which follow the same individuals across their lifetime. These methodologies are costly and time consuming; therefore, group comparisons can be used to provide initial indications about the course of cognition across the psychosis spectrum.

As such, the goal for this chapter is to examine neurocognitive performance in a transdiagnostic sample of adults, including individuals with diagnoses of FEP, UHR, FED, and HCs. Informed by previous literature, it was hypothesised that the neurocognitive performance of each clinical group would be significantly poorer than that of HCs, with impairments being greatest in the FEP sample.

METHODS

Participants

The present sample included 648 individuals aged 15-40 (mean age=25.5; SD=6) recruited into the PRONIA study. Chapter Four provides a full description of the inclusion and exclusion criteria for the study. Briefly, participants were individuals recruited from all study sites into one of four study groups: HCs, UHR, FED, or FEP.

Measures

In this cross-sectional study, participants completed a comprehensive neurocognitive test battery, with tests assessing the following domains: executive function, sustained attention, verbal learning & memory, working memory, visual memory, processing speed, social cognition, and aberrant salience. Chapter Four provides a full description of the

measures used in this test battery. An interviewer-rated questionnaire gathered demographic information including: Age, Gender, Ethnicity, and Education Years.

Statistical Procedure

Statistical analysis was conducted using IBM SPSS Statistics Version 26 (IBM Corp, 2019). Demographics were analysed using Pearson's Chi-Square tests for categorical variables, and one-way Analysis of Variance (ANOVA) for continuous variables. Neurocognitive data was prepared according to the procedure outlined in Chapter Four. One-way Multivariate ANOVA (MANOVA) analysed performance in each of the neurocognitive domains across the four study groups. MANOVA extends the one-way ANOVA by allowing the investigation of an independent variable with several levels upon *multiple* continuous dependent variables at once (Huberty & Olejnik, 2006), and is appropriate where, as in the present research, the dependent variables may represent separate domains of one underlying construct (Bray & Maxwell, 1982). Furthermore, the use of MANOVA reduces the chance of Type 1 error which can occur when conducting multiple ANOVAs (Warne, 2014). This technique is appropriate for the present analysis when, as in this case, performance on eight separate neurocognitive domains is the outcome of interest. While there has been some debate in the statistical literature as to the best post hoc procedure once a significant multivariate effect has been established, in the present thesis, univariate ANOVA and subsequent post hoc tests were chosen. Not only are these tests the recommended procedure by the statistical software (IBM Corp, 2019), but these techniques are thought to be most appropriate where the primary research question is to determine significant group differences (Enders, 2003), as is the case in both Chapters Five and Six of this thesis. Firstly, the data was checked for the basic assumptions of MANOVA. Although multivariate normality of data cannot be directly tested, the Shapiro-Wilk test was used to infer normality. This test

was significant, meaning that the null hypothesis of normality was rejected. Where non-normality was present in the cognitive data, this reflected the nature of the task (e.g. ceiling effects) and transformation was not appropriate. However, visual inspection of the Q-Q plots showed approximate normality. Box's test of equality of covariance matrices was significant, meaning that equal covariances cannot be assumed. However, visual inspection of the covariance matrices showed approximate equality. Further, the MANOVA has been shown to be robust to violations of the normality and homogeneity of variance assumptions (Finch, 2005). As such, the Pillai's Trace test was used as this particular measure is thought to be the *most* robust to violations (Olson, 1979; Sheehan-Holt, 1998). Following the MANOVA, results of the one-way ANOVA were inspected. As the neurocognitive domains did not have homogeneity of variance, Tamhane's T2 test was used for post hoc pairwise comparison which is conservative in the context of multiple comparisons and is appropriate where equal variances cannot be assumed (Shingala & Rajyaguru, 2015).

RESULTS

Participant Demographics

The demographic characteristics of the sample are presented in Table 5.1. Chi-squared and one-way ANOVA tests revealed no significant differences in Site, Education Years, and Ethnicity, meaning that the HCs were well matched to the clinical groups in those factors. There was a significant main effect of study group on the demographic characteristics of Age and Gender, with the percentage of males being lowest in the HCs and highest in the FEP group. However, this does reflect the fact that incidence of psychosis has been found to be higher in males than in females (McGrath et al., 2004; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012), especially until age 45 (Kirkbride et al., 2012), as in this sample.

Inspection of the demographics of this sample does show that average age of the total sample from each site was significantly different (Table 4.4) and that age significantly differed across each of the study groups (Table 5.1). In order to investigate whether there was an interaction effect of site and study group on the age of the sample, a factorial ANOVA was conducted with age as the dependent variable and site and study group as fixed factors. While there was a significant main effect of site ($F(5,624)=3.237$, $p=0.007$) and study group ($F(3,624)=2.825$, $p=0.038$) separately, the interaction term for these fixed factors was not significant ($F(15,624)=1.549$, $p=0.086$), meaning there was not a significant difference in the age of each study group across the sites. As there was no significant interaction between study group and site on the age of participants, this is unlikely to have significantly impacted upon the current results.

Neurocognitive Performance of the Sample

One-way MANOVA revealed a statistically significant main effect of study group on cognitive performance, F (24, 1917) = 5.238, $p < 0.001$; Pillai's Trace = 0.185, partial η^2 = 0.062. Univariate analysis revealed a significant main effect of group on the following domains: executive function ($F(3,644)=14.649$, $p<0.001$), sustained attention ($F(3,644)=13.920$, $p<0.001$), verbal learning & memory ($F(3,644)=20.974$, $p<0.001$), working memory ($F(3,644)=11.799$, $p<0.001$), visual memory ($F(3,644)=14.676$, $p<0.001$), processing speed ($F(3,644)=23.165$, $p<0.001$), and social cognition ($F(3,644)=3.035$, $p=0.029$). There was no significant main effect of group on aberrant salience ($F(3,644)=0.904$, $p=0.439$). Table 5.2 demonstrates the post-hoc pairwise comparisons for the domains upon which there was a significant main effect of study group.

Table 5.1
Demographic characteristics of the sample

	Total (N=648)	HC (N=243)	UHR (N=129)	FED (N=136)	FEP (N=140)	Statistic	*p-value*
Age							
Mean (SD)	25.5 (6.0)	25.9 (6.5)	23.8 (5.1)	26.3 (6.1)	25.5 (5.4)	F= 4.682	0.003*
Gender							
Male %	48.9	41.2	52.7	46.3	61.4	χ^2=15.743	0.001*
Site							
N (%)						χ^2=13.279	0.581
Birmingham	62 (9.6)	29 (11.9)	12 (9.3)	13 (9.6)	8 (5.7)		
Munich	188 (29)	59 (24.3)	42 (32.6)	45 (33.1)	42 (30)		
Cologne	120 (18.5)	48 (19.8)	20 (15.5)	25 (18.4)	27 (19.3)		
Basel	96 (14.8)	40 (16.5)	18 (14)	17 (12.5)	21 (15)		
Turku	64 (9.9)	30 (8.2)	13 (10.1)	11 (8.1)	20 (14.3)		
Udine	62 (9.6)	47 (19.3)	24 (18.6)	25 (18.4)	22 (15.7)		
Education Years							
Min-Max	8-25.5	9-24	8-23	8-25.5	9-22		
Mean (SD)	14.88 (3.2)	14.98 (3.2)	14.63 (3.0)	15.05 (3.4)	14.76 (3.1)	F= 0.541	0.654
Ethnicity							
N (%)						χ^2=16.207	0.182
White	536 (82.7)	213 (87.7)	104 (80.6)	110 (80.9)	109 (77.9)		
Asian	43 (6.6)	8 (3.3)	10 (7.8)	10 (7.4)	15 (10.7)		
Black	12 (1.9)	4 (1.6)	0	3 (2.2)	5 (3.6)		
Mixed Race	12 (1.9)	3 (1.2)	3 (2.3)	2 (2.5)	4 (2.9)		
Other	36 (5.6)	13 (5.3)	8 (6.2)	9 (6.6)	6 (4.3)		
Unknown	9 (1.4)	2 (.8)	4 (3.1)	2 (1.5)	1 (.7)		

N= Number of Participants. SD= Standard Deviation. F=One-way ANOVA. χ^2=Chi-squared. *= Statistically significant at a level of $p \leq 0.05$.

Table 5.2
A table showing the significant pairwise comparisons of neurocognitive domain scores by study group

Cognitive Domain	Group Mean (SD)				Tamhane's Post Hoc Comparison	Cohen's D Effect Size
	HC	UHR	FED	FEP		
Executive Function	0 (0.79)	-0.16 (0.91)	-0.1 (0.86)	-0.61 (1.08)	HC>FEP, p<0.001 UHR>FEP, p=0.001 FED>FEP, p<0.001	0.64 0.45 0.52
Sustained Attention	0 (0.92)	-0.05 (1.09)	0.07 (1.09)	-0.61 (0.97)	HC>FEP, p<0.001 UHR>FEP, p<0.001 FED>FEP, p<0.001	0.65 0.54 0.66
Verbal Learning & Memory	0 (0.91)	-0.24 (1)	-0.2 (1.1)	-0.88 (1.29)	HC>FEP, p<0.001 UHR>FEP, p<0.001 FED>FEP, p<0.001	0.79 0.54 0.57
Working Memory	0 (0.73)	-0.05 (0.81)	-0.11 (0.77)	-0.46 (0.78)	HC>FEP, p<0.001 UHR>FEP, p<0.001 FED>FEP, p=0.001	0.61 0.52 0.45
Visual Memory	0 (0.97)	-0.46 (1.19)	-0.12 (1.04)	-0.7 (1.23)	HC>UHR, p=0.001 HC>FEP, p<0.001 FED>FEP, p<0.001	0.42 0.63 0.51
Processing Speed	0 (0.77)	-0.38 (1.04)	-0.17 (1.01)	-0.86 (1.26)	HC>UHR, p=0.002 HC>FEP, p<0.001 UHR>FEP, p=0.005 FED>FEP, p<0.001	0.42 0.82 0.42 0.60
Social Cognition	0 (1)	-0.22 (1.21)	0.02 (1.18)	-0.32 (1.47)	Significant main effect of group but no significant post-hoc comparisons	

DISCUSSION

This chapter examined neurocognitive performance in a transdiagnostic sample including individuals with FEP, FED, at UHR, and HCs. Results from this investigation highlighted significant differences in the neurocognitive profiles of each group. In summary, when compared to HCs, FEP were significantly impaired in executive function, sustained attention, verbal learning & memory, working memory, visual memory, and processing

speed. The same significant impairments were also evident in the FEP group relative to the FED group, and to the UHR group in every domain other than visual memory. The UHR sample demonstrated significant deficits relative to HCs in visual memory and processing speed. In contrast to the hypothesis for this chapter, the FED group demonstrated no significant impairment in their neurocognitive performance relative to the HC group.

The finding of significant, widespread neurocognitive impairment in FEP is consistent with previous research which has also found such deficit to be a core component of the illness. Most studies of this population have found that FEP patients are significantly impaired in all neurocognitive domains measured (Albus et al., 2006; Eastvold et al., 2007; Shmukler et al., 2015; Zhang et al., 2015). In the present sample, the largest effect size was seen for impairment in processing speed, followed by verbal learning and memory. Mesholam-Gately, Giuliano, Goff, Faraone, and Seidman (2009) conducted a meta-analysis of 47 studies including a total sample of 2,204 individuals with a first-episode of schizophrenia. Their analysis also revealed generalised impairment across 10 neurocognitive domains with medium- to large- effect sizes, the largest of which were also seen for processing speed and verbal memory. These findings are replicated by other studies (Dickinson, Ragland, Gold, & Gur, 2008; Heinrichs & Zakzanis, 1998; Wilk et al., 2005), with some additionally finding large effect sizes for executive function (Bilder et al., 2000), and attention (Heinrichs & Zakzanis, 1998) that were not present in this sample. The FEP group also performed significantly more poorly in these domains than the FED group, underscoring the observation that neurocognitive impairment may be more severe in psychotic disorders than in other mental illnesses (Lee et al., 2015; Liang et al., 2018).

In contrast to the present findings, some previous research has identified significant deficits of FEP patients in social cognition (Bartholomeusz & Allott, 2012; Rowland et al.,

2013). Indeed, some research using the same task as the present study to measure social cognition (DANVA; see Table 4.4) found that FEP samples performed significantly worse than HCs in this domain (Thompson et al., 2012). One explanation is that the present study only utilised one subscale of the DANVA, measuring facial emotion recognition. Other studies have also utilised a subscale measuring vocal emotion recognition. Therefore, it is possible that the addition of another subscale to the present study may have provided a more rounded picture of social cognition in FEP.

The present study also found no significant main effect of group on aberrant salience. This is in line with the findings of the original study using the Salience Attribution Test, in which patients with schizophrenia did not exhibit significantly more aberrant salience than HCs (Roiser et al., 2009). In the original study, aberrant salience did vary according to the type of psychotic symptoms experienced by patients, and as such it may be that aberrant salience varies *within* psychotic samples.

Participants in this study with FED were not significantly impaired in any of the domains measured compared to HCs. Some evidence has suggested that MDD is associated with significant impairments in memory, executive functions, visual learning and memory, psychomotor speed, and attention, with small to medium effect sizes (Ahern & Semkovska, 2017; Marazziti et al., 2010; Snyder, 2013). A recent systematic review and meta-analysis by Goodall et al. (2018) evaluated studies which examined neurocognitive performance in young people with depression. When eliminating low-quality studies, significant impairments emerged in attention, verbal memory, visual memory, verbal reasoning/knowledge, and IQ. However, despite the sample being comprised of young individuals aged 12-25, few studies which were included in the analysis reported the length, or number of episodes, of depression. Therefore, the present findings are not necessarily

conflicting with this review, as it is possible that the sample included in this meta-analysis were experiencing a more severe or chronic trajectory of depression than the first-episode sample here. The present findings are in line with a recent study using two longitudinal birth cohort samples. Schaefer et al. (2017) examined data from the Dunedin study from New Zealand, and the E-Risk study from the UK. They isolated smaller participant groups who had never experienced MDD, who had received a diagnosis of MDD alone, or who had experienced MDD and additional comorbid disorders. Firstly, they observed no predictive value of childhood neurocognition to adult MDD. In addition, they examined both self-reported cognitive complaints and informant-reported cognitive impairments. They observed that these cognitive factors only significantly differed from the "never depressed" group in individuals who had MDD *and* comorbid disorders. There was no significant difference in these cognitive factors between the "never depressed" group and the individuals who had only experienced MDD (Schaefer et al., 2017). Taken together, these results may suggest that neurocognitive impairments are evident in depression when severe or chronic symptoms are present, or when depression is co-morbid with other mental disorders.

In the present study, inclusion in the FED study group was defined by meeting DSM-IV criteria for a major depressive episode within the past three months. Therefore, the sample included a proportion of individuals who had experienced a FED within three months of their baseline assessment, but may not have been experiencing symptoms at the time of neurocognitive testing. Many studies find that remission of clinical symptoms is associated with significant improvements in these neurocognitive domains (Ahern & Semkovska, 2017; Lee et al., 2012), while some studies also find evidence for deficits in attention and executive function which persevere during periods of remission (Lee et al., 2012). It is

possible that neurocognitive impairment in major depression is more strongly associated with the presence, and chronicity, of clinical symptoms. Indeed, it has been proposed that the experience of a depressive episode itself has a "scarring" effect on neurocognitive performance, with impairments becoming more pronounced with each episode of depression (McClintock, Husain, Greer, & Cullum, 2010; Paelecke-Habermann et al., 2005). Therefore, although the participants in this sample did not exhibit any scarring effects at present, it is possible that impairments may develop in individuals who go on to experience a repeated or chronic trajectory of MDD. However, the recent cohort study by Schaefer et al. (2017) found no evidence that neurocognitive performance declined following a major depressive episode, unless combined with other psychiatric comorbidity (Schaefer et al., 2017). The findings surrounding short- and long-term deficit in major depression are mixed, and impairment is likely to be associated with a range of other factors including comorbidity, depression subtype, and age of onset (Hammar & Guro, 2009; McClintock et al., 2010). Therefore further, longitudinal study would help to clarify the role of neurocognition in major depression.

When compared to HCs, UHR subjects demonstrated significant impairments in visual memory and processing speed. This is in line with previous results which demonstrate significant deficits of small to medium effect size in these domains (Brewer et al., 2005; Lin et al., 2013a; Niendam et al., 2007), with individuals at UHR performing at an intermediate level to HCs and FEP (de Paula et al., 2015; Simon et al., 2007). Some researchers have also identified additional deficits in domains such as working memory, verbal memory, executive function, and social cognition (de Paula et al., 2015; Eastvold et al., 2007; Fusar-Poli et al., 2012) which were not present in this sample. In the study by Carrión et al. (2018) they observed that only individuals at UHR who later transitioned to psychosis showed

significant neurocognitive deficits at baseline. The baseline neurocognitive performance of individuals who did not ultimately transition was comparable to that of a help-seeking control group (Carrión et al., 2018). As described in Chapter Four, the UHR study group comprised of individuals fulfilling either BS criteria, or one of the three psychosis-risk groups (Miller et al., 2003; Yung & McGorry, 1996). Often, these two criteria are conceptualised as representing an early (BS) and late (psychosis-risk groups) stage risk for psychosis. A study by Frommann et al. (2010) identified distinct profiles of neurocognitive impairment in these two groups. The early-stage UHR group demonstrated less severe impairment in executive control/ processing speed, whereas the late-stage UHR group showed more pronounced, and widespread, deficit (Frommann et al., 2010). It may be that the combination of these two UHR criteria may have masked some of the deficits observed in other studies. However, at present this distinction is theoretical, and there is little evidence to show that individuals do progress through these UHR stages in a clear and linear trajectory. Researchers widely acknowledge that the UHR concept is highly heterogeneous, and therefore almost all studies of this population will include individuals who will experience a wide range of clinical and functional outcomes.

Interestingly, the FEP group demonstrated significantly poorer performance than the UHR group in all of the aforementioned neurocognitive domains, with the exception of visual memory, where there was no significant difference between the two groups. Considering that the UHR group were significantly impaired relative to HCs in processing speed and visual memory, one might consider that visual memory in the UHR group has already progressed to the level of impairment seen in FEP. Several studies have found impairments in visual memory may predict transition from UHR to frank psychosis (Brewer et al., 2005; Kim et al., 2011; Lin et al., 2013a). Contrastingly, many studies find processing

speed to be particularly impaired in UHR (Keefe et al., 2006; Kelleher et al., 2013b; Niendam et al., 2006). As such, it is possible that tests of processing speed are particularly sensitive, and can therefore accurately detect significant differences not only between patients and controls, but also within individuals on the psychosis-spectrum. There are consistent findings that processing speed can significantly predict long term functional outcomes (Bowie et al., 2008; Carrión et al., 2011; Milev, Ho, Arndt, & Andreasen, 2005). As such, processing speed might be an important consideration in the development of screening or prognostic tools.

It is important that the present findings are interpreted within the context of the study's limitations. This study provides an insight into neurocognitive performance in a transdiagnostic sample at one time point. While the results are generally concordant with other cross-sectional studies, longitudinal studies will provide more detailed evidence about the trajectory and predictive power of neurocognition in the aforementioned mental disorders. Additionally, while cross-sectional comparisons of individuals at UHR with those experiencing a FEP can give an indication as to the trajectory of cognition over the psychosis spectrum, such studies assume that they are examining a similar population at different stages of illness. It is likely that the majority of individuals at UHR will not ultimately transition to psychosis. Therefore, longitudinal assessment of the same individuals who transition to psychosis is the only way to make more certain conclusions in this field. However, results such as those discussed here do still demonstrate that there are impairments associated with UHR status, thus warranting further investigation for potential intervention. Neurocognitive deficits are associated with a variety of negative long-term outcomes and interventions to improve these impairments have been found to have significant benefit for clinical and functional outcomes (e.g. McGurk, Twamley, Sitzer, McHugo, & Mueser,

2007). Thus, it would be potentially beneficial to provide neurocognitive intervention in the psychosis prodrome, regardless of whether this will prevent transition or not.

In conclusion, this study provides evidence for significantly different profiles of neurocognitive performance in different mental disorders. In this study, cognition was spared in FED, significantly impaired in FEP, and at an intermediate level in UHR. These results may suggest that neurocognitive impairment is particularly pronounced in psychosis-spectrum disorders. These findings are consistent with previous evidence, and highlight neurocognition as an important target for intervention in psychotic disorders. In the following chapters, this thesis will now explore whether neurocognition may relate to resilience in mental illness.

CHAPTER SIX

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NEUROCOGNITIVE PERFORMANCE OF INDIVIDUALS DISPLAYING RESILIENCE IN THE CONTEXT OF MENTAL ILLNESS

INTRODUCTION

The previous chapter gave an overview of the present sample's neurocognitive performance, providing context for the following examination of neurocognition as a potential protective factor. The findings of the previous chapter demonstrated that individuals experiencing a FEP, as well as those at UHR, demonstrated significant neurocognitive impairment relative to HCs, while participants experiencing a FED demonstrated no such deficits. The FEP group were significantly impaired relative to the HCs and the FED group in domains of executive function, sustained attention, verbal learning & memory, working memory, visual memory, and processing speed. Performance of the FEP group was also significantly poorer than that of the UHR group on all the aforementioned domains, with the exception of visual memory. The UHR group were significantly impaired relative to HCs in visual memory and processing speed. The present chapter will now return to the second aim set out for this thesis, beginning to explore resilience and the possible protective factors involved in more detail. It is important that we consider several methods for empirically measuring resilience, as a "gold standard" methodology is yet to be established in this area. This chapter will provide an overview of previous methods used to identify protective factors, before undertaking an initial investigation of neurocognition as a protective factor in this sample.

One method which has been used to identify protective factors is to utilise self-report scales of resilience. Scales such as the RSA (Friborg et al., 2003) and Connor-Davidson Resilience Scale (CD-RISC; Connor & Davidson, 2003) are intended to measure the ways that an individual copes with adverse situations, and how they view and plan for their future. Essentially, these scales measure the psychological and social protective factors, discussed in Chapter Two, which an individual perceives as being available to them. Individuals who

score higher on such scales would theoretically be more resilient, and better equipped to navigate adversity in their life. Higher scores on such scales have been associated with more beneficial coping styles (Campbell-Sills, Cohan, & Stein, 2006), less exposure to childhood trauma (Campbell-Sills, Forde, & Stein, 2009), fewer psychiatric symptoms (Bitsika, Sharpley, & Peters, 2010; Friborg et al., 2003; Hjemdal, Friborg, Stiles, Rosenvinge, & Martinussen, 2006; Hu et al., 2015; Marulanda & Addington, 2016), and improved functional outcomes (Bozikas et al., 2016); thus suggesting some clinical utility for these scales. In order to investigate protective factors associated with resilience, researchers have examined which other factors are associated with higher scores on these self-report scales. For example, higher self-esteem and spirituality were associated with higher resilience scores in a sample of patients with BD (Mizuno et al., 2016a). In a sample of American undergraduate students, higher spirituality, emotional intelligence, and support from friends emerged as significant predictors of higher scores on the CD-RISC (Howell & Miller-Graff, 2014). Iadipaolo et al. (2018) also identified that higher scores of self-reported resilience were associated with significant differences in the resting state functional connectivity of their participants, particularly relating to the default-mode network, the salience and emotion network, and the central executive network. Such investigations have begun to provide an understanding of the potential protective factors associated with resilience. However, there are several limitations to the use of such self-report measures of resilience, discussed further in Chapter Seven.

Researchers have also examined which factors are predictive of resilience by using regression analyses. Fritz et al. (2018) recruited a sample of healthy adolescents; some of whom had experienced childhood adversity. The presence of childhood adversity was not associated with significantly different responses to a social rejection task. However,

childhood adversity did predict better friendships at age 14 and 18 when the adolescents who had experienced such adversity demonstrated comparable mood levels to the HCs. Therefore, with a given level of mood symptoms, “resilient” individuals had more friendships than HCs. Researchers of the E-risk study (Moffitt & E‐Risk Study Team, 2002), which comprises a cohort of twins born in England and Wales, have also used these techniques to isolate protective factors. Crush, Arseneault, Jaffee, Danese, and Fisher (2017) examined which of a range of possible protective factors would predict low levels of psychotic symptoms in a subsample of individuals who had experienced multiple instances of victimisation (such as bullying or abuse) during childhood. They identified that a higher IQ and a more positive home atmosphere predicted lower levels of psychotic symptoms. However, the individuals in this sample did also present with high levels of depression and anxiety, and therefore these protective factors may be specific to the development of psychotic symptoms (Crush et al., 2017). In a second study by the same group, greater social support was also identified as a protective factor against the development of psychotic experiences in poly-victimised adolescents (Crush et al., 2018). Furthermore, a study of healthy adolescents by van Harmelen et al. (2017) calculated a measure of resilient functioning which encompassed psychosocial functioning within the context of the individual’s childhood family experiences; e.g. whether the individual was functioning better or worse than might be expected given their level of exposure to childhood abuse. In their sample, adolescent friendships significantly predicted higher resilient functioning at baseline and at one-year follow-up. In a sample of adolescents from a socio-economically disadvantaged environment, more positive cognitive interpretations were associated with better psychological functioning (Cortina et al., 2016).

Another methodology used to identify protective factors is to examine any specific factors which mediate the relationship between adverse events and subsequent negative mental health outcomes. The presence of positive attributes such as humour and politeness has been found to partially mediate the relationship between childhood trauma and psychotic experiences at three-year follow-up (Pan et al., 2018). Thus, these personal characteristics may serve as a protective factor against the development of psychotic experiences when an individual is exposed to childhood trauma. In addition, van Harmelen et al. (2016) identified two distinct protective factors which acted as mediators between adverse childhood experiences and poorer mental health outcomes in adolescence. In their study of British secondary school children, the authors identified that family support mediated the relationship between childhood family adversity and depressive symptoms at age 17. Furthermore, adolescent friendships mediated the pathway between childhood bullying and depressive symptoms (van Harmelen et al., 2016). These results reinforce the previously described model of personal and social protective factors associated with resilience (Friborg et al., 2003; Windle, 2011).

In addition to the studies mentioned in Chapter Two (Amico et al., 2011; Collishaw et al., 2016; Frangou, 2011; Wingo et al., 2010) recent research has also utilised methodology which compares individuals displaying varying levels of "observed" resilience on a number of different factors. Protective factors can be identified by examining which factors are most prevalent in the group demonstrating the highest levels of resilience. For example, van der Werff et al. (2013) classified members of their sample as "resilient" if they reported childhood maltreatment, but did not meet criteria for any psychiatric diagnosis. They compared these individuals to a "vulnerable" group, who had experienced maltreatment and developed psychopathology, and HCs, who had no experience of

maltreatment. They identified that the resilient group demonstrated increased negative connectivity between the left dorsal anterior cingulate cortex and the bilateral lingual gyrus and occipital fusiform gyrus when compared to both the vulnerable and HC group. Additionally, a large German cohort study identified that a range of personal and social protective factors (such as self-efficacy, optimism, and social support) were present to significantly different degrees in three groups of HCs, and individuals with possible- or probable- mental health problems. These protective factors were consistently highest in the HCs and lowest in those with probable mental health problems. They also identified a cumulative benefit of protective factors, in that the potential of presenting with mental health problems significantly reduced with the addition of each protective factor (Wille, Bettge, Ravens-Sieberer, & BELLA Study Group, 2008). However, levels of underlying risk were not accounted for at this stage of their analysis.

The studies presented here have utilised a range of methodologies and analytical techniques in order to identify potential protective factors which may be involved in the resilience process. Taken together, the findings suggest a range of psychological, social, cognitive, and neural mechanisms which may allow an individual to navigate adversity and avoid more negative long-term outcomes. While self-report methods have provided a useful insight into the resilience process, one could argue that they are not the most effective method available, as they largely measure higher levels of psychological and social protective factors anyway. More recently, researchers have been moving towards methods which capture more "observable" resilience; identifying individuals who are displaying better outcomes than might be expected with a given level of risk or adversity, and identifying which factors are more present in these groups.

The present chapter aimed to build from this reviewed literature, and move towards the identification of protective factors in more "observable" resilience. The present study compared the neurocognitive performance of individuals displaying varying levels of resilience, thus assessing its potential as a protective factor. It was hypothesised that there would be a significant difference in the neurocognitive performance of these three groups, with higher scores in the resilient group than in the HCs and the non-resilient group; indicating the presence of an additional factor which supersedes risk for mental illness, and is distinct and different from simply the absence of risk or symptoms in HCs.

METHOD

Participant recruitment and characteristics, inclusion criteria, measures, and procedure are all described in Chapters Four and Five, respectively. This study utilised the full neurocognitive test battery and the GAF.

Participants

For the purpose of this analysis, the sample as previously described in Chapter Four was further split into three distinct groups, reflecting different levels of "observed" resilience. The HC group remained unchanged; however, participants in any of the three patient groups were split into "resilient" and "non-resilient". This dichotomous split was based on the individual displaying relative "good" or "poor" functioning, despite their experience of psychopathology. A dichotomous split of scores on the GAF was used to determine levels of functioning. Only GAF scores pertaining to "disability and impairment" were used here. Scores of 0-60 on this measure reflect mild impairments in functioning to complete inability to function. Scores of 61 and above characterise individuals whose functioning ranges between some impairment but "is generally functioning pretty well", to functioning perfectly in all areas of life. As such, patients with a current GAF score of 60

and below at baseline were assigned to the "non-resilient" group, and patients with GAF scores of 61 and above were assigned as "resilient". As discussed in Chapter Two, resilience is a complex process which may fluctuate over time. These groups reflect individuals who are displaying varying levels of resilience at one point in time, and may well change in longitudinal analysis. The resilience groups created in this study are solely for the purpose of identifying protective factors, it is not appropriate to use these labels as clinically meaningful groups. The sample is described further in Table 6.1.

Although it would be circular to consider the presence of mental illness as a risk factor for mental illness itself, this analysis strategy has been included given the number of risks that the presence of mental-illness conveys for long-term mental and physical health, functioning, and wellbeing. Mental illnesses such as psychosis and depression are episodic illnesses, and therefore once an individual has experienced their first episode of illness, every effort should be taken to reduce the individual's risk of experiencing further episodes. Furthermore, as mentioned in the introduction to the thesis, the presence of one psychiatric diagnosis confers a large risk for the development of further diagnoses (Caspi et al., 2014). The increased risk of developing further disorders is bi-directional between diagnoses and irrespective of which disorder is developed first (Plana-Ripoll et al., 2019). Mental illness is also associated with a number of long-term outcomes (as introduced in Chapter One), including poorer social and role functioning, quality of life, and physical health to name just a few. Although resilience research is often associated with a preventative approach, in which we consider which factors may make an individual less likely to develop psychiatric symptoms following exposure to risk, it is also crucial that we use our understanding of protective factors to improve the lives of individuals who have already experienced an episode of illness in secondary or tertiary prevention strategies.

Although less common, this approach is not contradictory to that of other resilience research. In one of the most influential papers in the resilience field, Davydov et al. (2010) acknowledge that one function of the resilience process may be "harm reduction", in which mental health deteriorates following exposure to risk or adversity, but ultimately returns to premorbid levels. Furthermore, as shown by Wille et al. (2008), any individual who is exposed to enough stressors, even those with access to several protective factors, is still at risk for the development of mental illness. It is important that we acknowledge that the experience of psychiatric illness does not mean that an individual is not resilient, in fact this may be a natural response to high levels of stress or adversity, but instead research should focus on identifying factors which may be protective and promote a quick and lasting clinical and functional recovery following the first episode.

Statistical Procedure

Statistical analysis was conducted using IBM SPSS Statistics 26 Software (IBM Corp, 2019). Participant demographics were assessed using one-way ANOVA for continuous variables and Chi-squared tests for categorical variables. Neurocognitive domain scores were prepared as outlined in Chapter Four. A total score which was reflective of the level of psychopathology being experienced by the individual was created by summing the individual symptom scores of the following measures: SIPS positive, negative, disorganised, and general items, BDI, and SPI-A COGDIS items. The data was explored for normal distribution. Symptom Total Score was positively skewed and was thus altered using square root transformation. Where skewness was present in the neurocognitive data, it reflected the nature of the task, and therefore transformation was not appropriate. One-way Multivariate ANOVA (MANOVA) analysed performance in each of the neurocognitive domains across the three resilience groups. Firstly, as in Chapter Five, the data was checked for the basic

assumptions of MANOVA. Again, the Pillai's Trace test was used as this particular measure is thought to be the *most* robust to violations (Olson, 1979; Sheehan-Holt, 1998). Following the MANOVA, results of the one-way ANOVA were inspected. As the neurocognitive domains did not have homogeneity of variance, Tamhane's T2 test was used for post hoc pairwise comparison which is conservative in the context of multiple comparisons and is appropriate where equal variances cannot be assumed (Shingala & Rajyaguru, 2015).

RESULTS

Participant Demographics

Participants in the three resilience groups significantly differed according to gender, study group, site, IQ, and Current GAF score. There were no significant differences between the groups in age, mean years of education, or ethnicity (see Table 6.1).

Neurocognitive Performance in Three Resilience Profiles

One-way MANOVA revealed a statistically significant main effect of resilience group on cognitive performance, F (18, 1276) = 44.179, $p < 0.001$; Pillai's Trace = 0.768, partial $\eta^2 = 0.384$. Univariate analysis revealed a significant main effect of group on the following domains: executive function ($F(2,645)=9.532$, $p<0.001$), sustained attention ($F(2,645)=4.819$, $p=0.008$), verbal learning & memory ($F(2,645)=15.486$, $p<0.001$), working memory ($F(2,645)=5.868$, $p=0.003$), visual memory ($F(2,645)=23.405$, $p<0.001$), processing speed ($F(2,645)=29.782$, $p<0.001$), and symptom total ($F(2,645)=797.440$, $p<0.001$). There was no significant main effect of group on social cognition ($F(2,645)=2.073$, $p=0.127$) or aberrant salience ($F(2,645)=1.064$, $p=0.346$). Post hoc comparisons (Table 6.2) revealed that the performance of the resilient group did not significantly differ from that of HCs in any domain. The non-resilient group performed significantly poorer than the HC group on all domains for which there was a main effect of

group. Performance of the non-resilient group was also significantly poorer than the resilient group in the domains of visual memory and processing speed. Symptom Total Score significantly differed in each of the groups, with the HCs demonstrating the fewest symptoms, and the non-resilient group demonstrating the most symptoms.

Relationship to Symptom Levels

In order to investigate whether the observed neurocognitive differences were explained by symptom levels, Pearson's correlation investigated any associations between these variables in each of the three groups. The results from this correlational analysis revealed that Symptom Total Score was significantly negatively correlated with sustained attention in the HCs ($r=-0.148$, $p=0.021$) and positively correlated with executive function in the non-resilient group ($r=0.128$, $p=0.028$). As Symptom Total Score is not significantly correlated with the vast majority of neurocognitive domains in all three of the proposed resilience groups, this would suggest that the differing neurocognitive performance is not explained by clinical symptom levels alone.

Table 6.1
Demographics of the sample according to the newly established resilience groups.

	HC (N=243)	Resilient (N=111)	Non-Resilient (N=294)	F	*P*
Age					
Mean (SD)	25.9 (6.5)	24.5 (5.7)	25.5 (5.6)	F=2.202	0.111
Gender					
Male %	41.2	43.2	57.5	χ^2=15.926	<0.001*
Study Group N (%)					
HC	243 (100)	0	0		
UHR	0	45 (40.5)	84 (28.6)	χ^2=22.773	<0.001*
FED	0	48 (43.2)	88 (29.9)		
FEP	0	18 (16.2)	122 (41.5)		
Site N (%)				χ^2=44.891	<0.001*
Birmingham	28 (11.9)	23 (20.7)	10 (3.4)		
Munich	59 (24.3)	22 (19.8)	107 (36.4)		
Cologne	48 (19.8)	19 (17.1)	53 (18)		
Basel	40 (16.5)	14 (12.6)	42 (14.3)		
Turku	20 (8.2)	8 (7.2)	36 (12.2)		
Udine	47 (19.3)	25 (22.5)	46 (15.6)		
Education Years					
Min-Max	9-24	9-25	8-25		
Mean (SD)	15 (3.2)	14.8 (3.3)	14.8 (3.1)	F=0.198	0.820
Ethnicity N (%)				χ^2=13.121	0.108
White	213 (87.7)	93 (83.8)	230 (78.2)		
Asian	8 (3.3)	5 (4.5)	30 (10.2)		
Black	4 (1.6)	2 (1.8)	6 (2)		
Mixed Race	3 (1.2)	2 (1.8)	7 (2.4)		
Other	13 (5.3)	7 (6.3)	16 (5.4)		
Unknown	2 (0.8)	2 (1.8)	5 (1.7)		
IQ					
Mean (SD)	111.2 (15.2)	106.7 (17.3)	101.6 (19.4)	F=19.958	<0.001*
GAF Past Month Mean (SD)	84.6 (8.4)	71.6 (7.6)	45.6 (10)	F=1282.303	<0.001*

*Statistically significant at a level of $p \leq 0.05$. N=Number of participants.

Table 6.2
A table illustrating post hoc analysis of the three groups on the neurocognitive and symptom measures of interest.

Cognitive Domain	Group Mean (SD)			Tamhane's Post Hoc Comparison	Cohen's D Effect Size
	HCs	**Resilient**	**Non**		
Executive Function	0 (0.79)	-0.18 (0.9)	-0.34 (1)	HC>Non, p<0.001	0.38
Sustained Attention	0 (0.92)	-0.05 (1.03)	-0.26 (1.1)	HC>Non, p=0.008	0.26
Verbal Learning & Memory	0 (0.91)	-0.25 (1.01)	-0.52 (1.23)	HC>Non, p<0.001	0.48
Working Memory	0 (0.73)	-0.18 (0.79)	-0.23 (0.81)	HC>Non, p=0.002	0.3
Visual Memory	0 (0.97)	-0.02 (1.07)	-0.6 (1.18)	HC>Non, p<0.001 Res>Non, p<0.001	0.56 0.51
Processing Speed	0 (0.77)	-0.07 (0.92)	-0.63 (1.19)	HC>Non, p<0.001 Res>Non, p<0.001	0.63 0.53
Symptom Total Score	1.92 (1.61)	6.28 (1.77)	7.46 (1.59)	Res>HC, p<0.001 Non>HC, p<0.001 Non>Res, p<0.001	2.58 3.46 0.7
Social Cognition	0 (1)	-0.09 (1.19)	-0.21 (1.34)		
Aberrant Salience	0 (0.66)	0.07 (0.68)	-0.04 (0.61)		

*Statistically significant at a level of $p \leq 0.05$. "Non"= Non-resilient. "Res"= Resilient. SD= Standard Deviation.

Relationship to Study Group

As can be seen in Table 6.1, there were significant differences in the number of participants from each clinical study group comprising the two clinical resilience groups. Further analysis was conducted in order to investigate whether any significant differences in neurocognitive performance between the resilience groups were actually being driven by

the significant deficits of the study groups, identified in Chapter Five. For the two domains in which neurocognitive performance significantly differed between the resilient and non-resilient groups (visual memory and processing speed), a further factorial MANOVA was conducted in which both resilience group and study group were included as fixed factors. In addition to illustrating the main effects of these two factors, the MANOVA also investigated the interaction between them. Results from this MANOVA demonstrated that while there were significant main effects of resilience group and study group separately, these two factors did not significantly interact ($F(4,1282)=1.023$, $p<0.394$, Pillai's Trace=0.006). Thus, the significant differences in visual memory and processing speed of each resilience group were not dependent on which study group the participant was in.

DISCUSSION

In this chapter, the potential of neurocognition as a possible protective factor was examined by comparing the performance of individuals displaying varying levels of "observed" baseline resilience. For the present analysis, resilience was conceptualised as the retention of good functioning despite the presence of psychopathology. The first major observation is that a significant proportion of individuals do retain good functioning despite their experience of mental illness. Specifically, 27.4% of individuals in any one of the "patient" groups were demonstrating "good" functioning at their baseline assessment. The goal for resilience research is to better understand how this sample retains good functioning in the context of mental illness.

There was a significant main effect of resilience group on all domains other than social cognition and aberrant salience. The best performance was seen in HCs and the poorest performance in the non-resilient group. The non-resilient group showed significant deficits relative to HCs in all domains for which there was a significant main effect of group.

Performance of the non-resilient group was also significantly worse than the resilient group on measures of visual memory and processing speed. The resilient group demonstrated no significant deficits in neurocognitive functioning relative to HCs. However, in contrast to the hypothesis for this chapter, performance of the resilient group did not exceed that of HCs in any domain. These differing profiles of neurocognitive performance in the three groups were not meaningfully associated with clinical symptom severity, though this did also significantly differ between the groups.

The present results suggest that neurocognitive performance may be spared in individuals who are displaying resilience to the effects of mental illness on their functioning. Though research in this area is particularly limited, several previous studies have also suggested a protective effect of neurocognitive performance. Wingo et al. (2010) observed higher scores on nonverbal memory tasks in individuals who had not developed psychopathology despite experience of trauma compared to those who had developed psychopathology. Higher attentional control was significantly associated with higher scores on a measure of trait psychological resilience in a sample of German soldiers (Schafer et al., 2015). Genet and Siemer (2011) also studied undergraduate Psychology students, and identified that improved cognitive flexibility, which is usually considered to be an executive function, predicted higher scores on two measures of trait resilience. These findings, in addition to those of the present chapter, begin to suggest that higher neurocognitive functioning may act as a protective factor, allowing an individual to retain "good" functioning during periods of mental illness.

The present study provides a preliminary investigation of neurocognition as a protective factor; however, there are several limitations to this work. This study is cross-sectional, and identifies individuals displaying "observed" resilience at one time point.

Resilience (as discussed in Chapter Two) is a dynamic process which can fluctuate in one individual in different circumstances and at different time periods. It will be important, therefore, to reconceptualise the resilience groups according to long-term functioning and examine whether neurocognitive performance remains spared in the resilient group. While the present conceptualisation does fit with the previously discussed definition of resilience, this is just one operationalisation of the concept. The retention of good functioning in the context of mental illness reflects resilience at a later point of the illness trajectory, where clinical symptoms have already developed. Therefore, a different conceptualisation would be required to inform *preventative* intervention. Furthermore, this conception assumes that HCs have not experienced any risk for mental illness; therefore, an important direction for future work will be to account for risks, such as childhood adversity, in all participants.

Another limitation relates to the difficulty of defining the resilience groups. Presently, resilience was defined as retaining "good", as opposed to "poor" functioning, despite the presence of psychopathology. While a cut-off for current GAF scores of 60 was chosen to differentiate these groups, this is an arbitrary distinction. This chosen dichotomy may not necessarily translate to clinically meaningful groups; for example, it is unlikely that an individual who with a current score of 60 would demonstrate a meaningfully different level of functioning to an individual who scores 61. However, this is intended to be an exploration of the methods which could be used to measure resilience, and highlights the difficulties of operationalising this concept. Further, it was important to choose a score which would allow a fair proportion of the FEP participants to be included in the analysis. Poor functioning is often observed in FEP, and therefore setting the cut-off higher than 60 would have precluded the examination of neurocognition as a protective factor in the FEP group.

Furthermore, contrary to the proposed hypothesis, no domain scores were higher in the resilient group than the HC group. While the resilient group demonstrate neurocognitive performance not significantly different from that of HCs, one might argue that this simply reflects an absence of risk. For example, the presence of neurocognitive deficits is associated with a more severe illness trajectory, and thus those individuals with less of those deficits will experience a less severe course of illness. However, if that was the case, it is possible that the resilient group would perform at a more intermediate level, significantly different from both HCs and the non-resilient group. It is possible that these domains may function on a continuum of risk/resilience; whereby the presence of deficits confers risk, the absence of risk is associated with moderate benefits, but the presence of additional gains in these areas adds additional protection against the detrimental effects of mental illness. Again, further longitudinal research would help to confirm this theory.

In conclusion, the present study provides preliminary evidence that neurocognitive performance may be a protective factor associated with resilience. It is possible that intervention to strengthen these domains may lead to subsequent benefits in functioning. However, further research is first required to confirm this relationship and examine the effects of performance in these domains on longitudinal resilience. The resilience groups in this study were characterised by their functioning in the context of significant mental illness. Therefore, the results here are relevant for the later stages of the illness trajectory. At this stage, it can't be argued that the promotion of these domains would necessarily prevent the onset of illness, but they may improve an individual's ability to maintain a fulfilling life if they do experience mental illness. The exploration of neurocognition as a protective factor, and the methods which can be used to identify any such relationship, will continue in the next chapter.

CHAPTER SEVEN

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INVESTIGATING THE RELATIONSHIP BETWEEN NEUROCOGNITION AND SELF-REPORTED PSYCHOLOGICAL RESILIENCE

INTRODUCTION

In the previous chapter, resilience was conceptualised as the retention of "good" functioning in the context of psychopathology. Individuals who did not meet these criteria demonstrated significant deficits, relative to HCs, in executive function, sustained attention, verbal learning & memory, working memory, visual memory, and processing speed. This group also demonstrated significantly poorer performance than the "resilient" group in visual memory and processing speed. Individuals who were categorised as resilient displayed no significant neurocognitive deficits relative to HCs. Furthermore, the scores of the resilient group were particularly close to those of the HCs in visual memory and processing speed. These results suggest that neurocognitive performance is spared in individuals who show resilience to the effects of mental illness on their current functioning. This might mean that neurocognition is a protective factor involved in the resilience process. However, these cross-sectional findings would need further investigation to confirm this theory. As outlined earlier in this thesis, there are difficulties surrounding the conceptualisation of resilience, even with a relatively stable definition of the concept. As such, it is important to continue this investigation of the role of neurocognition in the resilience process, this time using an alternative conceptualisation of resilience.

As discussed in Chapter Six, one strategy which has commonly been used to conceptualise resilience is to use self-report measures. Higher scores on these scales are used to indicate higher resilience, and additional factors which are associated with higher scores on such measures may function as protective factors. Windle, Bennett, and Noyes (2011) reviewed nineteen different self-report scales which were intended to measure psychological resilience. While no gold-standard scale was identified, the RSA, used in this study, scored highly in their evaluation. This measure has been well-validated in a number of cultures

(Capanna, Stratta, Hjemdal, Collazzoni, & Rossi, 2015; Hjemdal, Roazzi, Dias Mda, & Friborg, 2015; Jowkar, Friborg, & Hjemdal, 2010), and higher scores on this measure have been associated with a range of clinical and functional benefits (as outlined in the previous chapter). The benefit of using a self-report scale to assess resilience is that, if validated, this would be a quick, accessible, and cost-effective method for clinicians to assess resilience and adjust treatment accordingly. It would provide an overview of how an individual typically addresses adversity and the assets and resources that the individual feels that they have available to them. The clinician can then tailor treatment to strengthen any protective factors which the individual feels that they are lacking, and thus improve their ability to overcome future adversities. Given the relative ease of disseminating self-report resources, this could also be used to address resilience if the concept were to be taken up by future public health interventions.

There is very little research which examines the relationship between neurocognition and self-reported psychological resilience. A recent study by Deng et al. (2018) utilised a large, transdiagnostic sample including individuals with schizophrenia, BD, and HCs. They identified significant correlations between higher scores on tasks measuring executive function, verbal comprehension, and working memory and higher scores on a self-report measure of psychological resilience in the whole sample. However, when the sample was split into the individual diagnostic subgroups, these significant correlations were no longer present. Furthermore, the differences in resilience scores between the diagnostic groups were not mediated by the neurocognitive variables. The results of this study suggest a possible association between neurocognition and psychological resilience, however, in their sample neurocognitive performance alone did not explain why some individuals score higher than others on these scales of psychological resilience.

The aim for this chapter was to extend the findings of the previous chapter, this time investigating whether neurocognition acts as a protective factor when resilience is operationalised as higher scores on a self-report resilience scale. The present analysis will first explore the validity of the RSA in this sample and its relation to other measures of wellbeing, before examining its relationship with the neurocognitive domain scores. It was hypothesised that higher scores on the RSA would be associated with fewer psychiatric symptoms, and better functioning and QOL. It was also hypothesised that higher scores on neurocognitive tasks would be associated with higher scores on the RSA.

METHOD

Participant recruitment and inclusion criteria, sample characteristics, and measures used are all described in Chapters Four and Five, respectively. This study utilised the full neurocognitive test battery, the RSA, CTQ, GF: Social, GF: Role, GAF, BDI, and WHOQOL.

Statistical Procedure

Statistical analysis was conducted using IBM SPSS Statistics 26 Software (IBM Corp, 2019). Neurocognitive domain scores were prepared as outlined in Chapter Four. While the Symptom Total Score (outlined in Chapter Six) does include BDI scores, these scores were also reported separately to examine relationships with depressive symptoms specifically. The data was explored for normal distribution. Symptom Total Score was positively skewed and was thus altered using square root transformation as in the previous chapter. Where mild non-normality was present in other variables, this was left untransformed, as it has been suggested that all of the statistical tests employed here are robust to such distributions (Havlicek & Peterson, 1976; Schmider, Ziegler, Danay, Beyer, & Bühner, 2010). The descriptive statistics of the RSA and other measures of mental health

and wellbeing (WHOQOL, GAF, GF: Social and Role, BDI, CTQ, and Symptom Total Score) are reported in Table 7.1 and, as they are all continuous measures, performance in each of the study groups was examined using one-way ANOVA. One-way ANOVA was appropriate in this context because the measures of interest represent separate components of mental health and wellbeing, as opposed to being drawn from one underlying construct. Bonferroni post hoc comparison was used to reveal the direction of any significant differences. Pearson's correlations were then used to examine associations between the RSA and the other wellbeing measures.

The relationship between baseline neurocognitive domain scores and baseline RSA Total Score was first established using Pearson's correlation in the whole sample. Due to significant differences in the RSA Total between HCs and each of the "Patient" groups, correlations between these variables of interest were also explored separately in these groups.

RESULTS

Descriptive Statistics of the RSA and Other Measures of Wellbeing

One-way ANOVA revealed a significant main effect of study group on all of the baseline wellbeing measures (see Table 7.1). Post hoc analysis indicated that HCs scored consistently and significantly higher on measures of positive wellbeing (GAF, GF: Social and Role, WHOQOL, RSA), and significantly lower on measures of clinical symptoms (BDI and Symptom Total Score) and on the CTQ. The FEP group scored significantly higher than the UHR group on RSA Total Score. When compared to the FED group, the FEP group scored significantly higher on the WHOQOL, and significantly lower than both other clinical groups on the measures of depression and functioning. There were no significant differences between the UHR and FED groups on any of these measures.

Table 7.1

Descriptive statistics of the Resilience Scale for Adults and other variables of interest at baseline

	Whole Sample	HCs	UHR	FED	FEP	F	p-value	Bonferroni Post Hoc Comparison	Cohen's D Effect Size
RSA Total Score									
Mean	158.49	184.1	137.26	143.31	148.35	134.094	<0.001*	HC>UHR, p<0.001	1.91
(SD)	(32.53)	(21.11)	(27.55)	(25.41)	(30.5)			HC>FED, p<0.001	1.75
Minimum	71	122	79	71	76			HC>FEP, p<0.001	1.36
Maximum	228	226	210	208	228			FEP>UHR, p=0.002	0.38
GAF									
Mean	64.68	84.62	56.74	56.12	45.68	366.748	<0.001*	HC>UHR, p<0.001	2.46
(SD)	(20.12)	(8.38)	(13.67)	(14.99)	(13.56)			HC>FED, p<0.001	2.35
								HC>FEP, p<0.001	3.45
								UHR>FEP, p<0.001	0.81
								FED>FEP, p<0.001	0.73
GF: Social									
Mean	7.05	8.46	6.54	6.44	5.68	177.408	<0.001*	HC>UHR, p<0.001	1.69
(SD)	(1.69)	(0.99)	(1.27)	(1.32)	(1.54)			HC>FED, p<0.001	1.73
								HC>FEP, p<0.001	2.15
								UHR>FEP, p<0.001	0.61
								FED>FEP, p<0.001	0.53
GF: Role									
Mean	6.86	8.48	6.23	6.19	5.27	190.541	<0.001*	HC>UHR, p<0.001	1.94
(SD)	(1.9)	(0.86)	(1.4)	(1.69)	(1.75)			HC>FED, p<0.001	1.71
								HC>FEP, p<0.001	2.33
								UHR>FEP, p<0.001	0.61
								FED>FEP, p<0.001	0.53

WHOQOL									
Mean	93.15	108.46	82.6	82.38	86.76	182.637	<0.001*	HC>UHR, p<0.001	2.13
(SD)	(17.66)	(11.2)	(13.05)	(14.21)	(14.59)			HC>FED, p<0.001	2.03
								HC>FEP, p<0.001	1.67
								FEP>FED, p=0.032	0.30
BDI									
Mean	16.53	4.25	25.27	25.88	20.7	178.408	<0.001*	UHR>HC, p<0.001	2.16
(SD)	(14.39)	(5.91)	(12.42)	(13.37)	(12.23)			FED>HC, p<0.001	2.09
								FEP>HC, p<0.001	1.71
								UHR>FEP, p=0.012	0.37
								FED>FEP, p=0.002	0.40
Symptom Total Score									
Mean	5.18	1.92	7.2	6.87	7.35	491.387	<0.001*	UHR>HC, p<0.001	3.21
(SD)	(3.04)	(1.62)	(1.67)	(1.55)	(2)			FED>HC, p<0.001	3.12
								FEP>HC, p<0.001	2.98
CTQ									
Mean	37.43	31.31	42	39.99	41.33	40.435	<0.001*	UHR>HC, p<0.001	1.07
(SD)	(12.02)	(6.7)	(12.46)	(14.42)	(11.96)			FED>HC, p<0.001	0.77
								FEP>HC, p<0.001	1.03

*Statistically significant at a level of $p \leq 0.05$. SD= Standard Deviation.

Relationship of the RSA to Other Measures of Wellbeing

As shown in Table 7.2, RSA Total Score was significantly positively correlated with the WHOQOL Total Score in the whole sample and in all individual study groups. The RSA was also significantly negatively correlated with the BDI, CTQ, and Symptom Total Score in the whole sample and in all study groups. There was a significant positive correlation between the RSA and the GAF in the whole sample, and in every individual study group except for FEP. RSA Total Score was significantly positively correlated with GF: Social in the whole sample, and in all three patient groups. The RSA was also significantly positively correlated with the GF: Role in the whole sample, as well as in every individual study group except for FED.

Table 7.2
A table demonstrating the correlation of several indicators of wellbeing with RSA Total at baseline

	Pearson's r p-value				
	Whole Sample	**HCs**	**UHR**	**FED**	**FEP**
GAF	0.54* p<0.001	0.15* p=0.022	0.23* p=0.008	0.28* p=0.001	0.1 p=0.456
GF: Social	0.52* p<0.001	0.12 p=0.077	0.32* p<0.001	0.24* p=0.005	0.27* p=0.001
GF: Role	0.49* p<0.001	0.19* p=0.003	0.19* p=0.029	0.122 p=0.159	0.25* p=0.003
WHOQOL	0.78* p<0.001	0.58* p<0.001	0.68* p<0.001	0.53* p<0.001	0.68* p<0.001
BDI	-0.67* p<0.001	-0.35* p<0.001	-0.53* p<0.001	-0.37* p<0.001	-0.51* p<0.001
Symptom Total Score	-0.68* p<0.001	-0.35* p=0.037	-0.48* p<0.001	-0.38* p<0.001	-0.44* p<0.001
CTQ	-0.48* p<0.001	-0.35* p<0.001	-0.4* p<0.001	-0.27* p=0.002	-0.34* p<0.001

*Statistically significant at a level of $p \leq 0.05$.

Are Baseline Measures of Neurocognition and Psychological Resilience Correlated?

Table 7.3
Correlation coefficients of the neurocognitive domain scores and RSA Total Score in the whole sample

Neurocognitive Domain	**Correlation with RSA Total Score**	
	Pearson's r	**p-value**
Executive Function	0.105	0.007*
Sustained Attention	0.041	0.293
Verbal Learning and Memory	0.129	0.001*
Working Memory	0.063	0.110
Visual Memory	0.116	0.003*
Processing Speed	0.153	<0.001*
Social Cognition	0.081	0.038*
Aberrant Salience	0.032	0.421

*Statistically significant at a level of $p \leq 0.05$.

As illustrated in Table 7.3, executive function, verbal learning & memory, visual memory, and processing speed were significantly positively correlated with baseline RSA Total when the whole sample is considered. As there were significant differences in RSA Total Score between the HCs and all of the "patient" study groups, it is also important to consider the correlations between these variables when these groups are separated. Correlations were also run in the HCs and a composite "patient" study group separately.

Table 7.4
Correlation coefficients of the neurocognitive domain scores and RSA Total Score in the Healthy Control group

Neurocognitive Domain	Correlation with RSA Total Score	
	Pearson's r	**p-value**
Executive Function	0.071	0.272
Sustained Attention	0.097	0.130
Verbal Learning and Memory	0.041	0.524
Working Memory	-0.026	0.683
Visual Memory	-0.029	0.655
Processing Speed	0.020	0.756
Social Cognition	-0.058	0.368
Aberrant Salience	0.044	0.499

As shown in Table 7.4, no neurocognitive domain was significantly correlated with RSA Total score in the HC group.

Table 7.5
Correlation coefficients of the neurocognitive domain scores and RSA Total Score in the "Patient" groups

Neurocognitive Domain	Correlation with RSA Total Score	
	Pearson's r	**p-value**
Executive Function	-0.010	0.847
Sustained Attention	-0.067	0.175
Verbal Learning and Memory	0.003	0.956
Working Memory	-0.021	0.670
Visual Memory	0.012	0.803
Processing Speed	0.024	0.629
Social Cognition	0.085	0.089
Aberrant Salience	0.036	0.473

As demonstrated by Table 7.5, there were also no significant correlations between the neurocognitive domains and RSA Total Score when all of the "patient" groups were

combined. These results suggest that any relationship between neurocognitive domain scores and RSA Total Scores are in fact driven by the significant differences in RSA Total Score between the different study groups, as opposed to a true relationship between the two measures. While a further linear regression analysis was planned, this statistical test is no longer appropriate when no linear relationship exists between the two measures of interest. These results fulfil the null hypothesis for this chapter, and no further analysis was conducted presently.

DISCUSSION

The aim for this chapter was to continue the exploration of neurocognition as a protective factor, using an alternative measure of resilience. As hypothesised, the RSA, a self-report measure of psychological resilience, was significantly positively correlated with scores on measures of wellbeing such as social and role functioning and quality of life, and significantly negatively correlated with measures of psychopathology such as depression. In this sample, scores on the RSA significantly differed between the study groups. RSA Total Score significantly positively correlated with neurocognitive domains of executive function, verbal learning and memory, visual memory, processing speed, and social cognition in the whole sample. However, subsequent analysis which split the sample into patients and HCs revealed no significant correlations between RSA Total Score and the neurocognitive domains in either group. This suggests that these initial significant correlations were driven by study group differences only, as opposed to a true association between the two measures. This finding is in line with the study of Deng et al. (2018), who also identified significant correlations between their neurocognitive measures and their self-report measure of resilience in the whole sample, but not in individual study groups.

When examining the descriptive statistics of mental health and wellbeing measures in this sample, several interesting observations can be made. Self-report scores of the FEP study group of this sample indicate significantly better wellbeing than the two other clinical groups (higher scores than FED on the WHOQOL and lower scores than both groups on the BDI). The FEP group also scored higher than UHR on the WHOQOL, however this difference was only present at a trend level ($p=0.055$). Furthermore, the FEP group scored significantly higher on the RSA, another self-report measure, than the UHR group. However, the FEP group scored significantly lower than the UHR and FED groups on observer-rated measures of functioning such as the GAF and GF: Social and Role. It is possible that these results reflect a lack of insight which can accompany a FEP (David, 1990). If an individual is less aware of the impact that their illness may be having on their life, they may provide higher ratings of their own wellbeing than an external observer. However, similar findings have also emerged from other studies which have not been related to a lack of insight. For example, Herrman, Hawthorne, and Thomas (2002) observed that clinicians provided consistently lower ratings of quality of life than their sample of Australians living with a chronic psychotic disorder. However, they observed significant correlations between the interviewer and patient scores. Further, the patients' scores were more highly correlated with a neutral indicator of wellbeing than the clinician ratings. Thus, they conclude that these discrepancies between interviewer and patient ratings of quality of life may arise from there being areas of the patients' lives that the interviewers do not know about, and find no evidence to reject the self-report ratings of patients (Herrman et al., 2002). This finding is also in line with those of Pruessner, Iyer, Faridi, Joober, and Malla (2011), who examined observed significantly higher levels of perceived stress in their UHR group than in FEP. Furthermore, all of the self-report measures used presently have been validated in previous

psychiatric samples which include individuals with psychotic disorders (Huppert, Smith, & Apfeldorf, 2002; Trompenaars, Masthoff, Van Heck, Hodiamont, & De Vries, 2005). Therefore, taking these results as reflecting valid self-reports of wellbeing, they suggest that QOL is significantly higher in FEP than in the UHR state and in FED.

As such, it is interesting to observe that while FEP is usually considered to be a particularly debilitating illness, individuals with less severe clinical symptoms may actually experience a lower QOL. It is possible that this may relate to the confusion and uncertainty of these types of mental illness. For example, there may not be the same services or opportunities to report these "less severe" symptoms. While patients may experience a long DUP (Drake, Haley, Akhtar, & Lewis, 2000; Norman & Malla, 2001), in some cases it is possible that psychotic symptoms may be more outwardly visible and thus lead to more prompt treatment. Furthermore, in 2016 the NHS of the UK introduced a new target for EI services, stipulating that 50% of FEP cases should have commenced treatment concordant with National Institute for Health and Care Excellence (NICE) guidelines within two weeks of referral. A recent study by Singh, Ghazi, White, Sarfo-Adu, and Carter (2018) identified that, with the help of whole-team interventions to reduce inappropriate referrals, the EI team in North London, UK increased the number of referrals commencing treatment within this two-week target raised from 21% in 2014 to 62% by their final cycle. Findings like these indicate a focus on the prompt treatment of FEP, which, in turn, may lead to a better QOL for the individual. It is possible that services for individuals at UHR, though established and effective in some areas (Broome et al., 2005; Fusar-Poli, Byrne, Badger, Valmaggia, & McGuire, 2013; Phillips et al., 2002; Yung, 2007), do not have the same emphasis on rapid time-to-treatment, leading to a period of uncertainty and confusion for individuals experiencing these symptoms.

In this sample, the RSA was significantly positively correlated with other positive indicators of mental health and wellbeing (such as the GF: Social, GF: Role, WHOQOL), and significantly negatively correlated with negative indicators of mental health (BDI & Symptom Total Score). RSA Total Score was not significantly correlated with GF: Social scores in the HCs, and was not significantly correlated with GF: Role scores in the FED group. The items of the RSA largely focus on factors such as social skills, family cohesion, and personal factors such as optimism. It is possible that the possession of these factors also benefits role functioning in the other study groups, but not in the FED group.

While this analysis appears to support the RSA as a useful measure of resilience, related to improved wellbeing and fewer clinical symptoms, it is important to discuss the use of such self-report measures in relation to the definition of resilience set out in Chapter Two of this thesis. As discussed, the present thesis conceptualises resilience as the *process* by which an individual utilises protective factors, thus leading to more positive outcomes than would otherwise have been expected. Self-report scales, such as the RSA, more accurately measure the amount of psychological and social protective factors that an individual feels they have available to them. While different types of protective factors are likely to interact, it is also possible that an individual may demonstrate resilience in the context of mental illness by possessing or utilising other protective factors, not measured by this scale. Furthermore, self-report resilience scales such as the RSA often conceptualise resilience as a trait, not a process. When completing these scales, participants are often required to identify how they respond to every type of adversity. By conceptualising resilience as a dynamic process, one can acknowledge that an individual may not respond to all instances of risk or adversity in the same manner. Furthermore, not all protective factors will be effective in every circumstance. No significant relationship was identified between

neurocognitive performance and self-reported psychological resilience. While this might be taken to demonstrate that neurocognition is not a protective factor, it is important to remember that this only means that having higher neurocognitive scores is not associated with having more of a different type of protective factor. Furthermore, scores on this scale relate to current protective factors only. Further investigation would be required to discern whether neurocognitive functioning is related to long-term psychological resilience.

There were several interesting findings from the analysis undertaken in this chapter. Firstly, the present findings demonstrate significantly poorer functioning and QOL, as well as more depressive symptoms, in UHR and FED than in FEP. These results underscore the need for intervention at an earlier time point in the illness trajectory. These experiences are clearly associated with significant distress and impairment to functioning and QOL, and may benefit from clearer and timelier pathways to treatment. The present analysis also demonstrated significant correlations between the RSA and other measures of wellbeing. These findings indicate that higher self-reported psychological resilience is associated with better functioning and QOL, and is associated with fewer clinical symptoms. This remained true when considering the whole, transdiagnostic, sample, as well as in the individual study groups. Given these findings, the use of a self-report measure such as the RSA may be a useful strategy for clinicians to identify how equipped the individual feels to address adversity, and may indicate their likelihood of clinical and functional recovery. Present analysis did not identify a significant relationship between neurocognitive performance and psychological resilience in this sample. These results do not signify neurocognition as a protective factor involved in resilience. However, it may be that, as explained in the resilience model of Chapter Three, neurocognition does not support the specific psychological and social protective factors which the RSA assesses. It is possible that

neurocognition may underlie other specific protective factors not captured by the RSA. Alternatively, neurocognition may still be involved in the resilience process instead by filtering, planning, and flexibility. Though it is important to remember the limitations of self-report measures of resilience, these results do show that the RSA is related to baseline wellbeing, functioning, and clinical symptoms. Further study is required to investigate whether these relationships remain true at long-term follow-up.

CHAPTER EIGHT

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DOES NEUROCOGNITION PREDICT THE EXTENT TO WHICH AN INDIVIDUAL FUNCTIONS RESILIENTLY FOLLOWING CHILDHOOD TRAUMA?

INTRODUCTION

Building from the two previous chapters, the goal for the present chapter was to investigate another method of assessing the role of neurocognition in the resilience process. As identified previously, one flaw of the method utilised in Chapter Six was the assumption that HCs are a distinct group which have not experienced any risk factors for mental illness. As such, the strategy used in this chapter built upon that by investigating whether neurocognitive performance might be associated with resilient functioning following exposure to an established risk factor: Childhood trauma. The term "childhood trauma" may refer to a range of adverse experiences, including physical, sexual, or emotional abuse, as well as physical and emotional neglect (Bernstein et al., 2003). However, the term may also be used to refer to broader adversity experienced during childhood such as bullying. Exposure to childhood trauma is well established in the literature as a risk factor for poorer clinical and functional outcomes. A meta-analysis by Varese et al. (2012) synthesised the findings of 36 studies representing 79,397 participants with a psychotic diagnosis. They identified that exposure to trauma was significantly associated with psychosis across all study designs. In the included studies with a case-control design, individuals with psychosis were 2.72 times more likely to have experienced childhood trauma than controls (Varese et al., 2012). Kelleher et al. (2013a) attempted to assess whether there was a causal relationship between childhood trauma and psychotic experiences. In their cohort of 1,112 adolescents there was a significant, bidirectional relationship between childhood trauma and psychotic experiences up to 12 months later. However, their findings suggested causality between the two factors in a number of ways. Firstly, childhood trauma preceded the onset of psychotic symptoms. Next, there was a significant dose-response relationship between the two factors; as exposure to childhood bullying increases, so did the risk of psychotic experiences. Finally,

when trauma exposure ceased, this was also associated with a cessation of psychotic experiences. Although it must be noted that these findings relate to psychotic experiences (as opposed to psychotic diagnoses) in a non-help seeking population of adolescents, this is compelling evidence that childhood trauma may be a significant risk factor for later experience of psychosis (Kelleher et al., 2013a). This relationship was also established in a later meta-analysis of 4,680 participants with psychotic diagnoses, in which exposure to childhood trauma was also significantly associated with the severity of hallucinations and delusions (Bailey et al., 2018). Exposure to childhood trauma has also been associated with a number of other, non-psychotic, mental disorders in adulthood. In a study of 6483 adolescents, McLaughlin et al. (2012) identified that childhood trauma was associated with 28.2% of all onsets of psychiatric disorders. This finding is replicated in a later population study by Copeland et al. (2018). In this study, 30.9% of their sample of 1420 participants had experienced at least one traumatic event by age 16. Each additional instance of trauma exposure was associated with increasing risk for the development of adult psychiatric disorders, across a broad spectrum of anxiety, depressive, and substance-use disorders. Furthermore, This relationship remained even after accounting for other childhood risk factors such as family hardship (Copeland et al., 2018).

Childhood trauma has also been associated with poorer long-term functional outcomes. In the population study by Copeland et al. (2018), trauma exposure also predicted poorer adult functional outcomes including health, illegal behaviours, wealth and/or education, and social function. Two studies of adults with established mental illness have also demonstrated significant associations between the experience of childhood trauma and poorer long-term social (Davidson, Shannon, Mulholland, & Campbell, 2009) and role (Lysaker, Meyer, Evans, Clements, & Marks, 2001) functioning. However, both of these

individual studies had small samples of 31 and 54, respectively. A narrative review of the literature in this area also demonstrated significantly poorer social and role functioning in individuals diagnosed with psychosis, bipolar disorder, and borderline personality disorder, who had also experienced childhood trauma (Cotter, Kaess, & Yung, 2015).

In summary, exposure to childhood trauma confers a significant risk for later development of psychopathology (across a number of mental health diagnoses), and for poorer long-term functioning. As such, in the present analysis, resilience was conceptualised as the extent to which an individual was functioning well following exposure to childhood trauma. The aim of this chapter was to investigate neurocognition as a potential protective factor, by examining whether such performance would predict higher scores on this type of resilience. This approach fits within the conceptualisation of the resilience process as it contains the three components: childhood adversity as the specific risk, neurocognitive performance as the potential protective factor, and functioning as the subsequently improved outcome. In order to build upon the previous investigations in this thesis, this relationship was investigated in the entire sample, including HCs. It was hypothesised that higher scores on neurocognitive tests would be associated with better than expected functioning, given an individual's level of trauma exposure. Based on the findings of Chapter Six in this thesis, it was hypothesised that better visual memory and processing speed in particular would predict this, more resilient, functioning.

METHOD

Participants

The same sample were included in this study as described previously in Chapter Four (page 73-76). Demographics for the sample can be found in Table 5.1 (page 98).

Measures

This study utilised the CTQ, GAF, and the neurocognitive test battery as described in Chapter Four of this thesis (pages 80-85).

Statistical Analysis

Statistical analysis was completed using IBM SPSS Statistics 26 software (IBM Corp, 2019). The data were prepared as detailed in Chapter Four (pages 85-88). The data were checked for the assumptions of multiple linear regression. First, the relationship between childhood trauma (CTQ Total Score) and functioning (GAF Score) was investigated using Pearson's correlation and subsequently linear regression. Informed by previous resilience research (e.g. Booth, Songco, Parsons, & Fox, 2020; Bowes, Maughan, Caspi, Moffitt, & Arseneault, 2010; Collishaw et al., 2016; van Harmelen et al., 2017) the unstandardized residuals were extracted from this regression line as a measure of how well an individual was functioning, compared to how well they would be expected to be functioning given their amount of exposure to childhood trauma. These residuals will henceforth be referred to as resilience to childhood trauma. Next, this study investigated whether neurocognitive performance was associated with these residuals by entering the cognitive domains as independent variables in a multiple linear regression, with resilience to childhood trauma as the dependent variable. Although, as discussed earlier, the cognitive domains could be thought of as representing the single underlying construct of cognition, the domains were checked for multicollinearity, which was not present. When Pearson's correlations between the domains were examined, these were no higher than 0.5, and the Variance Inflation Factor was approximately 1, which has been used to demonstrate that multicollinearity is not present in the independent variables (Mansfield & Helms, 1982).

RESULTS

Relationship Between Childhood Trauma and Baseline Functioning

CTQ Total Score and GAF score were significantly negatively correlated (r=-0.364, p<0.001). Given this linear relationship, a linear regression was then conducted with CTQ as the independent variable, and GAF score as the dependent variable. The model significantly predicted GAF score ($F(1,646)=98.487$, $p<0.001$), with an r^2 of 0.132. Higher CTQ scores were significantly associated with lower GAF scores (B=-0.609, p<0.001). As mentioned previously, the residuals from this regression were then extracted as a measure of resilience to childhood trauma.

Relationship Between Neurocognitive Performance and Resilience to Childhood Trauma

Six of the eight neurocognitive domains were significantly positively correlated with the measure of resilience to childhood trauma: Executive function (r=0.205, p<0.001), sustained attention (r=0.165, p<0.001), verbal learning and memory (r=0.278, p<0.001), working memory (r=0.167, p<0.001), visual memory (r=0.273, p<0.001), and processing speed (r=0.317, p<0.001). These variables were therefore included as predictors in the model. There was no significant correlation between social cognition (r=0.051, p=0.194) or aberrant salience (r=0.068, p<0.083) and resilience to childhood trauma, therefore these domains were not included in the subsequent regression.

Multiple linear regression examined the relationship between the aforementioned cognitive domains and the measure of resilience to childhood trauma. The model significantly predicted resilience score ($F(6,641)=18.753$, $p<0.001$), with an r^2 of 0.149, meaning that the model explained 14.9% of the variance in resilience to childhood trauma. Higher resilience to childhood trauma was significantly associated with verbal learning and memory (B=1.937, p=0.023), visual memory (B=3.024, p<0.001), and processing speed

(B=3.391, p<0.001). Processing speed contributed the most to the prediction of resilience to childhood trauma, with each 1 point increase in GAF score (relative to expected) associated with a 3.391 increase in processing speed performance. Table 8.1 demonstrates the regression coefficients of all cognitive domains in the regression model.

Table 8.1
A table showing the regression coefficients of the multiple linear regression

Variables	**B**	**Beta (β)**	**p-value**	**CI**
Executive Function	0.671	0.033	0.480	-1.194, 2.537
Sustained Attention	0.977	0.054	0.219	-0.583, 2.536
Verbal Learning & Memory	1.937	0.114	0.023*	0.269, 3.605
Working Memory	-1.127	-0.047	0.320	-3.349, 1.096
Visual Memory	3.024	0.181	<0.001*	1.731, 4.317
Processing Speed	3.391	0.189	<0.001*	1.805, 4.977

* Statistically significant at a level of p≤0.05. CI= 95% Confidence intervals for B.

DISCUSSION

In this chapter, resilience was operationalised as the extent to which an individual was functioning well given their level of exposure to childhood trauma. Firstly, this analysis established that there was a significant, negative, relationship between childhood trauma and baseline functioning. Residuals from this regression were then used to demonstrate how much better or worse an individual was functioning than the average level of functioning for their score on a measure of childhood trauma. This approach has been used previously to conceptualise resilience by authors such as van Harmelen et al. (2017), Bowes et al. (2010), Collishaw et al. (2016), and more recently Booth et al. (2020). With regards to resilience research, it is particularly interesting to understand how an individual might be functioning much better than other people are who have had the same level of exposure to childhood trauma. If it is possible to isolate any protective factors that might be at play, these could be

generalised to resilience intervention strategies. In this sample, a model of neurocognitive performance including six cognitive domains significantly predicted this measure of resilience to childhood trauma, and explained 14.9% of the variance in this measure. While this indicates that there are clearly additional factors contributing to the extent to which an individual functions well following trauma exposure, it does suggest that improving neurocognitive performance may have a small but significant effect on this positive outcome. In particular, verbal learning and memory, visual memory, and processing speed were significantly associated with resilience to childhood trauma. These findings are also concordant with previous findings of this thesis in which visual memory and processing speed were significantly different between individuals who were functioning well or poorly in the context of psychopathology. In addition, Wingo et al. (2010) also identified that visual memory was associated with resilience. In their study, they recruited a sample of individuals who had experienced trauma, and defined resilience as the experience of trauma with only mild subsequent depressive or PTSD symptoms. Their resilient group performed significantly better on their visual memory task than the non-resilient group. This finding was not related to the severity of any depressive or PTSD symptoms, and remained after adjusting for sex, ethnicity, and severity of trauma. Indeed, the authors note that an improvement of 4 points in visual memory was associated with a 20% increase in the probability of being in the resilient group given a similar exposure to childhood trauma (Wingo et al., 2010).

These findings are also in line with previous studies which have demonstrated better neurocognitive performance to be related to higher resilience (e.g. Genet & Siemer, 2011; Koenen et al., 2009; Wingo et al., 2010) and better functional outcomes (e.g. Allott et al., 2011; Lin et al., 2011; McIntyre et al., 2013), as presented in previous chapters. Furthermore,

previous studies have also examined the direct relationship between childhood trauma and neurocognition. For example, Vargas et al. (2019) conducted a meta-analysis of studies representing 3315 individuals with psychosis. They identified that childhood trauma was significantly, negatively, related to overall neurocognition, and the individual domain of working memory. These findings were not impacted by moderating variables such as age, gender, premorbid IQ, inclusion of affective psychoses, or chronicity of illness (Vargas et al., 2019). However, this work extends on the previous findings by demonstrating that neurocognitive performance is associated with a measure of the extent to which an individual is functioning well given their level of exposure to childhood trauma.

Childhood trauma was chosen because it is an established risk factor with links to increased risk for the development of mental illness such as psychosis (Kelleher et al., 2013a; Varese et al., 2012), and poorer functional outcomes (Copeland et al., 2018) in this context. However, of course it is important to remember that childhood trauma is not the only factor which affects an individual's subsequent functioning. This analysis only examined the potential of neurocognitive performance as a protective factor against one, specific, risk factor. As the resilience process is dynamic, it is entirely possible that an individual may utilise different protective factors to overcome a different type of risk. It may also be important to recall when interpreting these findings that the verbal learning & memory task was administered differently at the Finnish site of the PRONIA study. Scores on this domain, therefore, had a higher imputation rate than those of the other cognitive domains, and therefore may require more caution in their interpretation.

In summary, and as hypothesised in this chapter, neurocognitive performance significantly predicted the extent to which an individual was functioning well, given their level of exposure to childhood trauma. In particular, visual memory, processing speed, and

perhaps to a lesser extent, verbal learning and memory were significant predictors of this measure of resilience to childhood trauma. This approach had the benefit of including the whole sample, meaning that this measure of resilience to childhood trauma was calculated across the whole spectrum of mental illness, but the findings may differ if a different type of risk was investigated. The efficacy of this approach as compared to previous approaches used in this thesis, as well as an exploration of visual memory and processing speed in particular, will now be expanded in the General Discussion.

CHAPTER NINE

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GENERAL DISCUSSION

The concept of resilience has long held promise for the explanation of varying trajectories of functioning and wellbeing in the context of mental illness. However, progression of the field has been stunted by the lack of a clear definition of resilience, and empirical studies which fit with such a definition. Following an exploration of the definition of resilience, the aim for this thesis was to explore the potential of neurocognition as a protective factor, and to evaluate three different methodologies for doing so.

SUMMARY OF FINDINGS

Following extensive literature review, the thesis established a consensus definition of resilience as the dynamic process by which an individual utilises protective factors to offset the detrimental effects of risk or adversity, thus leading to better clinical and functional outcomes than might have been expected. Moving forwards, there should be a focus on identifying the specific protective factors which might be involved in this process. If empirical research can reliably identify such factors, new intervention strategies could be developed which aim to strengthen protective factors. Such interventions would be useful for individuals experiencing, or at risk for, mental illness, but could also be beneficial as public health interventions. This thesis focused on the potential of neurocognition as a protective factor in the resilience process. There is a wealth of research which demonstrates the negative impact of neurocognitive impairment on an individual's clinical and functional outcomes. However, there is little which considers whether above average neurocognitive performance might offer additional protection against the effects of mental illness. The four main findings of this thesis are as follows:

1. Neurocognitive performance significantly differs in the individuals of this sample with different psychiatric diagnoses. The FEP group of this sample were significantly impaired relative to HCs and FED in executive function, verbal learning & memory,

working memory, visual memory, and processing speed. The FEP group also showed significant impairments relative to the UHR group in all aforementioned domains other than visual memory. The UHR sample were significantly impaired relative to HCs in visual memory and processing speed. Interestingly, the FED group in this sample demonstrated no significant impairments in any domain measured.

2. When resilience was conceptualised as the retention of "good" functioning despite the experience of psychopathology, individuals who were classified as "resilient" did not demonstrate any significant neurocognitive deficits relative to HCs. Scores in this sample were particularly close to those of HCs in visual memory and processing speed. Individuals who were classified as "non-resilient" performed significantly worse than the HC group on executive function, sustained attention, working memory, visual memory, verbal learning & memory, and processing speed. Performance of the non-resilient group was also significantly poorer than the resilient group in the domains of visual memory and processing speed.
3. When a self-report scale of psychological resilience was investigated, higher scores on this measure was associated with fewer psychiatric symptoms, less exposure to childhood trauma, higher functioning, and better quality of life. However, no meaningful relationship emerged between scores on this measure and neurocognitive performance.
4. Finally, neurocognitive performance was significantly associated with the extent to which an individual was functioning well given their level of exposure to childhood trauma. In particular, better verbal learning and memory, visual memory, and processing speed were associated with more resilient functioning following exposure to childhood trauma.

IMPLICATIONS

There are several conclusions which can be drawn from this thesis. Firstly, resilience can be observed in a sample of individuals with varying experience of mental illness. 27.4% of this transdiagnostic sample comprising individuals experiencing UHR, FED, and FEP were rated by interviewers as at least "generally functioning pretty well" at the time of their baseline assessment, despite the presence of clinical symptoms. As the difference in functioning between these groups was not explained by the intensity of clinical symptoms alone, there must be other factors which differentiate the groups; further underscoring the importance of investigations into protective factors. Furthermore, higher psychological resilience (as measured by the RSA) was significantly correlated with higher QOL and functioning, fewer depression symptoms, and fewer total psychiatric symptoms. While these are cross-sectional findings, this is promising evidence that resilience is a field worth investing in.

There is a possible argument that the concept of resilience could also have a stigmatising effect. For example, the concept may give way to the idea that if an individual does develop a mental illness that they are "not resilient", or that they might have been able to control the development of symptoms by being more resilient. Chapter Two was intended to provide useful discussion into the ways that resilience can be conceptualised in order to avoid any stigma related to the concept. Resilience is likely to differ over time and circumstance within any individual, and the conceptualisation of the concept as a process allows for the possibility that anyone could be taught how to better utilise protective factors. Furthermore, this is spread across the whole spectrum of mental disorder; this was not confined to one diagnostic study group. In fact, the highest scores on the RSA were seen in the FEP study group, even higher than the HCs. Resilience is well captured by the study of

Wille et al. (2008). This large German cohort study investigated the influence of risk and protective factors on mental health in 2,863 adolescents. In this study, adolescents with between one and three potential risk factors (such as parental mental illness, family conflict, and low socio-economic status) showed a clear reduction in the prevalence of mental health problems when protective factors (such as personal resources, family resources, and social resources) were also present. Further, the prevalence of mental health problems further decreased with each additional protective factor. However, when adolescents were experiencing four or more risk factors, no such benefit of protective factors was observed (Wille et al., 2008). These results elegantly demonstrate that the presence of protective factors can significantly reduce the probability of developing mental illness in the context of risk factors. However, the study also demonstrates that, if exposed to enough risk factors, anyone is likely to develop psychopathology, no matter how many protective factors they also possess. These results can be used to counter any possible stigmatisation associated with resilience. Firstly, even in the subsample who had low risks but high availability of protective factors, there was still a 7% prevalence of mental disorder. Thus, the development of mental illness is a complex interaction between risk and resilience, and even individuals with many protective factors may still develop clinical symptoms. Secondly, as mentioned, anyone may develop psychopathology if exposed to many risk factors, regardless of how many protective factors they also possess. Research into resilience is important because there is a clear benefit of protective factors, however there should be no shame or stigma associated with the development of mental illness.

The second implication from these findings is that, in these cross-sectional investigations, neurocognition demonstrates some potential as a protective factor. In particular, visual memory and processing speed appear to consistently distinguish between

individuals with better and poorer outcomes. In Chapter Five, these were identified as the largest impairments in the FEP group, and the only significant impairments in the UHR group. However, Chapter Six also observed that these domains are spared in a group displaying resilience, and scores of the resilient group in these domains were almost identical to those of HCs. Finally, in Chapter Eight, visual memory, processing speed, and verbal learning and memory significantly predicted the extent to which an individual was functioning well given their level of exposure to childhood trauma. It is interesting that these domains appeared to be implicated in the resilience process in Chapters Six and Eight, but not when resilience was measured using a self-report scale in Chapter Seven. In the introduction of the thesis, the conceptualisation of resilience as a process was proposed and two potential mechanisms were outlined as to how neurocognition may function within this framework. First, neurocognition may specifically underlie other protective factors (for example cognitive processes such as memory, social cognition, and processing speed supporting social skills). Or second, neurocognition may support a "filtering" process in which an individual considers the best possible approach to deal with the specific risk they are encountering. Given the findings of this thesis, it would appear that cognition does not specifically support other protective factors as there was no meaningful relationship between cognitive performance and higher scores on a scale measuring psychological or social protective factors. Although, it may be possible that neurocognition may be related to other conscious or unconscious protective factors not captured by this self-report scale. However, neurocognitive performance was significantly higher in individuals who demonstrated good functioning in the context of psychopathology, and significantly predicted the extent to which an individual was functioning well given their exposure to childhood trauma. Therefore, it may be more likely that neurocognition supports the resilience process in this

"filtering" stage by allowing for an individual to consider their access to other protective factors, remember strategies which worked previously, and be flexible in their approach.

While a global neurocognitive deficit is often observed in psychosis (Bartholomeusz & Allott, 2012; Fioravanti et al., 2012; Shmukler et al., 2015), impairment in processing speed is usually seen with the largest effect size (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). In addition, several studies have observed that after accounting for processing speed, impairments in other domains are significantly reduced, or disappear completely (Ojeda et al., 2012a; Rodríguez-Sánchez, Crespo-Facorro, González-Blanch, Pérez-Iglesias, & Vázquez-Barquero, 2007). Such processing speed impairment is also observed in individuals at UHR for psychosis (Frommann et al., 2010; Kelleher et al., 2013b; Seidman et al., 2010). Processing speed has also been shown to predict functional outcomes in individuals at UHR (Carrión et al., 2011; Carrión et al., 2013) and with FEP (Bowie et al., 2008; Nuechterlein et al., 2011). In fact, some studies have found processing speed to be the most important predictor of functioning (Ojeda, Peña, Sánchez, Elizagárate, & Ezcurra, 2008) and QOL (Ojeda et al., 2012b) in schizophrenia.

Similarly, visual memory has often been found to be significantly impaired in psychosis (Brodeur, Pelletier, & Lepage, 2008; Seidman, Lanca, Kremen, Faraone, & Tsuang, 2003), UHR (Fusar-Poli et al., 2012; Lencz et al., 2006), and MDD (Hammar & Schmid, 2013; Lee et al., 2012). Visual memory deficits in psychosis have been related to significant differences in organisational strategy, such as planning and segmentation of the visual stimuli as opposed to examining the image as a whole (Kim, Namgoong, & Youn, 2008; Seidman et al., 2003). Training on these strategies has been found to significantly improve the performance of individuals with psychosis on such visual memory tasks (Rempfer, McDowd, & Brown, 2012). While neurocognition often predicts functional

outcomes in psychosis (Allott et al., 2011; Lee et al., 2013b; Torgalsboen et al., 2014) and UHR (Carrión et al., 2011; Carrión et al., 2013; Cotter et al., 2014; Lin et al., 2011), visual memory is rarely isolated as a significant predictor of functioning itself. It is interesting then, that performance on this domain was so similar in the resilient and HC groups of Chapter Six. Bodapati, Jenkins, Sharma, and Rosen (2017) found that visual memory specifically predicted anhedonia in individuals with schizophrenia. Thus, it is possible that any relationship between visual memory and resilience may be mediated by negative symptoms of psychosis. This explanation may have merit in understanding the resilience profiles of the present sample, as each of the patient groups demonstrated significantly higher negative symptom levels than the HC group. Alternatively, visual memory is often considered to be a state-dependent impairment, with such deficits significantly improving following the remission of clinical symptoms (Benoit et al., 2014; Lee et al., 2012). Coupled with evidence that visual memory impairments are significantly larger in individuals at UHR who make a transition to psychosis compared with those who do not (Brewer et al., 2005; Fusar-Poli et al., 2012; Lin et al., 2013a), it is possible that visual memory performance is a marker of illness severity. In a study by Wingo et al. (2010), visual memory significantly differentiated individuals displaying resilience to trauma. The authors suggest that visual memory may function as a proxy for emotional learning and information processing. This may offer an explanation as to how visual memory may support the filtering process described in the introduction of this thesis. If an individual is better equipped to process and remember emotional information, this may support their ability to decide upon the most effective strategy to overcome a given risk.

To a lesser extent, the findings of this thesis suggest that working memory may also be an important consideration for risk and protective factor research. In Chapter Six, working

memory performance was significantly impaired in the non-resilient subgroup, but preserved in the resilient group. However, when examining the group means of Table 6.1, one can observe very similar performance between the two patient groups, suggesting that even very small deviations in working memory performance may be associated with poorer outcomes in the context of psychopathology. Working memory is generally considered to be a limited capacity process by which an individual is able to maintain and manipulate relevant information for a limited period of time (Baddeley, 1992). Meta-analyses of studies investigating working memory performance in schizophrenia have identified significant impairments relative to HCs across a wide range of methodologies (Forbes, Carrick, McIntosh, & Lawrie, 2009; Lee & Park, 2005). Individuals at UHR for psychosis may also demonstrate significant impairments in working memory (Wood et al., 2003), with performance at an intermediate level between HCs and FEP (Goghari et al., 2014). A study by Pflueger, Gschwandtner, Stieglitz, and Riecher-Rössler (2007) identified that while individuals at UHR may be impaired in a number of neurocognitive domains, performance on working memory tasks provides the best method of distinguishing this group from HCs. Working memory deficits may also be a transdiagnostic risk factor. In a sample of 415 eight-twelve year-old children, Huang-Pollock, Shapiro, Galloway-Long, and Weigard (2017) identified that working memory deficits significantly predicted propensity to general psychopathology (the 'p' factor) and externalising disorders (such as Conduct Disorder or Attention-Deficit Hyperactivity Disorder).

There are several mechanisms by which working memory performance may be associated with long-term outcomes in mental illness. Working memory has often been found to be associated with negative symptoms (McGrath, Chapple, & Wright, 2001; Park, Püschel, Sauter, Rentsch, & Hell, 2003; Wood et al., 2003), which in turn mediate the

relationship to functional outcomes (González-Ortega et al., 2013; Lin et al., 2013b). As mentioned, the present patient sample was demonstrating significantly higher negative symptom levels than the HCs. Alternatively, it has been suggested that individuals experiencing, or at-risk for, psychosis have more difficulty with working memory tasks as they do not inhibit resting thoughts such as daydreams or thoughts of the self or others. This has been demonstrated by studies showing that during working memory tasks, individuals at UHR and with psychosis have been shown to demonstrate less suppression of the Default Mode Network (DMN; Fryer et al., 2013; Guerrero-Pedraza et al., 2012; Landin-Romero et al., 2015). The DMN is active during times of wakeful rest, and activity is decreased during demanding tasks (Raichle et al., 2001). Furthermore, an interesting study by Hahn et al. (2012) investigated the control of working memory content in individuals with schizophrenia. They constructed a working memory task in which participants were required to continually update which stimuli held the most importance. In contrast to their hypothesis, the authors observed that their schizophrenia group actually eliminated newly irrelevant information with more accuracy than the HCs. The authors suggest that this finding may indicate that individuals with schizophrenia keep a narrow focus, which may lead to impairment in real-world tasks which require the consideration of multiple options. Although this provides an interesting explanation for the observed relationships between working memory performance and functional outcomes, one must consider that if individuals were not adequately inhibiting resting thoughts, this would likely result in a generalised cognitive deficit, as observed in the FEP group but not the UHR group. As such, it is possible that this theory is only relevant to FEP samples. Further work is required to understand how these neurocognitive domains may influence resilience and functional outcomes in transdiagnostic samples.

These three neurocognitive domains show promise for differentiating between individuals who will experience better and poorer outcomes. However, it cannot be overlooked that, at present, the majority of evidence demonstrates that less deficit in these domains is associated with less functional impairment. One theory which has been proposed to explain such a relationship is that of the cognitive reserve hypothesis (e.g. Barnett, Salmond, Jones, & Sahakian, 2006; Stern, 2002). Both passive and active models of this process have been proposed. Passive cognitive reserve would refer to an individual who has a higher level of cognitive performance to begin with, thus, when challenged with the same risk or level of deficit as another individual, their subsequent level of cognitive functioning will still be higher, and thus perhaps avoid meeting levels of clinical deficit. Active cognitive reserve involves the efficiency of brain processes or the recruitment of alternative brain processes to overcome deficits in another area. In a recent study by Venezia et al. (2018), the authors observed significant neurocognitive deficits in a sample of individuals with MDD. However, deficits in processing speed, executive function, visual memory, and verbal memory were mediated by estimated intelligence. Thus, deficits were significantly less prominent in individuals with higher IQ. Furthermore, cognitive reserve (defined as a combination of premorbid IQ, education/ occupation status, and leisure activities) has been associated with significantly higher socio-economic status, shorter DUP, and better neurocognitive performance in FEP at baseline (Amoretti et al., 2018). The same conceptualisation of cognitive reserve has also been found to predict neurocognitive functioning, as well as clinical and functional outcomes at two-year follow-up (Amoretti et al., 2016). However, in their sample of individuals with FEP, Leeson et al. (2009) reported the importance of baseline, as opposed to premorbid, IQ for clinical and functional outcomes after three years. In this study, the authors observed distinct trajectories of IQ in FEP;

individuals who had chronic low IQ, those who had high IQ which declined, and those with a stable high IQ. Only the stable IQ group had significantly better long-term outcomes. These findings do not support the passive cognitive reserve hypothesis, as even individuals with a high, but declining, IQ demonstrated significantly poorer clinical and functional outcomes. The cognitive reserve hypothesis provides some explanation as to how individuals may display differing levels of neurocognitive deficit in the context of mental illness, and how individuals with higher cognitive reserve, and thus fewer deficits, may experience significantly better functional outcomes. This work possibly suggests that additional cognitive training might confer additional benefit for an individual's long-term outcomes, however, further work is required to understand this relationship. Furthermore, the cognitive reserve hypothesis assumes that higher cognitive capacity is always beneficial. For example, higher IQ might make an individual more able to rationalise the aberrant experiences that occur during the onset of psychotic disorder (Barnett et al., 2006). However, this thesis has conceptualised resilience as a highly dynamic process, therefore when evaluating the cognitive reserve hypothesis, and interpreting the present findings, it is important to remember that specific protective factors may be useful in one context but not in others. For example, a higher IQ might also mean that an individual is more aware of the effects that a trauma or adversity might have on their future. Furthermore, in a study from the Dunedin Birth Cohort, Koenen et al. (2009) observed that higher childhood IQ was associated with significantly lower adult depression and comorbidity, but was also associated with a significantly higher chance of developing adult mania. While neurocognition (particularly processing speed and visual memory in the present sample) may be involved in the resilience process and may be an important target to improve long-term outcomes, it is possible that

these abilities will not be beneficial in every risk or adversity than an individual may encounter.

COMPARISON OF METHODOLOGIES

One of the goals for this thesis was to compare and contrast three different methods of operationalising resilience and empirically testing a new protective factor which may be involved in the resilience process. In Chapter Six, resilience was defined as the retention of good functioning despite the experience of psychopathology. This approach fits with the conceptualisation of resilience as a three-step process, in that the presence of psychiatric symptoms serve as a risk factor for the development for further comorbidities and for poor long term functional outcomes. Thus, any factors which were specific to those individuals retaining good functioning could be considered to be protective factors. One major benefit to this approach is that it highlights the fact that resilience should be considered at all stages of the mental health continuum. Researchers and clinicians should be striving to improve resilience even in individuals who have already experienced an episode of illness. Promoting an individual's ability to deal with future adversities may reduce the risk of relapse and promote better functioning. This approach is also consistent with the "harm reduction" theory of resilience put forward by Davydov et al. (2010), in which mental health deteriorates following exposure to risk or adversity, but ultimately returns to premorbid levels A limitation to this approach is that HCs were considered as a separate group. However, it is entirely possible that such individuals may have experienced a risk for mental illness, but not have developed any psychiatric symptoms. For example, in the study by Wingo et al. (2010) they identified that 45.5% of their sample with previous trauma exposure exhibited no depressive or PTSD symptoms at baseline. Furthermore, in the study by Kelleher et al. (2013a), only 9.5% and 6.9% of adolescents who had been victims of bullying developed

psychotic-like experiences at 3- and 12-month follow-up, respectively. These figures were 13.3% and 12.9%, respectively for those who had experienced physical assault (Kelleher et al., 2013a). Figures from these studies indicate that although risk factors for mental illness, such as trauma, may increase the likelihood of mental illness, there are also a substantial number of individuals who do not develop psychopathology following exposure to this risk. As such, the subsequent data chapters considered the entire, transdiagnostic, sample, including HCs. Chapter Seven investigated whether neurocognition was associated with higher scores on a self-report scale of psychological resilience. The use of self-report scales to measure resilience certainly have their limitations. Firstly, they often only focus on psychological and social protective factors. Secondly, they often conceptualise resilience as a trait, asking individuals how they always approach adversity. Finally, self-report scales such as the RSA often do not account for whether an individual has experienced a specific risk for poor mental health or functioning, thus not fulfilling the first component of our established definition of resilience. Therefore, it is possible that this is a less effective method of empirically investigating new protective factors which may be involved in the resilience process. What the findings from Chapter Seven did show, however, is that higher scores on the RSA were associated with fewer psychiatric symptoms, higher social and role functioning, and higher QOL. Therefore, although limited, this method may prove to be a quick, accessible, and cost-effective method for clinicians to assess an individual's typical response to adversity and direct treatment goals towards improving the protective factors which the individual feels that they might be lacking. These scales could be said to be measuring assets and resources which *other* research has identified as being important for the resilience process. Finally, in Chapter Eight, resilience was conceptualised as the extent to which an individual was functioning well given their level of exposure to childhood

trauma. This approach also has the benefit of fitting clearly within the three-component definition of resilience which was established in the introductory chapters of this thesis. Furthermore, this approach can also encompass HCs who have experienced childhood trauma.

While each of these approaches have their strengths and limitations, one general point of note is that each of these approaches is only relevant for that one, specified, risk factor. Resilience is a dynamic process, and individuals are likely to respond differently to, and utilise different protective factors to overcome, other types of risk of adversity. It is important that resilience researchers are highly specific when reporting their findings.

STRENGTHS AND LIMITATIONS

This thesis provided an investigation into resilience which was both transdiagnostic and across illness stage. Researchers and clinicians are increasingly recognising the importance of transdiagnostic research. Such an approach in the resilience field can inform the identification of factors which may be protective against general psychopathology, as opposed to specific diagnoses. If incorporated into interventions, targeting such factors could be beneficial for the reduction of multiple clinical symptoms. The thesis also attempted to overcome limitations of previous research in which resilience is not clearly defined. Following extensive literature review, a consensus definition of the concept was established and maintained throughout all subsequent data analysis. Finally, the present thesis investigated and evaluated three different methods of researching resilience. Though self-report measures may be used as an effective proxy for the resilience process, such scales often only focus on psychological and social factors, and often conceptualise resilience as a trait, not a process. Using “observable” measures of resilience may help to confirm which protective factors are associated with subsequently improved long-term outcomes.

The findings of this thesis must also be interpreted in the context of the study's limitations. The data utilised is cross-sectional, and therefore any investigations of protective factors can only provide information about participants' functioning, mental health, and wellbeing at one time point. Given the strict study inclusion criteria, this information relates specifically to the time of illness onset. The identification of a reliable protective factor can only be made once the effects of such factors on long-term outcomes has been established. However, longitudinal data collection from this sample is already in place. Future follow-up data will provide the opportunity to evaluate the effect of resilience and protective factors on outcomes up to 18-months after baseline. In addition, the HCs in this study were not only screened for prior psychiatric symptoms, but were also excluded based upon additional factors such as illicit drug use. As such they represent a particularly "healthy" population, and future studies might look to recruit a sample which is more representative of the general population. Further investigation which also includes HCs would allow for more accurate study of resilience across the entire spectrum of mental health.

FUTURE DIRECTIONS

Based upon the findings, strengths, and limitations of the current work, several recommendations for further work in the resilience field can be made. Researchers in this area should continue to conduct empirical studies which continue to isolate protective factors involved in the resilience process. In order to build from the limitations of the present work, these investigations should be longitudinal, and examine the role of protective factors in superseding risk or adversity in all participants, HCs included.

The real benefit for resilience research would ultimately be the development of interventions which attempt to strengthen or improve known resilience factors. It is possible that such interventions could be employed with individuals who are already experiencing,

or at risk for, mental illness, or in the general public as a preventative measure. Thus, when an individual encounters an adversity or challenge to their mental health, they would be better equipped to utilise protective factors available to them, and ultimately experience better outcomes. Such interventions are already being tested, and there have been several promising trials in the general population. At present, these trials are often conducted using school or University student samples. For example, an intervention study by Steinhardt and Dolbier (2008) was designed to reduce stress, teach effective coping strategies, and foster meaningful connections in University students. In this study, the experimental group demonstrated significantly higher post-intervention scores on measures of self-reported resilience, effective coping, and protective factors (optimism, positive affect, self-esteem, and self-leadership), and significantly lower scores on measures of psychopathology than a waitlist control group (Steinhardt & Dolbier, 2008). The same intervention was also associated with significantly increased stress-related growth and, in turn, this growth was associated with higher self-esteem and adaptive coping strategies (Dolbier, Jaggars, & Steinhardt, 2010). The "Resilience and Coping Intervention" has also been investigated in a RCT of university students. This group intervention allows young people to identify shared problems and discuss solutions, thus attempting to improve protective factors such as coping strategies and social connectedness. In this RCT by Houston et al. (2017), the intervention group demonstrated significantly higher levels of hope, and significantly lower levels of stress and depression after three weeks, compared with a control group. However, there was no significant change in self-reported psychological resilience in either group (Houston et al., 2017). Challen, Machin, and Gillham (2014) investigated the effectiveness of a resilience training programme in 2844 UK secondary school children. Their RCT revealed a small significant effect on the reduction of depressive symptoms, though this effect was

not maintained at 1- and 2-year follow-up. However, the authors do note a strong ceiling effect, in that a large proportion of this general population sample reported few to no depressive symptoms at baseline (Challen et al., 2014). Tunariu, Tribe, Frings, and Albery (2017) observed gender differences in the response to a resilience intervention in their sample of school children. Boys demonstrated significantly higher levels of wellbeing, environmental mastery, and tolerance to uncertainty than girls. Girls, however, showed significantly higher appreciation for positive relationships and openness to diversity. Stallard and Buck (2013) also demonstrated that a nine-session resilience intervention was acceptable and feasible to deliver within the UK school curriculum.

Systematic reviews and meta-analyses of resilience intervention studies have also demonstrated that most interventions lead to positive outcomes when compared to control groups (Leppin et al., 2014; Macedo et al., 2014). Dray et al. (2017b) conducted a systematic review of studies with resilience-based interventions in children and adolescents. Their review of 57 such studies revealed that in all trials, resilience interventions significantly improved depressive symptoms, internalising problems, externalising problems, and psychological distress, when compared to a control group. At short-term follow-up, these trials significantly improved depressive and anxiety symptoms, while at long-term follow-up, the identified trials had a significant effect on internalising problems (Dray et al., 2017b). Chmitorz et al. (2018) conducted a fascinating systematic review which evaluated potential issues or inconsistencies within these intervention studies. They identify that just over half of the studies identified actually provided no clear definition of resilience. Furthermore, they noted inconsistencies in the ways that resilience was measured; sometimes using self-report resilience scales and other times using surrogate measures such as wellbeing or stress perception. They also acknowledge that researchers often do not complete sufficient baseline

examination of mental and physical health prior to the intervention in order to clearly demonstrate any intervention effects. Finally, they identify that no study assessed any potential adverse effects of the intervention (Chmitorz et al., 2018). This systematic review provides clear direction for future intervention studies, and reminds us that while these results look promising, there is also significant room for improvement.

It must also be acknowledged that some studies have found no significant benefit of interventions which attempt to strengthen protective factors. For example, a large RCT of a resilience intervention in 2149 Australian adolescent students found no significant effect for any of their measured mental health outcomes (Dray et al., 2017a). Furthermore, in their trial of a web-based resilience trial, Yap et al. (2018) observed a significant post intervention effect on parents' own evaluations of their parenting behaviours, but not on the mood or anxiety symptoms of their adolescent children.

Taken together, the results discussed here would suggest promising effects of interventions which attempt to strengthen protective factors in young people. It must be noted that presently these trials are largely completed in general population samples which may be subject to the "ceiling effects" discussed by Challen et al. (2014). However, these studies suggest that such interventions do benefit young people and allow them to develop strategies which reduce stress or subclinical psychopathology. Moving forwards, it would be interesting to see more studies which trial protective factors in individuals who are already experiencing mental illness, to see whether such interventions may improve important outcomes such as functioning and chances or recovery, or reduce future relapse. It is positive to see that several study protocols have already been registered which will continue the work trialling protective factor interventions to promote recovery in individuals already

experiencing clinical symptoms, or as a preventative measure in general population samples (e.g. Herrero et al., 2018; Thomas et al., 2016; Vella et al., 2018).

As discussed, an important direction for future research will be to plan and trial interventions which address protective factors, thus reducing the negative effect of mental illness on an individual's functioning and wellbeing, or acting as a preventative technique in the general population. Thus far, most trials have focused on strengthening psychological and social factors, which are by far the most researched and validated protective factors. Evidence from the present thesis would provide tentative evidence for cognitive intervention, in that neurocognition significantly differentiated individuals who had retained "good" baseline functioning, and was significantly associated with resilience to childhood trauma. As explored in Chapter Three, a large body of evidence has already begun to examine the effect of Cognitive Remediation Therapy (CRT), demonstrating that cognition is modifiable and thus a potential candidate for protective factor intervention. Overall, the evidence demonstrates that CRT can lead to significant, and sustained, improvement in cognitive performance with small- to moderate- effect sizes. This training can also significantly improve functional and, to a lesser extent, psychiatric outcomes (Kambeitz-Ilankovic et al., 2019; Revell et al., 2015; Wykes et al., 2011).

There are, however, a number of limitations to the field of cognitive training at present. Currently, little is known about the long-term effect of CRT, and the potential long-term effects of other variables such as length of training. Furthermore, at present the CRT literature has mainly focused on the deficits seen in psychosis. Although there have been several promising trials suggesting that CRT can lead to significant improvements in individuals with depression (Bowie et al., 2013; Lee et al., 2013c; Motter et al., 2016; Porter, Bowie, Jordan, & Malhi, 2013) and one systematic review showing promising effects of

CRT for individuals at UHR (Glenthøj, Hjorthøj, Kristensen, Davidson, & Nordentoft, 2017), less is known about the effect of CRT in other, non-psychotic, mental disorders. In the future, there could also be the possibility of personalisation in cognitive training. Not everyone will want or require training in every domain available. The personalisation of training programmes might make the therapy more focused, possibly more effective, and also more engaging for the individual.

Of course, given that most research in this area is focused on remediating the significant cognitive deficits seen in psychosis, there is the possibility that there are ceiling effects to the benefit of cognitive training. However, a number of studies have examined the effects of cognitive training techniques in healthy adults with promising results. For example, Schmiedek, Lövdén, and Lindenberger (2010) conducted a study in which 101 younger (age 20-31) and 103 older (age 65-80) adults completed 100 hours of cognitive training on tests of perceptual speed, working memory, and episodic memory. Their pre- and post- test performance was compared to that of two matched control groups. Baseline cognitive performance indicated that this sample was representative of other general population samples. Upon post-training testing on a new set of tasks, both groups showed significantly better performance than their control group counterparts on at least one test in each previously defined domain (Schmiedek et al., 2010). These results demonstrate that intensive cognitive training can improve performance beyond just the training tasks in both younger and older adults. Moreover, this evidence indicates that cognitive training techniques can be beneficial for individuals who were already demonstrating healthy baseline performance. However, 100 hours is of course a large commitment and may not be viable as a large-scale preventative intervention. A number of systematic reviews and meta-analyses have also demonstrated that cognitive training can significantly improve the

performance of healthy older adults across a range of domains measured such as memory, processing speed, and visuospatial skills (Kelly et al., 2014; Kueider, Parisi, Gross, & Rebok, 2012; Lampit, Hallock, & Valenzuela, 2014).

Overall, these studies of CRT demonstrate that cognition is modifiable. It can be improved (in order to reduce significant deficits) in individuals with psychotic disorders. This reduction in deficit can also lead to improvements in functioning and, less reliably, psychiatric symptoms. However, there is also an emerging body of research which finds that cognition can be significantly improved in individuals who were already demonstrating healthy cognitive functioning. Therefore, it is possible that neurocognition can be improved across the whole spectrum of performance. In line with the continuum theory of neurocognition mentioned by Zammit et al. (2004), it is possible that training not just to reduce deficit, but to provide additional gains in neurocognitive performance might also provide additional benefits for functioning. It would also be interesting, for example, to trial such training in the present FED sample who show no impairments in cognition but do show significantly more clinical symptoms than HCs and significantly poorer functioning and QOL. It is possible that targeting neurocognition as a protective factor and providing additional cognitive training could be used as a strategy to improve functioning in this group, and in individuals with healthy cognitive performance; however, further study is required to confirm this theory.

GENERAL CONCLUSIONS

In conclusion, resilience can be defined as a dynamic process in which the presence and use of protective factors enables an individual to retain more positive outcomes than might be expected following exposure to risk or adversity. Resilience is observable in a transdiagnostic sample of individuals experiencing mental illness, and higher psychological

resilience is associated with better baseline QOL and functioning, and with fewer psychiatric symptoms, and less experience of childhood trauma. Neurocognition is an important consideration in research which examines risk and protective factors for mental illness. It is significantly impaired to varying degrees in psychosis-spectrum disorders. However, it is spared in a transdiagnostic group displaying resilience, and was associated with resilience to childhood trauma. Verbal memory, processing speed, and working memory may be particularly important in distinguishing individuals who will experience better versus poorer outcomes following a risk for, or experience of, mental illness; these domains had the largest effect sizes of impairments in individuals at UHR and with FEP, but these scores were closest to HCs in transdiagnostic resilience group. They were also significant predictors of resilience to childhood trauma. These findings may have implications for the development of prognostic tools, and may be important targets for intervention.

At present, this thesis has provided evidence that less deficit in these domains are associated with less functional impairment. Thus, there is tentative evidence that neurocognition may function as a protective factor which can be drawn upon in the resilience process. It is possible that these factors exist on a continuum of risk to resilience. However, further work should continue to examine these factors across the whole spectrum of mental health (including controls who may have also been exposed to risk factors). Such work would help to confirm whether additional gains in neurocognitive ability adds additional protection. Trials have already demonstrated that neurocognitive ability can be improved, and thus has potential to be included in future protective factor interventions. Such interventions could be used to reduce negative outcomes in individuals already experiencing psychopathology, but could also be expanded as a preventative measure in the general population.

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APPENDIX A

INCLUSION & EXCLUSION CRITERIA FOR THE PRONIA STUDY

A. General Inclusion Criteria

1. Age 15 to 40 years
2. Language skills sufficient for participation
3. Sufficient capacity to consent

Any FALSE → inclusion not possible

B. Recent Onset Psychosis Criteria

a. Inclusion Criteria

1. DSM-IV-TR affective or non-affective Psychotic Episode (life time)
2. Criteria for DSM-IV-TR affective or non-affective Psychotic Episode fulfilled within past 3 months
   (Reference date: screening visit)
3. Onset of Psychosis (i.e. DSM-IV-TR diagnostic criteria for affective or non-affective psychosis fulfilled) within past 24 months
   (Reference date: screening visit)

All TRUE → proceed to B.b.

B.a.1 TRUE, B.a.2 or Ba.3. FALSE → inclusion not possible

B.a.1. FALSE → Proceed to C.

b. Exclusion Criterion

1. Antipsychotic medication longer than 90 days (cumulative number of days) with a daily dose rate at or above minimum dosage in the '1st episode psychosis' range of DGPPN S3 Guidelines.
   Note: 90 days during the past 24 months

TRUE → Exclusion

FALSE → Proceed to E.

C. Clinical High Risk Syndrome Criteria

a. Inclusion Criteria

1. COGDIS

AND/OR

2. Brief Intermittent Psychotic Symptom Psychosis-Risk Syndrome

AND/OR

3. Attenuated Positive Symptom Psychosis-Risk Syndrome

AND/OR

4. Genetic Risk and Deterioration Psychosis-Risk Syndrome

Any TRUE → check C.b.

All FALSE → proceed to D.

b. Exclusion Criteria

1. Antipsychotic medication for > 30 days (cumulative number of days) at or above minimum dosage of the '1st episode psychosis' range of DGPPN S3 Guidelines.
2. Any intake of antipsychotic medication (i.e., independent of duration of intake) within the past 3 months before psychopathological baseline assessments (including self-ratings and screening assessments) at or above minimum dosage of the '1st episode psychosis' range of DGPPN S3 Guidelines.

All FALSE → Proceed to E.

Any TRUE → Exclusion

D. Recent Onset Depression

a. Inclusion Criteria

1. DSM-IV-TR Major Depressive Episode (life time)
2. MDD criteria fulfilled within past three months

   (Reference date: screening visit)
3. Duration of first depressive episode no longer than 24 months

(Reference date: screening visit)

All TRUE → check D.b.

Any FALSE → inclusion not possible

b. EXCLUSION CRITERIA

1. More than one 1 MDD episode (life time)

2. Antipsychotic medication for > 30 days (cumulative number of days) at or above minimum dosage of the '1st episode psychosis' range of DGPPN S3 Guidelines.

3. Any intake of antipsychotic medication (i.e., independent of duration of intake) within the past 3 months before psychopathological baseline assessments (including self-ratings and screening assessments) at or above minimum dosage of the '1st episode psychosis' range of DGPPN S3 Guidelines

4. *All FALSE → Proceed to E.*

Any TRUE → Exclusion

E. GENERAL EXCLUSION CRITERIA

1. IQ below 70
2. Hearing is not sufficient for neuro-cognitive testing
3. Current or past head trauma with loss of consciousness (> 5 minutes)
4. Current or past known neurological disorder of the brain
5. Current of past known somatic disorder potentially affecting the structure or functioning of the brain
6. Current or past alcohol dependency
7. Current polytoxicomania (poly-dependency) or polytoxicomania (poly-dependency) within the past six months
   (Note: any combination with E.6. leads to exclusion)
8. MRI not possible (medical reasons)

Any TRUE → Exclusion

All FALSE → Inclusion according to B./C./D.

DGPPN S3 GUIDELINES

http://www.dgppn.de/fileadmin/user_upload/_medien/download/pdf/kurzversion-leitlinien/s3-praxisleitlinien-bd1-schizophrenie.pdf (accessed December 4th, 2013)

1st Episode

Tabelle 4.1. Empfohlene Dosierung (oral) der Antipsychotika in der Akuttherapie

Substanz	Empfohlene Startdosis (mg/d)	DI [1]	Zieldosis Ersterkrankte (mg/d)	Zieldosis Mehrfach-erkrankte (mg/d)	Höchste empfohlene Dosis (mg/d) [2]
Atypika					
Amisulprid	200	(1)–2	100–300	400–800	1200
Aripiprazol	(10)–15	1	15–(30)	15–30	30
Clozapin [3]	25	2–(4)	100–250	200–450	900
Olanzapin	5–10	1	5–15	5–20	20
Quetiapin	50	2	300-600	400-750	750
Risperidon	2	1–2	1–4	3–6–(10)	16
Ziprasidon	40	2	40–80	80–160	160
Konventionelle Antipsychotika					
Fluphenazin	0,4–10	2–3	2,4–10	10–20	20–(40)
Flupentixol	2–10	1–3	2–10	10–60	60
Haloperidol	1–10	(1)–2	1–4	3–15	100
Perazin	50–150	1–2	100–300	200–600	1000
Perphenazin	4–24	1–3	6–36	12–42	56
Pimozid	1–4	2	1–4	2–12	16
Zotepin	25–50	2–(4)	50–150	75–150	450
Zuclopenthixol	2–50	1–3	2–10	25–50	75

[1] DI (Dosierungsintervall): Empfohlene Verteilung der genannten Gesamtdosis über den Tag – Ein Zeitpunkt = 1, Zwei Zeitpunkte = 2 usw., Höchstdosierungen müssen ggf. auf mehrere Zeitpunkte verteilt werden.

[2] Höchste zugelassene Dosis nach Angaben der Fachinformationen. Insbesondere bei den neueren Antipsychotika werden jedoch auch in der klinischen Praxis oft höhere Dosierungen verwendet („off-label-use") und positive Erfahrungen damit (kasuistisch) berichtet.

[3] Clozapin wird üblicherweise nicht zur Behandlung von Ersterkrankungen eingesetzt.

HEALTHY CONTROL GROUPS

A. GENERAL INCLUSION CRITERIA

1. Age 15 to 40 years
2. Language skills sufficient for participation
3. Sufficient capacity to consent

All TRUE → proceed to E.

Any FALSE → inclusion not possible

B. GENERAL EXCLUSION CRITERIA

1. IQ below 70
2. Hearing is not sufficient for neuro-cognitive testing
3. Current or past DSM-IV-TR Axis-I disorder
   Note: Nicotine dependency is no exclusion criterion!
4. CHR criteria positive (life time)
5. Intake of:
   A. psychopharmacological substances for
   A.a) more than 5 times per year
   A.b) during the past month prior examination

   B. illegal drugs
   B.a) more than 5 times per year
   B.b) during the past month prior examination

   Note: No restriction regarding the intake of nicotine, coffee/caffeine and black tea.
6. Affective or non-affective psychosis or major affective disorder (MDD, Bip. Dis.) of 1° relatives*
   (defined by treatment or diagnosis)
7. Current or past head trauma with loss of consciousness (> 5 minutes)
8. Current or past known neurological disorder of the brain
9. Current of past known somatic disorder potentially affecting the structure or functioning of the brain
10. MRI not possible (medical reasons)

**except any of these disorders is secondary to a medical condition incl. dementia: can be included*

All FALSE → Inclusion

Any TRUE → Exclusion