

April Hargreaves  
Editor

# Schizophrenia

## Triggers and Treatments

Aine Maguire  
Assistant Editor

PSYCHIATRY - THEORY, APPLICATIONS AND TREATMENTS

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**PSYCHIATRY – THEORY, APPLICATIONS AND TREATMENTS**

# **SCHIZOPHRENIA**

## **TRIGGERS AND TREATMENTS**

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**SCHIZOPHRENIA**  
**TRIGGERS AND TREATMENTS**

**APRIL HARGREAVES**  
**AND**  
**AINE MAGUIRE**  
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*To my mother,  
who may not understand the words I write,  
but understands the necessary words to keep me writing.*

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## PREFACE

Schizophrenia is a debilitating illness, with an international prevalence approaching one percent. As such, at any one time, as many as 51 million people worldwide suffer from schizophrenia. It ranks among the top ten causes of disease related disability worldwide (Świtaj et al., 2012), and to date has no known cure. It has, however, been extensively researched since being initially identified by Dr Emile Kraepelin in 1887. We now have a good understanding of what constitutes the illness as is clearly delineated in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5, 2013). Here we see the diverse symptoms associated with the illness divided into three categories: positive symptoms (e.g., hallucinations, delusions, racing thoughts), negative symptoms (e.g., apathy, anhedonia, loss of motivation), and cognitive symptoms (e.g., disorganised thoughts, memory deficits, attention deficits). The introduction section of Chapter 2 of this book discusses in more detail the processes by which we came to our current understanding of the illness.

Despite this progress however, we still do not have a complete understanding of the causes of schizophrenia, or indeed, of the most appropriate treatments for the disorder. In this collection, we will visit some of the most recent research efforts attempting to understand both of these things.

The first three chapters of the book focus on triggers of schizophrenia and the remaining 5 chapters focus on the efficacy of various therapies. Chapter 1 reviews new etiological and therapeutic findings associated with a specific type of schizophrenia – early onset schizophrenia (that which occurs between the ages of 13 and 19). Here we learn about symptomatology and prognosis. We review certain illness triggers (genetics, the environment, neurobiology, and immunology) and gain an understanding of treatments (antipsychotics, electroconvulsive therapy, psychotherapy and psychosocial interventions). Chapters 2 and 3 investigate one of the newer theories in schizophrenia triggers: that of immunology. Chapter 2 takes an in depth look into the role of peripheral cytokine alterations in schizophrenia and the role they play in the somatic comorbidity of the illness. Chapter 3 focuses on a specific cytokine, IL-6, and the role it plays in the cognitive deficits associated with the disorder. Chapters 4, 5 and 6 investigate some of the more recent therapies for schizophrenia, from Integrative Neurocognitive therapy, to Cognitive Remediation therapy to Music therapy. Finally, in chapters 7 and 8, we see the design and implementation of a new therapeutic educational programme in oral health for patients with schizophrenia.

As I collated the 8 chapters of this book, I noticed a common thread weaving its way through each of them; to varying degrees all chapters involved discussions of cognition. My eagle eyed spotting of this thread may be due to my own research endeavours in schizophrenia, which have largely focused on the genetic underpinnings of cognitive deficits in the disorder, and the possible amelioration of such deficits through the use of various therapies (Cognitive remediation, and the administration of oral Co-enzyme Q10). Or it may have been the cognitively focused content of chapters such as chapter 3 (Immune activation and cognition: cognitive changes associated with IL-6 in patients with schizophrenia), chapter 4 (Integrated Neurocognitive Therapy: rehabilitation of patients with schizophrenia) or chapter 5 (Cognitive impairments in patients with schizophrenia in forensic mental health services). Let's face it, my un-honed detective skills were not a pre-requisite for spotting this common theme. But what I found particularly interesting is that, even in chapters which do not overtly purport to be about cognition, we see its presence. We see it in chapter 1 which looks

at early onset schizophrenia, where it discusses the debilitating cognitive deficits seen in these patients from first diagnosis, the influence of the COMT gene on cognition, and the potential treatment of cognitive deficits using oxytocin. We also see it in chapter 2, which identifies an association between inflammation and cognition, particularly in relation to both IL-4 and CRP. We see it in chapter 6 which discusses the cognitive benefits that music therapy offers, such as improved verbal fluency, memory and attention. In this chapter we also visit the case study of Paul, who through the implementation of rap therapy developed a clarity of thought and reduced disorganised thinking. And we see it in chapters 7, where cognitive deficits negatively impact the patients' ability to care effectively for their teeth, and chapter 8, where use of an appropriate cognitive behavioural intervention delivers oral autonomy and increased self-care to the very same patients.

In reality, it should come as no surprise that the subject of cognition appears in each of the chapters of this book. Cognitive dysfunction is a core feature of schizophrenia, predating the onset of psychotic symptoms, and is stable throughout the course of the illness in the majority of patients (Green & Harvey, 2014). As Green and Harvey (2014) declare, 'cognition in schizophrenia provides clues to pathophysiology, treatment and outcome'. In other words, it is a fundamental aspect of both triggers and treatments alike.

Editor

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*Chapter 1*

**EARLY ONSET SCHIZOPHRENIA:  
REVIEW IN THE LIGHT OF NEWER  
ETIOLOGICAL AND THERAPEUTIC FINDINGS**

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**ABSTRACT**

Schizophrenia is one of the most debilitating mental disorders due to the effect it has on the quality of life of the patient. It bears an even bigger burden when the onset of the disease occurs before adulthood because it affects a person whose cognitive, emotional and social development is still under formation. Progress in improving the quality of life of a patient with early-onset schizophrenia has been made along with the evolution of pharmacology and technology but we are far from the optimal state. Due to the complexity of the disorder, progress in treatment has been limited in recent years and reached a seeming plateau. A new level of understanding

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is required to improve therapeutic approaches specifically targeting early-onset schizophrenia. Research in genetics, epigenetics and other molecular processes seem to be the key to greater knowledge and showed some promising results; the impact of genes on vulnerability is becoming clearer, moreover there is greater understanding of the reciprocal effect of genes and the influence of environmental factors on gene expression. Furthermore, evidence is formulated on the effect these recent findings have on measurable neuropsychological results and clinically observed symptomatology. Newer research frames are being formed in mental disorders in general, bypassing the existing traditional classification systems, giving us a more exact picture of underlying pathophysiology and allow us to better understand, diagnose and treat complex disorders like early-onset schizophrenia; however, substantial progress is still required. This article reviews the current understanding and knowledge of early-onset schizophrenia with a focus on newer etiological findings, clinical presentation and a detailed overview of treatment based on literature, guidelines and good clinical practice.

**Keywords:** schizophrenia, early onset, etiology, therapeutic

## INTRODUCTION

Throughout history, the definition of psychotic disorders has been changing according to our understanding of etiological and phenomenological backgrounds of the illness. Defining and understanding early-onset schizophrenia has been especially challenging and has seen substantial changes due to its resemblance to adult-onset schizophrenia on one hand and other developmental disorders on the other. Until the 1970s, the diagnosis was given to children who today would be classified as children with autism spectrum disorder (Hollis & Palaniyappan, 2015). In the early seventies, Kolvin and Rutter set a delimitation between different types of psychosis in childhood and described a connection between schizophrenia that occurs in childhood and the one occurring in adulthood (Hollis & Palaniyappan, 2015). ICD 9 and DSM 3 removed childhood schizophrenia as a separate diagnostic entity and set the same diagnostic criteria for all ages. Nevertheless, the question whether children and adolescents should be diagnosed with schizophrenia remained and has been

dividing clinicians and researchers until the nineties (Hollis & Palaniyappan, 2015). Evidence that the diagnosis is justified is derived from longitudinal research showing relative diagnostic stability and poor prognosis compared to patients with non-schizophrenic psychosis (Hollis, 2000). Moreover, research focusing on brain structures showed similar neurobiological abnormalities in adolescents that are also observed in patients with adult-onset schizophrenia (Hollis & Rapoport, 2011). Current understanding of the illness is that early-onset schizophrenia lies on the same continuum as adult-onset schizophrenia (Hollis & Palaniyappan, 2015); however, we cannot surpass the fact that it has certain features in the sense of symptomatology, differential diagnostics and treatment that are specific to the developmental period of the onset.

## **GENERAL OVERVIEW**

### **Epidemiology**

The life prevalence of schizophrenia is around 1% (Remschmidt & Theisen, 2011), whereas the prevalence of early-onset schizophrenia between the ages 13 and 19 is 0.23% (Remschmidt, 2001; Gilberg, 2000). Before the age of 13, the prevalence is around 1.6-1.9/100.000 (Gilberg, 2000). Before the age of 15, the boy:girl ratio is 3:1 and after that it becomes equal (Remschmidt, 2004).

Based on the age of the onset, two types of schizophrenia in childhood and adolescence are established: Very early-onset schizophrenia with clinical manifestation before the age of 14 and early-onset schizophrenia with clinical manifestation before the age of 19 (Remschmidt & Theisen, 2012). However, the age of onset also varies across studies with definitions for childhood onset schizophrenia before the age of 13 and before the age of 18 for adolescent-onset schizophrenia (Clemmensen, Vernal, & Steinhausen, 2012). Due to easier quotation, early-onset schizophrenia will be used for both types in this review and we will consider the definition by Remschmidt and Theisen (2012).

## **Premorbid Functioning, Prodromal Phase and Ultra-High-Risk State**

Studies have shown that the IQ of children who have been diagnosed with schizophrenia is lower than in general population; 10-20% of children and 1.34% of adolescents who receive a diagnosis of schizophrenia have an IQ below 70 (Remschmidt, 2001). This is considered a premorbid state and not a consequence of schizophrenia, occurring in all age groups (Aylward, Walker, & Bettes, 1984). Abnormalities in psychosocial functioning are present in the majority of youth that develops schizophrenia and even more so when the onset is very early. Common premorbid characteristics are problems with social integration, behavioral problems, learning disabilities, speech language disorders, and developmental delay (Remschmidt & Theisen, 2012). These features are often also characteristic for autism spectrum disorder (Pina-Camacho, Parellada, & Kyriakopoulos, 2016). Moreover, a study by Rapoport and colleagues (2009) indicated that as many as 30-50% of patients with childhood schizophrenia have a preexisting autism spectrum disorder. Differential diagnostics is of importance here since many prodromal symptoms of early-onset schizophrenia can be misdiagnosed as autism spectrum disorder or co-occurrence of both disorders is many times neglected as a possible option (Pina-Camacho, Parellada, & Kyriakopoulos, 2016).

Prodromal phase is the stage of the disease before psychotic symptoms arise. Its symptoms are less specific and usually form gradually. A decrease in functioning, social withdrawal, unusual suspicious and ideas of reference, odd and bizarre behavior, complaints about nonspecific somatic issues are most common characteristics of this period. Since it is very nonspecific, this phase is frequently difficult to recognize, especially in children and adolescents, and often mistaken for other emotional or somatoform disorders. It can be confirmed in retrograde when psychotic symptoms occur (Remschmidt and Theisen, 2012).

The concept of ultra-high-risk state has been formed in the last years with the intention to capture this population and set guidelines for therapeutic interventions. The concept itself is not a diagnostic category but

often used in literature due to its clinical usefulness. It can be found in DSM 5 and is categorically defined as attenuated psychotic syndrome, under a broader category of other schizophrenia spectrum disorders (APA, 2013). Even though the concept is supposed to be valid for adults and children and adolescents, the majority of the studies only included adults. Lately, there has been an increase in studies involving children and adolescents, however they rely on smaller sample sizes and different methodologies than the ones conducted in adults. Moreover, assessment instruments most commonly used have not been appropriately validated for this population, nor have there been any clinical trials about the psychopharmacological treatment, even though this is common clinical practice (Tor et al., 2017).

## **Symptom Characteristics of Early-Onset Schizophrenia and Differential Diagnostics**

Children and adolescents experience a variety of versatile symptoms that are difficult to classify to subtypes indicated in the ICD 10 (Remschmidt & Theisen, 2012). Very early-onset schizophrenia is characterized by a more subtle beginning; patients experience negative symptoms, hallucinations of different modalities and less systemized delusions. Systemized delusions are in general rare before the age of 12 and become more common in adolescence (Remschmidt & Theisen, 2012).

Cognitive symptoms include thought disorganization, dissociation, thought blocking and perseverations. Patients with early onset schizophrenia are more often disorganized than patients with adult-onset schizophrenia; they are more likely to experience thought incoherency, their perception of themselves is less adequate (Hollis & Palaniyappan, 2015). When addressing thought incoherence, one must be mindful of the child's age and premorbid cognitive abilities. In connection to cognitive deficits, speech disorders like logorrhea or deceleration of speech, poverty or absence of speech, perseverations and stereotypies like echolalia or neologisms can be present as well. In such case one must consider the possibility of autism

spectrum disorder, especially when a child is younger than 8 years old (Remschmidt & Theisen, 2012).

David and colleagues (2011) found that children with schizophrenia experience hallucinations very often. Hallucinations are usually auditory (e.g., commentating voices or conversations, they can also occur in the form of noise, laughter or whistling) and were observed in 95% of patients. Visual hallucinations are more common in children under the age of 13 and were identified in 80% of patients. Olfactory hallucinations occur in 30% and kinesthetic in 61% of patients but almost exclusively in patients who also experience visual hallucinations (David et al., 2011). When faced with visual hallucination, intoxication should be ruled out (Remschmidt & Theisen, 2012).

Negative symptoms occur in the form of changed social functioning, flat affect, irritability, fear or suspicion, apathy and anhedonia and omission of activities that the person enjoyed in the past (Remschmidt & Theisen, 2012). Puig and colleagues (2017) compared the occurrence of persistent negative symptoms between early-onset and adult-onset first episode psychosis, reporting almost double higher rates of negative symptoms in early-onset cases, and this was associated with greater cognitive, but not social deficits. Noteworthy, the study was based on a sample of patients of first episode of psychosis, not early-onset schizophrenia specifically.

Motor disorders can be divided into different types; from clumsiness to motor deficits of the body, stupor, and catatonic states. Unusual movements and stereotypies such as finger movements are frequent. The development of compulsive behaviors or rituals with unusual and unexpected movements was reported (Remschmidt & Theisen, 2012). The findings by Mayoral and colleagues (2008) support the neurodevelopmental hypothesis of neurological soft signs in early-onset psychosis. It is presumed that the neurological abnormalities witnessed in schizophrenia could be the result of early impairment in the brain function that is first manifested in the form of motor developmental abnormalities during childhood and later, during adolescence, in the form of neurological soft signs.

When assessing children and adolescents with psychotic and other described symptoms, other diseases with a similar clinical presentation

should be eliminated. When there is no decrease in global functioning and the child is very young, the psychotic symptoms can be benign. If the onset is acute and transient, intoxication with psychoactive drugs or medication should be considered, as well as central nervous system disorders, bipolar disorder (in adolescents), autism spectrum disorder (in children) or a form of another mental disorder (e.g., obsessive-compulsive disorder, post-traumatic stress disorder, borderline personality disorder or other more rare psychiatric illnesses) (Remschmidt & Theisen, 2012; Hollis & Palaniyappan, 2015).

## **Prognosis**

Psychosis as a part of schizophrenia that occurs before the age of 13 was described to usually have a very poor prognosis with a progressive course of the illness through adolescence and adulthood (Remschmidt & Theisen, 2012). It was reported that adolescents who still experienced psychotic symptoms six months after the first episode, had only 15% chance of a full remission. Based on some recent studies, in general the course of the illness was worse and the outcome poorer in early-onset schizophrenia than adult-onset schizophrenia (Remschmidt & Theisen, 2012; Hollis & Palaniyappan, 2015, Fleischhaker et al., 2005; Reichert et al., 2008). Clemmensen and colleagues (2012) systematically reviewed outcomes for patients with early-onset psychosis from 21 previous studies and concluded that outcomes for early-onset group carried poorer prognosis compared to the adult manifestation.

However, in contrast to these findings, a study by Amminger and colleagues (2011), which compared the long-term outcomes in groups with early-onset and adult-onset schizophrenia spectrum disorder, found that individuals with an early onset had significantly fewer positive symptoms and significantly superior functioning on measures assessing global, social/occupational, and community functioning compared to patients with adult-onset disorder. This study investigated long term outcomes of patients, which were diagnosed and treated in the same clinical facility. Some other

studies which compared outcomes in early-onset and adult-onset cases found no significant differences in symptomatology and functioning (Pencer, Addington & Addington, 2005; Schimmelmann et al., 2007).

Since the existing literature shows contradictory findings, further investigation is needed to clarify this dilemma. Nevertheless, the findings of the study by Amminger and colleagues (2011) optimistically suggest that individuals with early-onset schizophrenia may specifically benefit from early intervention and require treatment which includes developmentally orientated, psychosocial, cognitive-behavioral and psychopharmacological interventions adapted to the needs of this group.

Diaz-Caneja et al. (2015) performed a systematic review on longitudinal observational studies assessing correlates and/or predictors of clinical, functional, cognitive, and biological outcomes in early-onset psychoses. The most relevant predictors for worse outcome were shown to be premorbid difficulties and symptom severity (especially negative symptoms at baseline). Other predictors for worse outcome was longer duration of untreated psychosis and lower IQ at baseline, whereas age of onset and sex were not found to be relevant predictors. According to Remschmidt and Thiesen (2012), patients with acute onset, productive symptoms such as delusions and hallucinations, have a more favorable outcome than patients with more subtle, less noticeable symptomatology, and whose cognitive functioning declines more rapidly.

A longitudinal study following patients with early-onset schizophrenia for 42 years showed that the suicide risk in these patients is higher than in those with a later onset (Remschmidt & Thiesen, 2012). The suicide incidence in schizophrenia in general is 4-6%, 20% of the patients try to commit suicide at least once during their lifetime (APA, 2013). Patients with early-onset psychoses which show greater severity of symptoms and have depressive symptoms are at greater risk for suicidal attempts (Diaz-Caneja, 2015).



## **PATHOPHYSIOLOGY AND ETIOLOGY**

### **Genetic Background**

Observations have been made that schizophrenia often runs in families. Heritability of schizophrenia is estimated around 80% (Sullivan, Kendler & Neale, 2003). Monozygotic twins have a 40-50% concordance rate (Gejman, Sanders & Duan, 2010). First research attempts to identify different schizophrenia susceptibility loci showed poor replication, because schizophrenia was found to be a complex, non-Mendelian illness, in contrast to Mendelian illnesses with a single major locus and rare highly penetrant alleles. Association studies, which test the differences in allele frequency between cases (individuals with schizophrenia) and control subjects, have shown to be a better research option (Cariaga–Martinez, Saiz-Ruiz & Alelú-Paz, 2016). They identified numerous candidate genetic variants connected to schizophrenia, highly associated to schizophrenia phenotypes (Mantripragada, Carroll & Williams, 2010). These genes have previously been related to neurotransmitters and neurotransmitter receptors or enzymes, which are a part of processes on neuronal pathways.

A breakthrough in statistics represents the start of GWAS [Genome Wide Association Study], enabled by the Human Genome Project. This was made possible by new technological findings and methods in genetics, such as sequencing techniques of the whole genome and the CNV [copy number variations] detection. GWAS assumes that any region across the genome can be a focus for influencing phenotypic variation (Hirschhorn & Daly, 2005; Wang, et al., 2005; Girard et al., 2011), and represents a powerful alternative to the aforementioned analyses given the possibility to study SNPs [single nucleotide polymorphisms] and CNVs. More than one hundred SNPs and more than fifteen CNVs were detected in numerous GWAS on schizophrenia up to date. An entire researcher confederation, the Psychiatric Genetic Consortium, is actively working on genetic data sharing, meta-analysis, data cleaning and organization from GWAS, leading to an important body of information in schizophrenia genetics (Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011;

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Takahashi et al., 2015; and Rees et al., 2015). To summarize, newer findings show that the genetic input in schizophrenia is either a contribution of smaller changes [polymorphisms of genes] that are common in the population and have a small input, but they accidentally coincide; or a greater contribution in the form of rare larger genetic changes with a higher impact on the phenotype [CNV] (Kotlar, 2015). GWAS studies confirmed what was already observed clinically; that schizophrenia is associated with other mental illnesses, mostly with bipolar disorder, autism spectrum disorder and cognitive impairment (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Addington & Rapaport, 2009; Levy et al., 2012; Kotlar, 2015). Scientific findings now coincide with clinical observation problems as well as diagnostics.

Genetic research focusing specifically on early-onset schizophrenia is rare. The existing data shows that some candidate genes observed in schizophrenia with adult age onset have a bigger penetrance in early onset schizophrenia (Hollis & Palaniyappan, 2015). In NIMHs cohort group 10% of participants had cytogenetic irregularities, 5% among these in the section 22q11, which is a known area connected to schizophrenia and other mental illnesses (Sporn et al., 2004). Cases of early onset schizophrenia show a larger burden of irregularities of CNV regions, especially in those patients who had developmental motor, speech or social inclusion problems (Addington & Rapaport, 2009). Interestingly, there is a significantly higher percentage of irregularities of sex chromosomes than in schizophrenia with adult onset or general population (Addington & Rapaport, 2009; Hollis & Palaniyappan, 2015).

## **Environmental Factors and Epigenetics**

It has been shown that environmental factors also play a crucial role in the incidence of schizophrenia in general. Existing literature most frequently focuses on viral infections of the mother during the pregnancy, as well as malnutrition, obstetric complications, central nervous system damages,

intoxication and exposure to ionic radiation (Nicolson et al., 1999; McGrath & Susser, 2009). Obstetric complications were also specifically connected with cases of early-onset psychosis (Moreno et al., 2009). However, these factors have a lower predictive value than genetic factors (Hollis & Palaniyappan, 2015). More circumstantial and less researched are those influences whose impact on pathophysiology is even less clear and more complex, for example early object relations, upbringing, acute and chronic stressors, nutrition, exposure to substances and materials in the environment etc. As in other complex diseases, in schizophrenia in general multiple deviations of epigenetic mechanisms were observed. These include changes in DNA methylation, histone changes, noncoding RNA modifications and other similar processes.

Several possible mechanisms were proposed to explain the comorbidity between schizophrenia in all age groups and substance use (e.g., Gage & Munafo, 2015; Hartz et al., 2018). First, substance use may lead to the onset of schizophrenia. Second, schizophrenia may cause the development of substance addiction (the self-medication hypothesis), and third, shared underlying risk factors, both environmental and genetic may predispose to schizophrenia and substance use such as is suggested for cannabis (Verweij et al., 2017; Hiemstra et al., 2018).

The risk that the consumption of cannabis poses for the presentation of psychosis, as well as schizophrenia, has long been a research area of interest. Many recent studies showed a positive correlation between cannabis use and the increased risk of psychosis or an earlier onset of psychosis in individuals with genetic vulnerability, especially cannabis use during adolescence (Volkow et al., 2016; Di Forti, 2014), but also vice versa - higher schizophrenia polygenic risk scores in patients who used cannabis prior to illness onset (Hiemstra et al., 2018; Aas et al., 2018).

One of the first confirmed connections between genes and environmental factors was the finding that the COMT genome [polymorphism Val158Met] is connected with the risk of schizophrenic psychosis later in life when the individual consumed cannabis in adolescence (Caspi et al., 2005), also this polymorphism has shown connection with more subclinical psychotic symptoms in young adults with

an at risk mental state for psychosis (Nieman et al., 2016). Recently, the gen AKT1 was linked to the interaction of cannabis and risk for schizophrenia in general (Di Forti et al., 2012).

Other, not yet confirmed areas of epigenetic research encompass the influence of fetal hypoxia and some genes on the volume of hypo-campus (Haukvik et al., 2010), the interaction between obstetric complications and hypoxia-activated genes on the risk for schizophrenia (Nicodemus et al., 2008), the connection between childhood trauma and serotonin transporters (Aas et al., 2012), and the influence of the COMT gene on cognition (Alemany et al., 2013). Epigenetic research holds much potential in the future.

## **Psychological and Social Factors**

To date, several biopsychosocial models have been proposed regarding underlying trajectories of schizophrenia, less often early-onset schizophrenia. With the advancement of genetics and neuroscience, psychiatry adopted a more biological approach where psychosocial factors mostly contribute to a developmental change. The existing literature suggests that there is a clear indication of a gene-environment interaction when it comes to onset, course and outcome of the illness (Bouras, 2017; Misiak et al., 2017; Riglin et al., 2018).

The proposed models focus mostly on the effect of childhood trauma and adverse events on the stress-vulnerability hypothesis, which presents a combination of biological vulnerability, stress and protective factors (Rudnick et al., 2012), and the hypothesis of stress-sensitivity (Haug et al., 2015; Mayo et al., 2017). Studies investigating the role of psychological stress on the onset of psychosis (Tienari et al., 2004; Bebbington et al., 2011; Misiak et al., 2017; Kocsis-Bogár, Mészáros & Perczel-Forintos, 2018) suggest there is a link between dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and psychotic symptoms, with stress as a mediator inducing subcortical dopaminergic activation attributable to HPA axis dysregulation. This dysregulation can be found in the prodromal phase in

patients with an experience of a first psychotic episode (Chaumette et al., 2016). Looking at stress more precisely, it was found that childhood trauma has a more long-lasting effect on the HPA axis, with subsequent stress-sensitivity, compared to trauma in adulthood or recent stressful events (Heim et al., 2008). In addition to the stress hypothesis, childhood trauma has also been found to be associated with sensitization of the mesolimbic dopamine system and concomitant changes in brain structures (Aas et al., 2012). Limitations regarding these findings are that no study so far focused specifically on early-onset schizophrenia and all studies have methodological flaws (Hollis & Palaniyappan, 2015). On the positive side, it has been proven that a safe and supportive environment can be a protective factor for children with a genetic burden of schizophrenia (Tienari et al., 2004). Gonzales-Pinto and colleagues (2011) found that there is lower prevalence of psychosis in subjects who were highly predisposed for psychosis if the family environment was positive, highlighting how important the child's upbringing is, especially if a child has a genetic risk for psychosis.

When looking at impacts of psychosocial factors on the course of early-onset schizophrenia, it was established that individuals coming from poor socioeconomic status do not have a greater chance of an onset but that it contributes to worse effects of the illness on negative symptoms (Gallagher & Jones, 2017). Good communication and coping skills of the individual and the family serve as a protective factor during recovery, whereas deviant family communication skills and emotion expression can worsen acute psychotic episodes and cause more frequent relapses (Hollis & Palaniyappan, 2015).

## **Neurobiological and Developmental View**

### ***Structural Changes on the Brain***

The end of the 1980s brought a discovery that the number of synapses drastically decreases in adolescence, a phenomenon called pruning. Since the symptoms of schizophrenia usually start in adolescence, it was assumed

that the cause of the illness could be pruning (Feinberg, 1982). In the last decade molecular and genetic research showed that complement genes, more exactly their signal path, are involved in the dysfunction of this process. Thus, immune cells and microglia remove synapses that are marked with the complement protein during normal development. Greater expression of C4 complement [most likely genetic and epigenetic influence] has been causally linked to a higher risk for schizophrenia (Johnson & Stevens, 2018). GWAS studies also support the role of C4 complement in the risk for schizophrenia (Sekar et al., 2016; Dhindsa & Golstein, 2016).

Abnormalities can also be seen in the maturing of the prefrontal cortex, which is the part of the cerebral cortex regulating higher cognitive functions such as emotion control, planning, work memory; a process that takes place in late adolescence and early adulthood. This is most likely also linked to synaptic elimination (Keshavan, Anderson & Pettefrew, 1994). Additionally, the process of myelination is changed in patients with schizophrenia in general. This can be seen in autopsy findings, which show a decrease of myelin in the cortex (Matthews, Eastwood & Harrison, 2012). This way a disturbance in myelination and inhibitor influence as a result of too many synapses could cause cognitive deficits (Catts et al., 2013). These findings could be in line with previous research indicating the loss of neuropil (axons, dendrites and glia) and not neurons (Harrison 1999, Matthews, Eastwood & Harrison, 2012).

Evidence that pathological changes are formed in the critical period of adolescence, even before the psychotic symptoms appear, is emerging. The decrease of gray matter was described in many areas of the brain. In individuals with the first psychotic episode mainly decrease in gray matter of the prefrontal, medial temporal and orbitofrontal area of the brain was described in comparison to chronic patients, where a decrease of gray matter in other parts of the brain was noticed as well (Lysaker, 2018). There is considerable evidence that specific nodes within the limbic system are abnormal in children and adolescents with schizophrenia. What is less clear is the time course for emergence of these deficits and the specificity of these abnormalities in children and adolescents with schizophrenia (White et al., 2008). Relative to healthy individuals, patients with early-onset

schizophrenia had significantly lower global sulcal indices in both hemispheres and a lower local sulcal index in the left collateral sulcus (Penttilä et al., 2008). Janssen and colleagues (2008) found that patients with early-onset schizophrenia showed gray matter volume deficits in the left medial and left middle frontal gyrus; bipolar I disorder was related to a gray matter volume deficit in the left medial frontal gyrus, compared to other patients with first episode of psychosis who did not have a diagnosis of early-onset schizophrenia or bipolar disorder after a 1-year follow up.

The study by NIMH following a cohort of patients with early-onset schizophrenia showed many changes in the structure of the brain. Progressive decrease in the volume of gray matter was found in the frontal, temporal and parietal lobe, and ventricular enlargement was also observed. In general, the decrease of the volume of the brain from the back to the front can be observed (Rapaport & Gogtay, 2011; Hollis & Palaniyappan, 2015). Progressive gray matter reduction of comparable magnitude to the early-onset schizophrenia cohort has also been noted in the adolescents with schizophrenia in the first 2 years after onset of the illness (Arango et al., 2012). It seems that not all described changes can be attributed to the onset of psychotic symptoms; some are present even before the onset. This was showed when examining individuals with a high risk for schizophrenia in retrospect, realizing they did not develop schizophrenia (Pantelis et al., 2003; Fusar-Poli et al., 2011).

### ***Changes in Synaptic Transmission and Biochemical Processes***

In this area of research, specific evidence based on early-onset schizophrenia is lacking. There are some recent studies which note changes in biochemical processing in schizophrenia is in general an important factor in pathophysiology of the disease.

Besides gray matter atrophy in the first phases of schizophrenia, an increased activity of the dopamine (Howes et al., 2011) as well as the glutamate system was suggested (Balu et al., 2013). Newer neurobiological models of our understanding of pathophysiological changes also support this. These models include, besides an older model of increased activity of dopamine, the meaning of other neurotransmitters, especially GABA and

glutamate. Human genetics as well as animal studies show a causal relationship between glutamate receptors (NMDA) and schizophrenia (Balu et al., 2013, Timms et al. 2013). Studies performed with MR spectroscopy show lower levels of N-acetyl aspartate and consequently changes in glutamate transmission in patients with schizophrenia. Moreover, the synthesis of neurotransmitter GABA is also decreased (Haller et al., 2014). It is assumed that the change in the regulation of dopamine is responsible for positive symptoms. The change in the complex interaction between GABA signalization and NMDA hypofunction in prefrontal cortex and hippocampus is supposed to be responsible for negative symptoms and cognitive symptoms (Shorter & Miller, 2015). These findings open new possibilities not only for better understanding of the illness but for the treatment as well.

### **Immunological View**

Recent years were marked by a finding that inflammation and oxidative stress could potentially be an important pathophysiological aspect in some cases of schizophrenia. Studies confirmed heightened levels of anti-inflammatory cytokines and other signs of elevated immune activity in individuals with psychosis (Song et al., 2013; Haller et al., 2014; Bergink et al., 2014), or lower antioxidant level (Flatow et al., 2013). In a meta-analysis, Miller and colleagues (2011) also found the connection with increased cytokine levels and schizophrenia, independent of antipsychotic medication; some cytokine levels showed alterations with the clinical state of schizophrenia (elevation with exacerbation), others remained elevated during the course of the disease and antipsychotic treatment. Simsek and colleagues (2016) found significant correlation between interleukin-10 and interleukin-4 with negative symptoms of early-onset schizophrenia. In the systematic review and meta-analysis by Fraguas and colleagues (2017) the association of inflammatory and oxidative markers with clinical, cognitive, and neurobiological outcomes, especially in longitudinal assessments, in patients with early-onset psychosis has been reported.



Clinically, there are cases of encephalitis resulting from an autoimmune response of NMDA receptors with symptoms of psychosis or schizophrenia (Finke et al., 2012; Gable et al., 2017). Antibodies can be directed against other proteins; for example, voltage-gated potassium channels (Zandi et al., 2011). Additionally, epidemiological data shows that there is a connection between psychosis and frequent autoimmune illnesses; individuals with one condition often have a higher risk for the development of the other (Benros et al., 2012).

A strong GWAS study shows a strong connection of schizophrenia and genetic changes in the major histocompatibility complex (MHC) region on chromosome 6, which indicates how important immunology is in pathophysiology (Mokhtari & Lachman, 2016).

Foremost, the importance of this immunological view has been seen also in clinical syndromes with psychotic symptoms and other changes in mental status, such as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), encephalopathy as part of the Hashimoto thyroiditis, systemic lupus erythematosus, phospholipid syndrome and autoimmune encephalitis (Al Hakeem et al., 2016).

## **TREATMENT OF EARLY ONSET SCHIZOPHRENIA**

To minimize the effect the process of the disease has on the child's or adolescent's development and education, the diagnosis and treatment must be quick and decisive. Multiple and prolonged episodes of schizophrenia in all age groups are known to have worse neuropsychological, neurophysiological and structural consequences compared to the first psychotic episode (Harrigan et al., 2003; Compton & Esterberg, 2005; Norman et al., 2007; Ienciu et al., 2010; Franz et al., 2010) and diminish the therapeutic response to conventional forms of treatment (Sheitman & Lieberman, 1998; De Haan, van der Gaag & Wolthaus, 2000; UpToDate, 2018).

## **Prodromal Treatment**

NICE guidelines suggest that psychotherapeutic interventions, such as Cognitive Behavioral therapy and/ or family therapy, should be offered in the time of possible prodrome, and to follow guidelines for treatment of patients with emotional disorders, developing personality disorder or drug abuse. NICE guidelines strictly advise against prescribing antipsychotics to children and adolescents whose symptoms do not meet the criteria for a psychotic episode or schizophrenia (NICE, 2016).

For the treatment of prodrome, a combination with psychosocial interventions and omega-3 fatty acids in the dose 500-1000 mg twice per day is recommended by UpToDate (2018) guidelines. The administration of omega-3 fatty acids is not evidence-based, since a larger study did not confirm the promising expectations a smaller study previously indicated (Amminger et al., 2010; McGorry et al., 2017). However, the guidelines conclude, that the general good effect omega-3 fatty acids have on the central nervous system and the lack of negative side effects make the use sensible in the prodromal phase.

Two naturalistic studies, one prospective and the other retrospective, found that treatment with antidepressants but not with antipsychotic drugs was associated with reduced rates of progression to a psychotic disorder of adolescents with prodromal symptoms or at other states of high risk for schizophrenia (Cornblatt et al., 2007; Fusar-Poli, 2015). Yet, the use of SSRI antidepressants is not included in guidelines as a treatment option for prodrome in early-onset schizophrenia/psychosis.

## **Treatment for First-Episode Psychosis**

The recommended treatment for a newly discovered case of early-onset schizophrenia is pharmacological with atypical antipsychotics in a combination with psychosocial interventions (Remschmidt & Theisen, 2012; McClellan et al., 2013; Hollis & Palaniyappan, 2015; UpToDate, 2018; NICE, 2016). The treatment begins immediately when the diagnosis

is set, the setting or the increase of the dose is slower and more cautious in order to avoid side effects. When increasing the dosage, the response of the symptomology, the somatic and neurological status and if any side effects occur should be thoroughly tracked – from the clinician’s and the patients’ point of view (NICE, 2016).

In recent years, five atypical antipsychotics (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone) have received FDA approval for use in children and adolescents with schizophrenia, four have been approved for pediatric bipolar mania and two for use in autistic youth with significant irritability (Correll, Kratochvil & March, 2011). Another one, lurasidone, gained approval for the use in children and adolescents with schizophrenia and depression within bipolar disorder in 2017 and 2018, respectively.

Three large randomized studies checked for efficacy and safety of typical (classical) antipsychotics in children and adolescents. All found a significant high risk for extrapyramidal side effects and strong sedation (Kumra et al., 2008; Taylor, Paton & Kapur, 2015). In general, the guidelines conclude that prescribing typical antipsychotics should be avoided in this age group (UpToDate, 2018; NICE, 2016).

Randomized clinical trials have shown several atypical antipsychotics (with the exception of ziprasidone) to reduce positive and negative symptoms of schizophrenia in youth in comparison with placebo: olanzapine, aripiprazole, quetiapine, risperidone, lurasidone (UpToDate, 2018).

In several randomized studies, efficacy of these atypical antipsychotics was similar after reviewing the results and the effect sizes. The efficacy of ziprasidone showed to be minor (Pagsberg et al., 2017), in one study even not greater than placebo in treatment of early-onset schizophrenia (Findling et al., 2013), also there were some safety issues regarding its use (mainly the greatest effect on prolongation of QTc interval compared with other atypical antipsychotics), therefore it is not included in the guidelines (Taylor, Paton & Kapur, 2015; UpToDate, 2018).

Studies comparing efficacy of medications for early-onset schizophrenia are limited in numbers and size compared to studies for adult population. Randomized control studies and standardized double meta analyses tested

different antipsychotics and concluded that there is small difference in efficacy between available medications, with the exception of clozapine in resistant early-onset schizophrenia. However, they found significant changes in unwanted side effects (Kumra, Frazier & Jacobsen, 1996; Sikich et al., 2004; McClellan et al., 2007; Kumra et al., 2008; Kumra et al., 2009; and Maloney, Yakutis & Frazier, 2012).

Pagsberg and colleagues (2017) conducted a meta-analysis and compared data from 12 clinical studies. Results captured 2158 adolescents with a diagnosis from the schizophrenic spectrum and compared seven antipsychotics - risperidone, aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, ziprasidone, and a classical antipsychotic molindone. The meta-analysis showed that there are no significant changes in the efficacy, except for ziprasidone, which showed a smaller efficacy. There were no significant changes in cognitive and affective symptoms or social behavior. All antipsychotics were better than placebo, except ziprasidone and asenapine. Most tolerable were aripiprazole and quetiapine, but not absent from side effects.

As noted, atypical antipsychotics are often considered as the preferred treatment and are included in guidelines as first-line treatment for early-onset schizophrenia. However, large adult trials raise questions as to whether atypical antipsychotics truly have superior efficacy than typical antipsychotics. Furthermore, many patients do not maintain the same medication treatment long term, often owing to lack of efficacy, side effects, or noncompliance (McClellan, Stock, & AACAP CQI, 2013).

Side effects, such as weight gain, metabolic disorders, prolactin level changes, extrapyramidal symptoms also occur often with their use, and on average appear more common and more intense in pediatric population compared to adults (Correll, 2008.). Galling and colleagues (2016) also found an increased risk for diabetes mellitus in adolescents treated with antipsychotics compared to healthy controls and psychiatric controls, with the main risk factors being olanzapine treatment and exposure time of treatment.

## **Treatment of Acute Agitation within a Psychotic Episode**

Psychomotor agitation and aggressive behavior are considered to be more common in patients with early-onset schizophrenia/psychosis in comparison to adults, estimated that it occurs in about 25% (Frazier et al., 2007; Nevels et al., 2010). The onset of psychosis in children and adolescents can be acute but organic causes of such state must always be excluded, since this is what usually causes such abrupt onset. In smaller children, it is harder to differentiate whether it is an acute onset of a psychosis or a delirium since the latter commonly includes hallucinations (UpToDate, 2018).

There is a lack of information about intramuscular use of antipsychotics in children and adolescents for quick stabilization of highly agitated or aggressive patients. The recommendation is the use of fast acting benzodiazepine or an antipsychotic. Most recommended is the use of intramuscular lorazepam. When a patient is agitated and cannot be verbally calmed down or redirected, the treating physician must use special protective measures such as physical restraints to ensure the patient's and the staff's safety, and to apply further appropriate medical procedures (UpToDate, 2018).

## **Antipsychotic Polypharmacy**

Toteja et al. (2014) performed a review study reporting the prevalence of antipsychotic polypharmacy in antipsychotic-treated youth. They found a higher prevalence of antipsychotic polypharmacy was correlated with a bipolar disorder or schizophrenia diagnosis and it involved combinations of atypical antipsychotics. However, even in samples predominantly consisting of non-psychotic patients the use of antipsychotic polypharmacy was not uncommon (with the most common diagnoses being ADHD and conduct disorder).

## **Long-Acting Injectable Antipsychotics (LAIs)**

Although long-acting injectable antipsychotics (LAIs), especially atypical LAIs have been approved and are widely used in adults, there is limited evidence for the use of long-acting formulations in children and adolescents. From studies that were concluded on adult patients with first-episode psychosis, several results indicate that atypical LAIs can be an efficient and a safe choice in early stages of the illness and can represent a better prognostic option as oral preparations (Emsley et al., 2013; Lachman, 2014; Kim et al., 2008). Zhornitsky and colleagues (2012) found that LAI antipsychotics were linked to better compliance with therapy, and according to Tiihonen and colleagues (2006), patients on LAI antipsychotics had a significantly lower risk for re-hospitalization compared to patients on oral medications.

Fortea and colleagues (2018) conducted a retrospective study of adolescents treated with different atypical LAIs. No differences were observed between different atypical LAIs. As concluded, they may be a safe treatment option during adolescence in inpatients with psychotic disorders.

Lachman (2014) concludes that LAI antipsychotics could be a potential therapeutic option in those adolescents with worse, persisting symptoms, incompliance and/or comorbid drug use.

## **Treatment of Resistant Form of Early-Onset Schizophrenia**

Clozapine is known as the most efficient antipsychotic for the treatment of schizophrenia, also for early-onset schizophrenia (Kumra, Frazier & Jacobsen. 1996; Shaw et al., 2006; Kumra et al., 2008; Kumra et al., 2009). The use is limited because of possible negative, even life-threatening side effects such as agranulocytosis or epileptic seizures. Because of these possible side effects, the FDA has not officially approved this medication for the use in a pediatric population. Nevertheless, it is a treatment of choice for resistant early onset schizophrenia (McClellan, Stock & AACAP CQI, 2013; NICE, 2016).

Some randomized control studies supported the advantage of clozapine in treatment of positive as well as negative symptoms of early-onset schizophrenia. Kumra and colleagues (2008, 2009) found it is more efficient than haloperidol or high dose olanzapine. A longitudinal comparative study between different antipsychotics that captured long-term treatments for early-onset psychoses with antipsychotics lasting from 3 until 10 years showed clozapine was more efficient than haloperidol, risperidone, and olanzapine in terms of clinical improvement and tolerability as well as long-term functioning (Cianchetti & Ledda, 2011). A retrospective cohort study concluded that treatment with clozapine should in some cases be prescribed sooner; they found positive effects in otherwise poor prognosis of early-onset schizophrenia (Trinczek et al., 2016).

According to guidelines, clozapine should be introduced for treating early-onset schizophrenia when treatment with other two antipsychotics in optimal doses after an optimal time has not been successful (Taylor, Paton & Kapur, 2015; Lurie et al., 2015; NICE, 2016). Clozapine should be introduced slowly and carefully. Before the introduction, levels of leukocytes and neutrophils should be checked and monitored weekly up to 6 months, after that every two weeks for the next 6 months and every 4 weeks after a year the medicine was initially prescribed. Vital signs, EKG, lipidogram, glucose and glycated hemoglobin, waist circumference and body weight should also be measured before prescribing the medicine. If neutropenia occurs, the decision is based on the level of neutropenia. In minor cases, the patient's blood should be checked multiple times a week, and in moderate to severe cases the treatment with this drug is discontinued with a continuation of tracking the patient's blood.

### **Other and Newer Medications for the Treatment of Early Onset Schizophrenia**

Some newer atypical antipsychotics are in the final stages of clinical testing or already received a license by the FDA. Some are already listed for use in the adult population. Iloperidone was licensed in 2009 for the

treatment of schizophrenia. Asenapine has an indication for the treatment of schizophrenia and manic episodes within bipolar disorder in adults. Since 2015, it can be used for manic and mixed episodes in a pediatric population aged 10-17.

In general, newer antipsychotics (Lurasidon, Asenapine, Iloperidone) show lower efficacy than already established atypical antipsychotics in adult schizophrenia (Leucht et al., 2013). A deduction about the efficiency in a pediatric population could be drawn from this meta-analysis. The meta-analysis concluded that the medication should be chosen based on the individual needs of the patient and according to the clinical picture (Leucht et al., 2013).

Findling and colleagues (2015) evaluated the safety and efficacy of asenapine in adolescents with schizophrenia in a randomized, double-blind placebo-controlled trial. After 8-weeks of acute treatment, there was no statistical significance in treatment results, although improvements in PANSS score after 26 weeks of open-label extension on asenapine were numerically greater. Also, no new or unexpected safety concerns were detected in any phase of treatment with asenapine.

Guidelines by the American Academy for Child and Adolescent Psychiatry from 2013 recommend that other medication, which reduce side effects of antipsychotics and improve certain symptoms of the disease, can be used additionally in the treatment of early-onset schizophrenia. They list antiparkinsonians for the treatment of extrapyramidal symptoms, beta-adrenergic blocking agents for the treatment of akathisia, antidepressants for the treatment of depression and negative symptoms, mood stabilizers for emotional instability and aggression, and benzodiazepines for the treatment of anxiety, insomnia, akathisia, and primary treatment of catatonic symptoms. None of these medications has been systematically researched on in early-onset schizophrenia (McClellan & Stock & AACAP CQI, 2013).

Besides the aforementioned, efficiency of oxytocin and N-acetylcysteine is of interest in early-onset schizophrenia (Klein & Bepalov, 2014). Based on numerous effects on the central nervous system, oxytocin theoretically offered results in all areas hindered by schizophrenia, mostly social cognition, learning, memory, and stress response. However, studies



did not give a univocal answer, considering there were no clear guidelines about the optimal length of treatment, dosage, and tests used to measure the effects (Shilling & Feifel, 2016).

A review study done by Sommer and colleagues (2014) compared findings of 26 double blind randomized control studies about the use of anti-inflammatory medications as a possible augmentation in the treatment of schizophrenia in general. Aspirin, estrogens, and N-acetylcysteine showed important positive effects, whereas celecoxib, minocycline, davunetide, and fatty acids did not.

Some recent studies on schizophrenia treatment in general focused on drugs targeting glutamate receptors. There was some data published on glycine transporter inhibitors, with some promising results on negative and cognitive symptoms. Also, there has been some interest in developing allosteric potentiators of metabotropic glutamate receptors. There are currently a large number of glutamatergic compounds in development, with a great deal of excitement about their potential as novel therapeutic agents in schizophrenia (Stone, 2011).

Future development of psychopharmacology will probably focus also on cholinergic and cannabinoid receptors. Moreover, it will most likely go in the direction of personalized methods of treatment based on pharmacogenetics and biomarkers, which will ensure greater success and most importantly, greater safety.

## **Unwanted Side Effects of Treatment of Early Onset Schizophrenia and Its Treatment**

### ***Extrapyramidal Symptoms (EPS)***

EPS most commonly appear when treating with typical antipsychotics. Comparative research shows that it can also appear when treating with atypical antipsychotics, but the risk is significantly lower (McClellan, Stock & AACAP CQI, 2013). EPS is more common in children and adolescents with intellectual disabilities, organic disorders of the central nervous system, and in patients treated with psychopharmacology for the first time

(McClellan, Stock & AACAP CQI, 2013). Dystonia and akathisia appear more often in the initial phases of treatment, but the presence of malignant neuroleptic syndrome must be ruled out. To prevent EPS, antiparkinsonians, especially in a population with dystonia, can be used (McClellan, Stock & AACAP CQI, 2013; NICE, 2016).

### ***Weight Gain***

Weight gain is one of the most important unwanted side effect with atypical antipsychotics (De Hert et al., 2011). Certain mediations represent a higher risk than others. Comparing typical and atypical medications, especially risperidone, clozapine and olanzapine, typical antipsychotics seem to cause significantly less weight gain than the atypical (Masi & Liboni, 2011). No comparison was made between typical antipsychotics and quetiapine, aripiprazole and ziprasidone. Meta-analysis done by De Hert and colleagues (2011) summarized findings of 24 studies, which captured 3000 pediatric patients. They found that ziprasidone causes the least weigh gain, followed by aripiprazole. Quetiapine and risperidone represent moderate risk, olanzapine and clozapine the highest. Negative consequences of weight gain are dyslipidemia, diabetes, increased blood pressure, polycystic ovaries syndrome, and osteoarthritis. The psychosocial consequences, such as social withdrawal, lower self-esteem, incomppliance with therapy, etc. should not be neglected (Lachman, 2014).

### ***Metabolic Syndrome***

Weight gain is the most important factor in metabolic syndrome; the presence of at least three conditions: obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol levels, hypertension and hyperglycemia (Masi & Liboni, 2011). All antipsychotics, and especially olanzapine and clozapine, are connected to increased levels of lipids and glucose (Masi & Liboni, 2011). Moreover, antipsychotics cause abnormalities such as high low-density lipoprotein (LDL), low HDL, and high triglycerides. Changes are not always associated with weight gain; however, they are mostly connected to insulin resistance. Due to the risk of diabetes, which can happen also in the first months after prescribing the

therapy, patients with higher risk should be monitored monthly (Woods et al., 2002). It should be kept in mind that, independent of psychopharmacology, mental disorders increase the risk of metabolic disorders (Susce et al., 2005).

### ***Endocrine Symptoms***

Children, adolescents and adults can, when treated with antipsychotics, develop hyperprolactinemia; however, it seems to be more common in children and adolescents (Woods et al., 2002). This can limit the use of these medications in a pediatric population, where hormonal changes happen in this developmental period itself. Hyperprolactinemia can be caused by typical and atypical antipsychotics, most commonly by haloperidol, olanzapine, ziprasidone, quetiapine, clozapine, and aripiprazole. The latter can even cause a decrease in prolactin (Correll & Carlson, 2006). The greatest effects are amenorrhea, menstrual cycle dysfunction, breast augmentation, galactorrhea [in boys and girls], and sexual dysfunction [low libido, anorgasmia, erectile dysfunction] (Lachman, 2014).

### ***Neuroleptic Malignant Syndrome (NMS)***

NMS is most common in the first weeks after introducing antipsychotics but can occur anytime during the treatment with typical or atypical antipsychotics (Masi & Liboni, 2011). NMS appears in the form of hyperthermia, muscle rigidity, tachycardia, low or high blood pressure, instability of the autonomous nervous system, rhabdomyolysis or disturbance of consciousness. Unrecognized or untreated, it can lead to worse disturbances of consciousness or death. Differential diagnostics can mislead the clinician to think it is catatonia, EPS or infectious disease. NMS can cause heightening of creatine phosphokinase (CPK) or leukocytosis; however, this is not a rule and treatment should not be delayed due to the absence of these signs. Low elevations of CPK can also be present in agitated patients treated intra-muscular or in need of restraints because of muscular metabolism. The risk of NMS is greater with higher doses of antipsychotics, polytherapy, younger age, and male gender. Treatment demands immediate omission of the drug causing the state and intensive medical care. Muscle

relaxants or dopamine agonists, such as bromocriptine can be introduced (Masi & Liboni, 2011; Lally & MacCabe, 2015).

### ***Hematological Unwanted Side Effects***

All antipsychotics can cause a slight leukopenia, which most often does not have a clinical significance. Clozapine is connected to a greater risk for agranulocytosis and requires regular blood checks. This can happen in the first weeks of the treatment but also later (Gerbino-Rosen, Roofeh & Tompkins, 2005). Agranulocytosis and neutropenia occur rarely when treating with other antipsychotics.

### ***Epileptic Seizures***

All antipsychotics can cause certain abnormalities on EEG; however, the risk is greater when treating with clozapine. A review study indicated that epileptogenic spasms are present in 4% of adolescent patients treated with clozapine, and up to 60% had epileptiform EEG changes (Kumra et al., 1997).

### ***Hepatotoxicity***

Hepatotoxicity caused by antipsychotics is connected to higher liver tests and fatty liver, sometimes in connection to weight gain. Baeza et al. (2018) found elevated levels of hepatic enzymes in less than 3 percent of children and adolescents on second-generation antipsychotic treatment in a 1-year follow up. A case study by Kumra and colleagues (1997), described 2 children diagnosed with early-onset psychosis on second-generation antipsychotic medication developed liver damage with liver enzyme abnormalities and confirmatory evidence of hepatic fat infiltration. When off the medication, the fat infiltration of the liver decreased again.

### ***Cardiovascular Unwanted Effects***

Cardiovascular unwanted effects are orthostatic hypotension, elevated heart frequency, and changes in EKG. In children and adolescents, clinically significant deviations are rarely described. The most worrisome is the prolonged QTc interval, due to higher risk of partial arrhythmia. It can be

caused by all antipsychotics, but the risk is greater in treatment with ziprasidone (Taylor and Paton, and Kapur 2015, UpToDate 2018). There are only a few studies with ziprasidone in a pediatric population (Masi & Liboni, 2011). Some rare studies found that aripiprazole does not cause prolonged QTc (AACAP, 2000; McNally et al., 2007; Correll 2008). Cases of elevation of heart frequency were described when treating children with pervasive developmental disorder with risperidone, but without clinical significance (Masi et al., 2003). Before introducing an antipsychotic, EKG should be done as a part of a routine check, but especially in those patients with a known cardiovascular illness. When the QTc is more than 500 ms a change in antipsychotic for aripiprazole should be considered (AACAP, 2000; McNally et al., 2007).

### ***Sedation***

Sedation and sleepiness are common and a very disturbing side effect of antipsychotic. It depends on the dose of the medication; however, some patients develop a tolerance. Studies name aripiprazole as the least sedative, and olanzapine and clozapine as most sedative (Correll, 2008).

## **Electroconvulsive Therapy (ECT) as a Treatment for Early Onset Schizophrenia**

NICE guidelines do not mention ECT as a possible treatment for early-onset schizophrenia. It is mentioned as an alternative treatment in severely ill patients with catatonia, where the state is dangerous for the patient (NICE, 2016).

AACAP guidelines mention ECT as a therapeutic option in severely ill adolescents who are not responding to psychopharmacological treatment or the patients does not tolerate it well (McClellan, Stock & AACAP CQI, 2013; Tharyan & Adams, 2005). The use of ECT in a pediatric population has not been a subject of systematic research (Ghaziuddin et al., 2004). An emphasis is on the clinical evaluation of estimated gain and possible risks

regarding cognitive deficits. Written consent of guardians is needed (McClellan et al., 2013).

## **Psychotherapy Treatment and Psychosocial Interventions**

According to existing NICE (2016) and AACAP guidelines (McClellan, Stock & AACAP CQI, 2013) psychotherapeutic and psychosocial interventions should be introduced from the beginning of treatment together or even before psychopharmacological treatment.

Aim of prevention and early identification programs for high risk youth and those who develop schizophrenia is to promote positive family communication, minimize stigma and secondary trauma and to encourage optimism for the future while providing treatment for comorbid conditions and prodromal symptoms (McCarthy & Goldmark, 2018). Psychotherapeutic approaches have an important role already in the prodromal phases with cognitive behavior therapy (CBT) as most recommended (Morrison et al., 2004).

During the course of the illness, individual supportive treatment is of tremendous importance together with psychoeducation of the patient and the family about the disease and treatment options, problems they might face and the possibilities for solving these problems.

CBT, cognitive remediation therapy (CRT), supportive family counseling, social skills training, art and music therapy together with more specialized interventions based on the patient's deficits (cognitive deficits, resocialization, work therapy, relaxation, etc.) are recommended. Consisted with the results in adult-onset samples, Puig and colleagues (2014) showed that CRT delivers significant as well as reliable cognitive improvements, especially in verbal and working memory, and executive functions. Moreover, they found functional gains such as improvements in daily-living skills and global functioning after treatment in adolescents with early-onset schizophrenia.

There is a great emphasis on teaching the patients strategies how to help themselves when distressed and how to cope with different problems and challenges (e.g., problem focused learning with examples, skills learning). A study by Calvo and colleagues (2015) showed that when we empower the adolescent and the family and teach them how to cope and adjust to stressful situations early in the treatment, this can result in less visits to the emergency department. It is essential that the patient receives help in all areas that are crucial for the quality of life, such as health, education and employment, social inclusion and personal development (Remschmidt & Theisen, 2012, McClellan, Stock & AACAP CQI, 2013; Hollis & Palaniyappan, 2015; NICE, 2016). CRT can also help with the parent's self-perceived burden (Puig et al., 2014), which should not be ignored.

Studies on long-term longitudinal outcome with psychosocial interventions focusing specifically on early-onset schizophrenia are extremely rare; literature is also scarce when looking into long-term outcomes of antipsychotic use with a combination with psychosocial interventions for this population (Cornblatt et al., 2015). The conclusion by reviewing the existing literature is that when there is a combination of early onset, history of developmental delays, poor premorbid functioning and greater symptom severity, the outcome for individuals is usually poor (Bearden et al., 2011).

Moreover, the presence of trauma in patients with early-onset schizophrenia works by the principle of cumulative adversity causing less favorable clinical and functional outcomes (Haug et al., 2015). However, as mentioned before, the study by Amminger and colleagues (2011) challenged this established believe. They suggest that early detection programs and specialized treatments have more effect in improving long-term functional outcomes in people with early-onset schizophrenia than those with a later onset.

The future should strive in the direction of ensuring a cooperation between the patient, his family and their mental health specialists, which could be achieved by psychoeducation and supportive services for the whole family throughout the process of early identification, treatment and recovery.

## CONCLUSION

Early-onset schizophrenia with childhood onset is very rare. There is, however, a remarkable increase in schizophrenia during adolescence. Age and developmental stage seem to influence symptomatology. The presence of less specific prodromal symptoms can be demonstrated in child and adolescent schizophrenia before the first clinical manifestation of psychotic symptoms. Worse course and outcome were thought to be connected to younger age of onset, although current research presents controversial findings, with some evidence supporting better prognosis or no difference at all.

The patients' premorbid personality also seems to be of importance. Moreover, common premorbid characteristics are problems with social integration, behavioral problems, learning disabilities, speech language disorders, and developmental delay. Differential diagnostics is of importance, since these difficulties are also common in other diagnoses, such as autism spectrum disorders, moreover, co-occurrence of more disorders is possible. Differential diagnostics should cover intoxication and neurological disorders, and especially in adolescence, other psychiatric diagnoses such as bipolar disorder, personality disorders and other.

From the epidemiological view, research on genetics of early-onset schizophrenia supports a bigger penetrance of some candidate genes for schizophrenia, more irregularities of CNV regions, and more frequent changes in sex chromosomes. Some environmental factors could also be important in the pathophysiology; however, they seem to have a lower predictive value than genetic factors. Gene-environment interactions are supported by evidence in adult-onset and early-onset schizophrenia, some of most researched examples is the elevated risk of disease with use of cannabis in genetically vulnerable individuals.

Regarding treatment of possible prodrome, psychosocial interventions such as CBT and family therapy, along with the use of omega-3 fatty acid supplements, are recommended. For early-onset schizophrenia, atypical antipsychotics in conjunction with psychosocial interventions are considered first-line therapy. There is some growing clinical evidence



supporting the use of atypical long-acting injectable antipsychotics in early-onset schizophrenia. In cases of therapy resistance, treatment with clozapine is advised in clinical guidelines. Some new psychopharmacological options are being evaluated, but further research is needed. Guidelines suggest that medication should be chosen based on the individual needs of the patient and according to the clinical picture.

The burden of side-effects of antipsychotic therapy in children and adolescents seems even bigger in comparison to adults; therefore, careful choice of medication, regular clinical evaluation and blood screens should be performed and doses should be optimized throughout treatment to minimize the risk and intensity of side-effects. If needed, additional medication should be applied based on current guidelines.

Future development of psychopharmacology will probably go in the direction of personalized methods of treatment based on pharmacogenetics and biomarkers, which will ensure greater success and most importantly, greater safety.

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*Chapter 2*

**PERIPHERAL CYTOKINE ALTERATIONS  
THROUGH SCHIZOPHRENIA CONTINUANCE  
AND IN SOMATIC COMORBIDITY**

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**ABSTRACT**

The similar underlying immunological patterns that were observed in some somatic states and mental disorders, maybe due to the same immune disturbance in early childhood. Further, it is well known that somatic disease could be followed by behavioral changes, and vice versa, that the mental disorders could lead to somatic dysfunction, considering that the possible mutual interactions could be immune mediated. These processes are not exclusive for the central nervous system, but rather are systemic, and they justify the usefulness of peripheral biomarker measurement for early recognition, establishing the correlation between diverse clinical

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symptom presentation and development of new therapeutic protocols in mental disorders.

In the previous decade our research group has focused in exploring cytokine networks in psychosis, considering first episode psychosis, early schizophrenia and schizophrenia in remission. It is possible that the serum increase of interleukin (IL)-4 that we measured in psychotic episode induces regulatory T cells, increases Transforming Growth Factor-beta (TGF- $\beta$ ) levels and suppresses IL-17 production. Further, elevated sera levels of IL-23 were found regardless of the phase and applied therapy and may induce Th2 cell differentiation. These results implicate that the type-17 immune response is blunted in early phase illness, and Th1/Th2 balance is shifted toward Th2 in psychotic patients, which remains relatively persistent during disease. The predominance of type-2 immune response also seen in asthma confirmed the results presented in epidemiological studies about cooccurrence of asthma and schizophrenia and could give an additional explanation for previously postulated localized inflammation of small brain vessels in schizophrenia. TGF- $\beta$  immunosuppressive activity at the periphery counteracts or limits this ongoing pro-inflammatory process and downregulates chronic inflammation. The fluctuation of IL-6 level in the natural history of schizophrenia could explain the etiopathogenesis of schizophrenia, but also the decrease of IL-6 following antipsychotic therapy could be a predisposing factor for the development of obesity and obesity-related metabolic disorders in schizophrenia.

New signaling pathways of innate immunity that are involved in neuroinflammation at the same time could explain the cardiometabolic changes in schizophrenia. Galectin-3 (Gal-3) sera levels were elevated in remission and IL-33 and its soluble receptor (sST2) levels were elevated in acute phase. The positive correlation of IL-33 with positive symptoms in remission suggests its potential role in underlying mechanisms of psychosis onset and sST2 could have neutralizing properties in the context of excessive IL-33 secretion and also in amelioration of negative symptoms. Also, schizophrenia relapse characterized by an increase in IL-33 may be a facilitating factor leading to more frequent occurrence of breast carcinoma in female schizophrenia patients.

New Genome Wide Association Studies and meta-analyses of cytokines in schizophrenia have also emphasized the role of immune molecules in schizophrenia. The thorough and integrative analysis of cytokines interplay through schizophrenia continuance is still lacking. The summarized understanding of specific peripheral and central cytokine production could reveal new possibilities for schizophrenia treatment and prevention of somatic comorbidity.

**Keywords:** first episode psychosis, schizophrenia, cytokines, somatic comorbidity



## INTRODUCTION

In 1869 Emil Krepelin first classified most of the mental disorders into two groups: in the first, mental disorders that predominantly occur during adolescence, are chronic and lead progressively to dementia (lat. *dementia praecox*), and the second group of psychoses that do not lead to dementia (lat. *psychosis maniaco-depressiva*) (Fischer & Carpenter, 2009). Bleuler introduced in 1911 the name of schizophrenia (lat. *schizein* – to split, *phrenos* – soul), emphasizing the importance of dissociation of various psychological functions, observed in a patient with schizophrenia (Ashok et al., 2012). Krepelin believed in a unique `morbogenic process` in the basis of this disorder, while Bleuler believed that schizophrenia is actually a group of diseases with a similar clinical presentation (Keller et al., 2011).

In the mid-twentieth century, the nuclear model of schizophrenia highlights the significance of `pathognomonic` symptoms, incorporating Lagfelt's definition of real schizophrenia with poor prognosis and Schneider's first-line symptoms (Carpenter, 2011; Keller et al., 2011). The psychopathology of the disturbed ego boundaries and the distortion of reality are designated as nuclear properties, rather than the hitherto emphasized hypobulia and dissociative pathology.

The positive-negative distinctions in schizophrenia were firstly considered by Jackson or Reynolds (Berrios et al., 1985), then discussed by Strauss and Crow (Strauss et al., 1974; Crow, 1985), revised by Andreasen and colleagues (1995) and eventually Kay (1990) defined four dimensions of schizophrenia: positive, negative, excitation and depressiveness. Fifth-dimensional concept was presented by Stahl (1999) and included not only positive and negative symptoms, but also cognitive, aggressive/impulsive and anxiety/depressive symptoms. Kanchanatawan and colleagues (2018) have recently reported that schizophrenia phenomenology consists of two symptom dimensions that are strongly correlated:

- a) Psychotic, Hostility, Excitation, Mannerism and Negative symptoms (PHEMN),
- b) Depressive, Anxiety and Psycho-Somatic symptoms (DAPS).

Different perceptions of schizophrenia syndrome and the inconsistency of diagnostic criteria lead to misunderstandings among clinicians and researchers in assessing this disorder (Lewis et al., 2009). The question of setting the subject of schizophrenia in modern neurosciences followed two directions (Möller, 2009; Carpenter, 2011):

- a) Identification of more homogeneous entities of disorder within the framework of schizophrenia syndrome (categorical approach);
- b) Decomposition of schizophrenia syndrome into pathological domains (dimensional approach).

In The International Classification of Diseases (ICD-11) the term 'primary' suggested that the core features are psychotic processes, Schneiderian first-rank symptoms have now been de-emphasized and subtypes of schizophrenia have been eliminated because it was shown that they are not useful in treatment selection (Reed et al., 2019). So, now the set of dimensional descriptors has been introduced in ICD-11: positive symptoms (delusions, hallucinations, disorganized thinking and behaviour, experiences of passivity and control); negative symptoms (constricted, blunted or flat affect, alogia or paucity of speech, avolition, anhedonia); depressive mood symptoms; manic mood symptoms; psychomotor symptoms (psychomotor agitation, psychomotor retardation, catatonic symptoms); and cognitive symptoms (particularly deficits in speed of processing, attention/concentration, orientation, judgment, abstraction, verbal or visual learning, and working memory). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) considers a conceptual psychosis continuum, eliminates the classic subtypes and is focused on dimensions of psychopathology (Tan and van Os, 2014).

Many ethological factors of schizophrenic disorder are known, although etiopathogenetic mechanisms of illness are not still elucidated completely. At today's level of knowledge, we can say that schizophrenia is most likely multifactor-induced, i.e., factors of biological, psychological and social nature participate in its occurrence and manifestation. The up-to-date knowledge about schizophrenia pathogenesis tries to integrate all known

bio-psycho-social models. Individual and specific interaction of these factors is not only characteristic of the process of developing schizophrenia, but also of the clinical symptomatology nature and the prognosis of schizophrenia. The phenomenological uniqueness of each patient with schizophrenia determines precisely the complexity of influences; their overlapping nature and their greater or lesser expression in 1) certain stages of mental disorder, 2) certain stages of individual life and 3) biological periods of the patient.

In a wide range of possible factors, the role of the immune system at the onset and development of schizophrenia was shown to be significant (Yolken & Torrey, 1995; Müller et al., 2000, Cazzullo et al., 2003). Numerous findings support the hypothesis that schizophrenia is caused by a combination of genetic and epigenetic factors (Ikezu & Gendelman, 2008). The idea of `two hits` (Maynard et al., 2001) directed the studies that explore cytokines in two possible directions: the effects of cytokines in the development of the central nervous system and the acute effects of cytokine administration on the generation of psychotic symptoms. Evidence of reciprocal communication between the immune and nervous system and the alteration of the immune response in patients with schizophrenia support the `cytokine hypothesis` of schizophrenia (Reale et al., 2011), by which changes in cytokine cascades have the role in the pathophysiology of this disease as well (Watanabe et al., 2010).

The concept of `early adult illness programming` refers to the possible impact on prenatal and early postnatal development, which can lead to permanent changes in emotional and behavioral functions (Bale et al., 2010). Cytokines are important not only for behavioral changes during acute disorders, but can also cause long-lasting behavioral changes (Bilbo & Schwarz, 2009), i.e., early infections can cause a corresponding immune response with adaptive or maladaptive consequences for later behavior of a person. Studies have also shown that the molecular basis of schizophrenia changes from an early stage to a chronic form, along with evidence of the progressive nature of the schizophrenic process (Monji et al., 2012). A short-term disorder was associated with transcription, metal binding, RiboNucleic Acid (RNA) and vesicular transport, while long-term disease was associated

with inflammation, response to stimuli and immune functions (Narayan et al., 2008).

Ongoing research in the field of psychoneuroimmunology is justified by both clinical applicability and potential in development of new therapeutical protocols (Pariante, 2015). It is now obvious that emotions and behavior are guided by or could induce inflammatory changes (Bergink et al., 2014). But, there are still persisting prejudices about the validity of the peripheral immune biomarker measurements in mental disorders, maybe predominantly because of the argument that the central nervous system is an immune privileged site and that the events and interactions at the periphery could not reflect changes in the central nervous system. The recent discovery of functional lymphatic vessels that are lining the dural sinuses and could transfer immune cells through cerebrospinal fluid into deep cervical nodes has fundamentally changed the previous concept (Louveau et al., 2015; Louveau et al., 2017) and suggested a dynamic interaction between the central nervous system and peripheral immune system that regulates the activity of immune cells in the central nervous system (Negi & Das, 2017). The brain has been shown to coordinate signals of innate immune response with acquired immune response (Kim et al., 2015). Bidirectional influences of the brain-gut axis have also been observed: changes of microbiota have an impact on behavior and different mental states could provoke microbiota changes (Kanji et al., 2018).

The challenge is to establish biological markers, which at the preclinical stage can identify people at risk of getting sick and improving strategies for early therapeutic interventions (Oertel-Knöchel et al., 2011). At today's level of research related to mental disorders, the establishment of any biological constants is a significant step in the objectification of the methodology. The impossibility of the exact monitoring of biological parameters in the cerebrospinal fluid, and also in relation to the applied medication, is compensated in some way by the use of indirect methods. Monitoring of cytokine concentration in peripheral blood is a convenient and accessible alternative for exploring and could mirror the changes in the central nervous system.

## **CYTOKINES AS IMMUNE MEDIATORS AND NEUROTRANSMITTERS**

Cytokines are a diverse group of proteins and can be considered as hormones of the immune system. These small molecules are secreted from different cells, and can act as signals between cells, in physiological and pathological conditions (Kronfol & Remick, 2000).

Cytokines are also mediators of communication between neural elements in all aspects of the development of the nervous system, including cell proliferation, migration, differentiation and programmed cell death (Bilbo & Schwarz, 2009). In animal models of the adult brain, cytokines have been shown to play an important role in neuroplasticity, that is, the capacity of the brain to change, which is a prerequisite for learning and memory processes (Purves et al., 2004). In brain damage, cytokines coordinate the response of neuroimmune elements, including astrocytes and microglial cells. Their additional role, with the primary coordination of immune function, is mediation in communication between the peripheral immune system and the central and peripheral nervous system (Ikezu & Gendelman, 2008).

Cytokines can pass selectively through the blood-brain barrier from the blood and bind to receptors on neurons and glia in the brain (Yarlagadda et al., 2010). Cytokines do not always have to reach the brain, but can also be synthesized in the central nervous system. For example, the glial cells produce interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), Transforming Necrosis Factor-alpha (TGF- $\alpha$ ) and interleukin-12 (IL-12) (Gladkevich et al., 2004). Although most cytokines in the brain are secreted by glial cells, some studies suggest that under certain conditions neurons can also produce cytokines (Breder et al., 1988; Freidin et al., 1992). Many cytokine receptors are localized in the central nervous system, such as IL-4, IL-6 receptors, interleukin-10 (IL-10), TNF- $\alpha$  and interferon-gamma (IFN- $\gamma$ ) (Gladkevich et al., 2004). The existence of cytokine receptors on neurons indicates that cytokines have a direct effect on neuronal function.

Of particular interest in the research world is the possibility that immune mechanisms influence neuroplasticity, and consequently behavioral changes (Bilbo & Schwarz, 2009). Due to an infection, injury, acute or chronic stress, the delicate physiological balance between immune and neural processes is disturbed. In conditions of damaged brain homeostasis, nerve hyperexcitability, hormonal changes, reduced production of neurotrophic factors and suppression of neurogenesis are observed, resulting in a negative influence on the plasticity of the brain (Yirmiya & Goshen, 2011). Neurotrophic factors can be mediators of beneficial immune effects on neural plasticity (Yirmiya & Goshen, 2011). Neurotrophic factors such as Brain Derived Neurotrophic Factor (BDNF), neurotrophic growth factor and vascular endothelial growth factor regulate various forms of nerve plasticity, during development and in adults (McAllister et al., 1999). It is important that several types of immune cells can secrete these factors (Elkabes et al., 1996; Nakajima et al., 2001), especially after exposing cells to different cytokines, including IL-1, IL-6 and TNF- $\alpha$  (Gadient et al., 1990; Schulte-Herbruggen et al., 2005). We have reviewed (Minic Janicijevic et al., 2018) that the impact of pro-inflammatory cytokines on neurogenesis depends also on their interactions with neurotrophic factors, such as BDNF. Cytokines could inhibit, but also stimulate BDNF expression, and vice versa, BDNF could have an impact on cytokine secretion.

The relationship between cytokine levels and behavior, changes in body temperature, and neuroendocrine activity was considered, taking into account that all these functions are regulated by the central nervous system (Quan & Herkenham, 2002). Studies have shown that cytokines can activate the axis of the pituitary-hypothalamus-adrenal gland (Berkenbosch et al., 1987; Besedovsky and del Rey, 1987; Sapolsky et al., 1987), cause fever (Duff & Durum, 1983), prolong slow sleep (Krueger et al., 1984) and reduce food intake (McCarthy et al., 1986) or water intake (Chance & Fischer, 1991). In this context, IL-1 is most tested, although other cytokines may produce some of the above effects, e.g., TNF- $\alpha$  (Kapas et al., 1992; Kapas and Krueger, 1992), IFN- $\gamma$  (Dinarello et al., 1984; Kimura et al., 1994), IL-6 (LeMay et al., 1990), Macrophage Inflammatory Protein (MIP-1)

(Davatelis et al., 1989), IL-12 (Atkins et al., 1997) and IL-2 (Ribeiro et al., 1993).

In healthy subjects the involvement of inflammation in physiological neurotransmission and brain development was examined and an association between inflammation and cognition was found (McAfoose, 2009; Boulanger, 2009). It is still not clear whether inflammation could precede or is a consequence of cognitive impairment (Manu et al., 2014). Acute systemic inflammation can induce cognitive changes (Harrison et al., 2014; Kullmann et al., 2014; Szabo et al., 2014), but also epileptic neurological activity increases the release of IL-1 $\beta$  (Librizzi et al., 2012).

## **CYTOKINES REPRESENTING DIFFERENT TYPES OF IMMUNE RESPONSES**

The focus of our research group was to explore cytokine networks in psychotic disorders, but not exclusively in the context of division into pro-inflammatory cytokines (which enhance the immune response in order to accelerate the elimination of pathogens and release of inflammation) and anti-inflammatory cytokines (which suppress the immune response). Dichotomous division is rather simple and in many studies attempts have been made to determine the prevalence of proinflammatory or anti-inflammatory (immunosuppressive) cytokines (a review given in Miller et al., 2011). The division of cytokines by types of immune responses more adequately reflects the complexity of possible interactions within the cytokine network, which is why the current interpretation of the etiopathogenesis of schizophrenia disorder is adopted by this concept (Meyer et al., 2011).

Th lymphocytes direct the function of other immune cells to cytokine secretion. In relation to the secreting cytokines, the activated Th cells can be subdivided into Th1, Th2 and Th17 cells (Korn et al., 2007). Macrophages, NK, Natural Killer T cells (NKT cells) and Dendritic Cells (DCs) can also secrete cytokines. It is more appropriate to label the immune response with

type-1, type-2 or type-17, with the distinction criterion being a specific cytokine profile.

Cytokines of the type-1 (IFN- $\gamma$ , TNF- $\alpha$ , IL-2, IL-12, IL-18) activate macrophages and mediate in the destruction of intracellular pathogens or in autoimmunity. Type-2 cytokines (IL-4, IL-5, IL-9, IL-10, IL-13) activate B cells and participate in a humoral immune response, including the production of antibodies against extracellular pathogens (Müller & Schwarz, 2010). The type-17 immune response characteristic is interleukin-17 (IL-17), a potent mediator of the inflammatory response in autoimmune diseases (Tzartos et al., 2008; Steinman, 2007). It has been shown that this cytokine plays a key role in acute inflammation, in which neutrophils dominate (Miossec et al., 2009). Recent findings suggest that the type-17 immune response, as a negative regulator, has the effect of interleukin 27 (IL-27), produced mainly by DCs and monocyte macrophages (Korn et al., 2007; Yoshida et al., 2009). Regulatory T cells (Treg) and IL-6, TGF- $\beta$  and IL-27, have an important role in controlling the immune response, and decreased activity of these cells increases the likelihood of developing autoimmune diseases (Cools et al., 2007).

A member of IL-1 family, IL-33 has been extensively explored in neuroinflammation (Dinarello, 2009), together with its receptor ST2. ST2 has both a transmembrane full-length form (ST2L) and soluble form (sST2), which attenuates the systemic effects of IL-33 (Mueller & Jaffe, 2015). It has not been resolved yet what kind of immune cells first initiate IL-33 production (Lu et al., 2015). It is interesting that animal studies suggest it has an important role in neurodevelopment, even in the absence of an inflammatory response (Wicher et al., 2013).

Additionally, in the context of innate immunity mediators it is important to mention that Galectin-3 (Gal-3) is the most studied member of galectin family (Funasaka et al., 2014). Gal-3 can be a) found in different cells types, b) expressed in various parts of the cell, c) secreted into the extracellular matrix in diverse tissues and circulation (reviewed by Radosavljevic et al., 2016) and d) involved in processes initiated after neuronal damage and neuroinflammation (Lalancette-Hébert et al., 2012; Yip et al., 2017).



## **CYTOKINE PROFILES OF PSYCHOTIC PATIENTS PRIOR TO THE USE OF ANTIPSYCHOTICS**

Research on animal models has shown that TNF- $\alpha$  suppresses neurogenesis processes and directs the differentiation of neural circulatory cells into astrocytes rather than in the direction of neurons (Yirmiya et al., 2011). It has been shown that TNF- $\alpha$  has adverse effects on memory processes, but when the homeostasis of the brain is disturbed, TNF- $\alpha$  may have a protective role (Yirmiya et al., 2011). Our findings point to lower levels of TNF- $\alpha$  in psychotic patients compared to healthy controls (Borovcanin et al., 2012). Also, we did not find differences in serum levels of cytokine type-1 IFN- $\gamma$ , between patients and control subjects. According to previous results, cytokine type-1 TNF- $\alpha$  was associated with the severity of symptoms of schizophrenia (Kronfol et al., 2000). Misiak et al. (2018) in their systemic review assessed cytokines and cognitive impairment in bipolar disorder and schizophrenia and reported correlation for TNF- $\alpha$  and cognitive performance. Studies have shown different results in relation to serum concentrations of TNF- $\alpha$  in patients with schizophrenia (Kim et al., 2004). Contrary to our findings, several studies have shown elevated serum levels of proinflammatory cytokine TNF- $\alpha$  in schizophrenia and the first psychotic episode (O'Brien et al., 2008; Meyer, 2011). Other authors did not find a difference between the serum concentrations of TNF- $\alpha$  in sera of patients with schizophrenia in stable antipsychotic therapy and those in acute exacerbation that were not medically treated compared to healthy control subjects (Schmitt et al., 2005; Potvin et al., 2008; Reale et al., 2008; Kunz et al., 2011). However, genetic findings may be able to support our results. Gene expression of TNF- $\alpha$  was significantly reduced in patients with schizophrenia versus controls (Reale et al., 2008), which is in line with the blunted type-1 immune response in schizophrenia (Freudenreich et al., 2010). As very low values of this cytokine are obtained, further monitoring in a significantly larger sample is necessary, with the use of more sensitive tests.

In the group of psychotic patients, we observed significantly higher levels of type-2 cytokine IL-4, compared to the control group (Borovcanin et al., 2012). In accordance with our findings, Miler and associates (Müller & Schwarz, 2010) have suggested the Th1/Th2 disbalance and predominance of Th2 response with schizophrenia. It has also been shown that IL-4, as a key type-2 cytokine, has increased in the cerebrospinal fluid of patients with juvenile form of schizophrenia (Mittleman et al., 1997). However, in several studies, lower levels of type-2 cytokines (Cazzullo et al., 2002; Kim et al., 2004) were shown, while others did not determine the difference in type-2 immune responses between schizophrenia patients and healthy subjects (Rothermundt et al., 1998).

Animal models have shown that IL-4 production actively influences alternative activation of microglia and macrophage in the central nervous system (Ponomarev et al., 2007). We also found high serum levels of IL-4 in patients with schizophrenia in relapse, compared to patients in the first psychotic episode. The results can be analyzed depending on the phase of this chronic mental disorder and as a result of the previous application of antipsychotic therapy.

In patients with schizophrenia social cognitive dysfunction is recognized as one of the predictors of social and community functioning (Couture et al., 2006; Irani et al., 2012; Fett et al., 2011.). Interestingly, it has also been associated with activation of an innate immune response (Glaser et al., 2005; Dickerson et al., 2004). Chronic social stress could shift the polarity of the adaptive immune response to promote the anti-inflammatory Th2 cytokine response (Glaser et al., 2001), also seen in schizophrenia (Miller et al., 2001). Patients diagnosed with schizophrenia display deficits in domains of social functioning, such as Theory of Mind (ToM) and Emotion Perception (EP). ToM and EP scores showed to be correlated with IL-4 levels even before the appearance of full-blown symptomatology and independently of general cognitive functioning (Ntouros et al., 2018). Ntouros and colleagues consequently suggested prophylactic role of IL-4 with respect to cognition and especially EP in chronic schizophrenia patients.

By investigating the cognition-inflammation relationship in schizophrenia the authors suggested a negative association between high sensitivity C- Reactive Protein (CRP) and cognition (Ribeiro-Santos et al., 2014), positive correlation between IL-2 and non-verbal intelligence (Asevedo et al., 2014), increased sera levels of soluble Tumor Necrosis Factor Receptor 1 (sTNF-R1) and IL-1 Receptor antagonist (IL-1Ra) were negatively associated with general cognitive abilities across schizophrenia and bipolar disorder patients and healthy controls (Hope et al., 2015) and findings of robust correlations between elevated IL-1-beta messenger RNA (IL-1 $\beta$  mRNA) levels, lower verbal fluency scores and reduced Broca's area volumes were presented (Fillman et al., 2016). The positive correlation of BDNF and both levels of IL-2 and IL-8 was established, low BDNF and TNF- $\alpha$  levels were associated with Positive and Negative Syndrome Scale (PANSS) cognitive factor with an impact of antipsychotic medications (Zhang et al., 2016).

There was a significantly positive correlation of IL-2 levels with the PANSS cognitive factor and its negative correlation with positive symptoms (Tan et al., 2015). IL-18 was positively associated with the visuospatial/constructural domain of cognitive deficits in first-episode drug naïve patients (Zhang et al., 2013) and the immediate and delayed memory indexes in schizophrenia (Wu et al., 2016). The anti-inflammatory cytokine IL-10 was associated with self-referential ToM bias in the delusional cohort and serves as a useful biomarker for distinguishing delusional patients from both non-delusional patients and healthy controls (Dunne et al., 2017). Kindler and colleagues (2019) proposed the model for kynurenin pathway dysregulation in schizophrenia, considering induction through inflammatory mechanisms, with brain volume loss and attention impairment via extensive glutamatergic blockade.

The discovery of the type-17 immune response also resulted in a revision of the Th1/Th2 paradigm in schizophrenia. While type-1 and type-2 cytokines antagonize each other in the expression of their response, type-1 and type-17 cytokines have no opposing roles (Chabaud et al., 1999). It has been shown that type-1 cytokine IFN- $\gamma$  induces a type-17 immune

response (Chabaud et al., 1999). Our findings confirmed this and showed reduced levels of cytokine TNF- $\alpha$  and IL-17 in a group of psychotic patients.

Our results showed parallel increasing of IL-4 and TGF- $\beta$  levels in a group of psychotic patients. It has previously been shown that IL-4 can down-regulate the production of IL-17 (Harrington et al., 2005; Park et al., 2005), even when the level of IFN- $\gamma$  is unchanged (Lubberts et al., 1999; Lubberts et al., 2000).

The mechanism underlying IL-4 mediated suppression of IL-17 is still unknown. It is possible that IL-4 induces regulatory T cells, resulting in an increase in TGF- $\beta$  levels and suppression of IL-17 production (Sarkar et al., 2007). Alternatively, IL-4 can block the costimulatory, molecular-mediated production of IL-17, downregulation of receptor or ligand expression or their function (Sarkar et al., 2007).

It has been shown that IL-27 negatively affects the development of Th17 cells (Yoshida, 2009). Despite the fact that we found lower IL-17 levels in the serum of patients with schizophrenia, we did not discern differences in serum IL-27 levels between the pre-treated treatment groups.

In addition to the above findings, that type-1 and type-17 responses were blunted and type-2 overweighted in schizophrenia, our results also suggest an anti-inflammatory response through the production of TGF- $\beta$  regulatory cytokine. Concentrations of TGF- $\beta$  in the serum of psychotic patients are elevated.

We also found elevated levels of TGF- $\beta$  in both groups relative to healthy ones. TGF- $\beta$  has been included in the group of immunosuppressive cytokines since it inhibits the activation and differentiation of T cells (Gorelik & Flavell, 2002). Literature data also indicate that serum levels of TGF- $\beta$  were significantly elevated in patients with schizophrenia in relapse and in the first psychotic reaction, compared to the control group of subjects (Miller et al., 2011; Meyer, 2011).

Activated microglia seems to positively affect the secretion of anti-inflammatory and neuroprotective cytokine TGF- $\beta$  and neurogenesis (Yirmiya & Goshen, 2011). TGF- $\beta$  signal pathways may be hyperactive in schizophrenia within neuroprotective mechanisms (Kalkman, 2009).

Functioning on TGF- $\beta$  signaling pathways to new psychopharmaceuticals can enable the re-establishment of synaptic transmission in many neuropsychiatric disorders (Krieglstein et al., 2011). We highlighted the possible role of TGF- $\beta$  as biomarkers and showed that elevated levels of TGF- $\beta$  increase the risk of psychosis (reviewed in Borovcanin et al., 2016). According to our findings, TGF- $\beta$  can be a useful biomarker in schizophrenia (Borovcanin et al., 2012).

The major source of TGF- $\beta$  are regulatory T cells, and it has been observed that patients with schizophrenia have a higher proportion of anti-inflammatory regulatory T cells and IL-4 productive lymphocytes (Drexhage et al., 2011). Regulatory T cells suppress pro-inflammatory response, producing immunosuppressive IL-10 and TGF- $\beta$  (Levings et al., 2002; Taylor et al., 2006). It has recently been shown that IL-6, in combination with TGF- $\beta$ , inhibits the formation of regulatory T cells and induces the formation of Th17 cells (Bettelli et al., 2006; Veldhoen et al., 2006; Mangan et al., 2006). We did not find significant differences in serum IL-6 levels among observed groups.

In our study, the IL-17/TGF- $\beta$  ratio was significantly lower in a group of patients with first psychotic episode than healthy participants. The lower coefficient of IL-17/TGF- $\beta$  can be explained by directing the naive T cells towards the regulatory, rather than the Th17 cells. We must point out that this hypothesis has its limitations, since these cells are not the only source of these cytokines. We did not establish a statistically significant correlation between serum cytokine levels and total PANSS score and subscores. Our results showed a poor negative correlation between the IFN- $\gamma$ /TGF- $\beta$  ratio of psychotic patients and the subscale of negative symptomatology, the subscale of general psychopathology and the overall PANSS score. It is indirectly possible to conclude that an increase in the IFN- $\gamma$ /TGF- $\beta$  coefficient causes the lower scores in the subscale of negative and general psychopathology.

In our study, we showed that during the first psychotic episode and in chronic schizophrenia, the type-1 and type-17 relapse responses were reduced and the type-2 responses were increased.

The finding of anti-inflammatory or immunosuppressive activity, by increasing systemic production of TGF- $\beta$  in schizophrenia, can be explained as a reaction to inflammation or an attempt to limit the proinflammatory process and prevent the development of chronic inflammation.

In the literature searched, we did not find data on reduced serum levels of IL-17 and decrease in the rate of IL-17/ TGF- $\beta$  in psychotic patients, which suggests new possibilities for understanding the pathophysiology of schizophrenia prior to the application of antipsychotic therapy.

Results of our studies suggested that Th1/Th2 balance is shifted toward Th2 in patients with psychosis. Serum levels of IL-4, as type-2 key cytokine, were higher in psychotic patients, in comparison to a control group in our sample. We have also measured increased systemic production of TGF- $\beta$  and decreased IL-17 serum levels in psychotic episode. It seems that TGF- $\beta$  signaling could be involved in CNS injury and aberrant synaptic transmission restoring, and we have shown that TGF- $\beta$  could be a valuable marker for psychosis.

Further, it is possible that decreased levels of IL-17 are a consequence of increased levels of IL-4, which induces regulatory T cells with increase of TGF- $\beta$  and impact on IL-17 levels. In patients in the early phase of schizophrenia, enhanced anti-inflammatory/immuno-suppressive activity could be an attempt to limit ongoing pro-inflammatory process and prevent chronic inflammation development. But, the Th2 driven inflammation could be especially important in schizophrenia morbidity and comorbid somatic states.

Noto and colleagues (2018) have recently hypothesized a strong Immune Inflammatory Response System (IRS – M1 macrophages + Th-1 + Th-17) coupled with an anti-inflammatory response (Compensatory Immune-Regulatory System - CIRS), suggesting that CIRS may contribute to recovery from the acute phase of illness in first episode psychosis. It was discussed by Pratt et al. (2018) that there are still ongoing attempts to establish peripheral markers that are related to `state` or `trait` in patients with schizophrenia, but without clear utility.

## **CYTOKINE PROFILES OF PSYCHOTIC PATIENTS IN THE USE OF ANTIPSYCHOTICS**

Studies conducted prior to the beginning of the era of administration of antipsychotics pointed to the dysfunction of the immune system of patients with schizophrenia and their value is therefore great (Yolken & Torrey, 1995). Clinical response to antipsychotic treatment may be related to immune parameters. Studies in animal models show that cytokines mediate the metabolism of neurotransmitters: dopamine, serotonin, noradrenaline, and acetylcholine (Rapaport & Bresee, 2010; Ley et al., 2010). Cytokines can mediate the activity of several monoaminergic systems: the increase of cytokine levels reduces serotonin bioavailability, can inhibit dopamine synthesis and augment glutamate release (reviewed in Baumeister et al., 2016). It has been already observed and discussed that the immunological imbalance of psychotic patients can be corrected by antipsychotic agents (Zhang et al., 2005) and anti-inflammatory therapy (Müller et al., 2002; Müller et al., 2004; Riedel et al., 2005; Akhondzadeh et al., 2007).

Psychopharmacological studies indicated that antipsychotics have pharmacological properties that can produce neurotrophic, neurogenetic and neuroprotective effects (Monji et al., 2009). In brain cell culture models, anti-inflammatory and neuroprotective effects of antipsychotics have been shown (Zheng et al., 2008; Kato et al., 2008). Various and contradictory results of the possible effects of atypical antipsychotics on the cytokine system were presented, but the association of cytokine levels with response to this therapy was not clearly established (Zhang et al., 2005; Reale et al., 2011).

Numerous antipsychotics exhibit modulatory effects on the immune system, especially on cytokines on the periphery (Pollmächer et al., 2000; Drzyzga et al., 2006). It is assumed that antipsychotics strongly enhance anti-inflammatory activity in two ways. The first is the increase in the peripheral production of anti-inflammatory cytokines, and the second by the reduction of pro-inflammatory cytokines. The capacity of antipsychotics to normalize pro-inflammatory changes can be an important additional

mechanism of action that allows the clinical efficacy of antipsychotics in the treatment of psychotic symptoms (Meyer, 2011). Appropriate control of microglial activity can be encouraging for the treatment of schizophrenia. There are claims that immunosuppressive or immunomodulatory drugs may therefore be useful, at least in the treatment of acute schizophrenia (Monji et al., 2009).

When determining the cytokine profile of patients with schizophrenia, it is necessary to consider the possible effects of numerous factors, such as body mass index, smoking habits, and especially the influence of drugs. The possible effect of antipsychotic therapy on the patient's cytokine profile cannot be ruled out, even when the correlation between cytokine levels and the type or dose of antipsychotic drugs administered has not been shown (Kunz et al., 2011), as is the case in our studies. Previously, results have been presented indicating that antipsychotics can suppress Th2 cytokines (Pae et al., 2006). Our results highlight different cytokine profiles after treatment in patients in the first psychotic episode who have not previously been treated with antipsychotics, and those with schizophrenia in relapse, who have already been treated with antipsychotic drugs (Borovcanin et al., 2013).

It has been shown that the serum levels of IL-4 reduce with therapy, in both observed groups, regardless of the chosen antipsychotic, so that after the applied therapy there is no statistically significant difference in the level of IL-4 in healthy subjects and patients. Data from the literature indicate that the *in vitro* IL-4/IFN- $\gamma$  coefficient did not differ depending on the type of antipsychotic therapy applied (Avgustin et al., 2005), and clinical data on the possible impact of IL-4 antipsychotics are scarce. Our results indicate that the treatment of antipsychotics results in the re-establishment of Th1/Th2 equilibrium, by lowering the type 2 cytokines of IL-4 (Borovcanin et al., 2013).

IL-6 secretes the activated monocytes and some authors include it in type-2 cytokines, although it acts as a proinflammatory cytokine (Müller & Schwarz, 2010). The interest in IL-6 exists not only from the immune, but also from the neurochemical and neuropharmacological aspects, as it has been shown that it is not produced exclusively by glial cells, but also by



neurons (Breder et al., 1988; Freidin et al., 1992). The decrease in IL-6 in the use of antipsychotics was shown in previous studies (Kronfol & Remick, 2000; Kim et al., 2004; Schmitt et al., 2005; Singh et al., 2009; Potvin et al., 2008; Meyer, 2011), which is consistent with our results. Others point out that clozapine affects plasma IL-6 increase over a two-week, but not longer-term treatment (Maes et al., 1994, 1997; Pollmacher et al., 1996; Hinze-Selch et al., 1998), while a more extensive study showed that risperidone and haloperidol did not significantly affect serum IL-6 levels in patients with schizophrenia (O'Brien et al., 2008; Reale et al., 2011). It was also shown that IL-6 decreased in plasma in the exacerbation of symptoms of schizophrenia after discontinuation of haloperidol (Watanabe et al., 2010). Two studies found a significant positive correlation between levels of IL-6 and psychopathology at the beginning, as well as between changes in levels of cytokine IL-6 and psychopathology following the administration of antipsychotics (Miller et al., 2011). In several studies the negative correlation between IL-6 and cognitive performance was point out, but that was not confirmed in the most of the studies (Müller et al., 2010; Potvin et al., 2008).

Patients who are resistant to antipsychotics have been shown to have continuously elevated levels of IL-6, and it is not possible to restore balance after treatment with antipsychotic agents (Meyer, 2011). It is possible that this is a confirmation of clinical findings on the heterogeneity of schizophrenia syndrome. The decrease in IL-6 concentrations by antipsychotics in our patients correlates with the fact that they were not resistant to applied therapy, which is the assertion of other authors (O'Brien et al., 2008). Our results showed an increase in serum TGF- $\beta$  levels and a decrease in serum IL-27 concentration in patients in the first psychotic episode after one-month therapy and statistically significantly lower serum IL-17 levels in the first psychotic episode compared to healthy ones. These results could be attributed to the effect of antipsychotics, and also to complex interaction between TGF- $\beta$ , IL-27, and IL-17 in the early stage of the disease.

The influence of typical and atypical antipsychotics on stimulated secretion of IL-17, but also in *in vitro* conditions, has already been

examined. It has been demonstrated that all antipsychotics, at different doses, increase the production of IL-17 (Himmerich et al., 2011). In our study, we found lower IL-17 concentrations in the first psychotic episode in relation to healthy ones after therapy. We also showed a weak negative correlation between IL-17/TGF- $\beta$  with subscales of negative and general psychopathology. It is possible that the previous administration of antipsychotics in schizophrenia is the reason that the values of this cytokine are higher than in the first psychotic episode. The research group of Debnath and colleagues has presented reduced IL-17F levels in schizophrenia, suggesting dysregulation of this pathway in schizophrenia (Subbanna et al., 2018). Recently Debnath and Berk (2016) have recapitulated the knowledge about functional implications of altered levels of cytokines related to IL-23/IL-17 axis in schizophrenia, and the impact of complement activation and altered gut microbiota on these pathways.

The immunosuppressive role of IL-27 is particularly important in the prevention of excessive inflammation (Yoshida et al., 2009; Gabay & McInnes, 2009), which can be used in the treatment of some autoimmune disorders (Xu et al., 2010). In the first psychotic episode, we showed a decrease in IL-27 levels after antipsychotic therapy, which may not be the desired effect. The suppression of IL-27 production may indicate predominance in the Th17 direction, instead of Treg following the administration of antipsychotics. It is also necessary to consider the possible effects of other cytokines, e.g., IL-23 in schizophrenia, before and after the applied therapy. We showed that TGF- $\beta$  antipsychotic treatment had a significant increase in the first psychotic episode, which may indicate a possibility for early treatment in schizophrenia. We have discussed that at the illness onset TGF- $\beta$  have an immunosuppressive activity, but IL-23 could have pathogenic effects that are probably not related to IL-17 (Borovcanin et al., 2015).

Further, we have explored new innate inflammatory pathways, IL-33/ST2 and Gal-3 (Borovcanin et al., 2018). Serum levels of Gal-3 were lower in acute psychosis, but significantly elevated in remission of schizophrenia. We established that sera levels of IL-33 correlate with positive PANSS symptoms in remission of schizophrenia. To give the

complete explanation it should be added that sST2 could have neutralizing properties and ameliorate negative symptoms (Borovcanin et al., 2018).

After antipsychotic treatment, serum concentrations of TGF- $\beta$  were higher in patient groups (first episode psychosis and schizophrenia in relapse), compared to healthy subjects. IL-4 and IL-6 levels were significantly decreased after antipsychotic treatment in both groups of patients and reduced in the first episode psychosis group. Decreased IL-27 levels in first episode psychosis patients were observed after antipsychotic treatment indicating the predominance of Th17 response. Serum levels of IL-23 stay elevated in all phases of this mental disorder and regardless of applied therapy, suggesting that it could be considered as a trait marker. Gal-3 levels showed to be higher in stable phase of schizophrenia.

In patients with first psychotic episode, antipsychotics downregulated the IL-17 pro-inflammatory response, but, in patients with schizophrenia in relapse, antipsychotics instead seem to affect the Th2 response. The low-grade inflammation in schizophrenia could be Th1/Th17 dependent in the early phases, but later on the Th2/TGF- $\beta$  response, including high IL-6 levels, could possibly lead to autoimmunity (summarized in Figure 1).

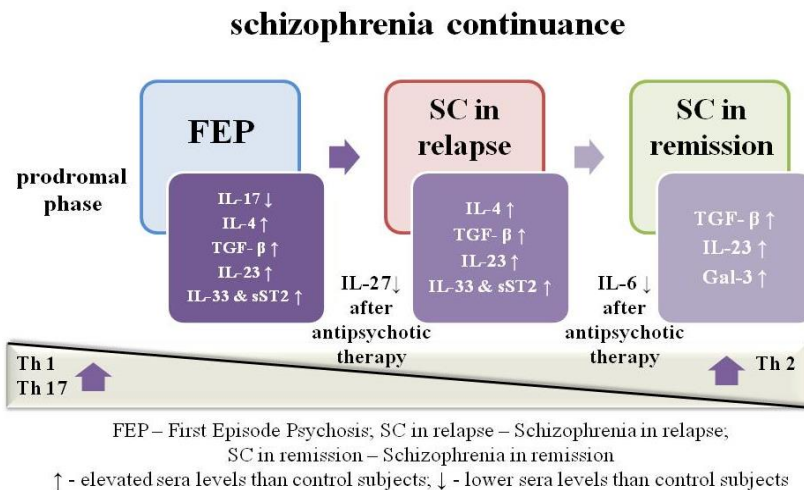


Figure 1. Peripheral cytokine alterations through schizophrenia continuance. The low-grade inflammation in schizophrenia could be Th1/Th17 dependent in the early phases and later on Th2/TGF- $\beta$  response could predominate.

## **PERIPHERAL CYTOKINE ALTERATIONS AND SOMATIC COMORBIDITY IN SCHIZOPHRENIA**

Similar underlying immunological patterns have been observed in different somatic states and mental disorders, possibly due to the same immune disturbance in early childhood (Baumeister et al., 2016). Further, it is well known that somatic diseases could be followed by behavioral changes, and vice versa, that the mental disorders could lead to somatic dysfunction, considering that the possible mutual interactions could be immune mediated (Pillinger et al., 2018).

Pillinger et al. (2018) have recently published a thorough and very important meta-review of the central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis, summarizing effect size for both, central nervous system (CNS) and non-CNS system dysfunctions in schizophrenia. In this review the authors observed statistically significant differences in alterations in immune parameters, that are greater than brain structural and neurochemical alterations, also pointing out that these outcomes remain similar after the antipsychotic naïve sensitivity analyses. The models of potential relationships that exist between CNS and non-CNS alterations in psychosis are presented, suggesting that schizophrenia should be considered as a multisystem disorder.

People with schizophrenia have different incidences of some autoimmune diseases compared to the general population (Mahendran et al., 2004). Data suggest a lower rate of rheumatoid arthritis in schizophrenia (Eaton et al., 1992; Vinogradov et al., 1991). An inadequate Th1 response can explain the negative association between rheumatoid arthritis and schizophrenia (Freudenreich et al., 2010). Others consider simultaneous occurrence of schizophrenia and insulin-dependent diabetes mellitus (Finney, 1989). There is a possibility that the autoimmune process develops in certain types of schizophrenia syndrome, especially considering the fact that IL-6 increases in therapeutic activity (Lin et al., 1998), which, in the production of TGF- $\beta$ , directs Th cells in the direction of Th17.

## **Concept of Mild Localized Encephalitis in Schizophrenia**

Similar mental changes have been seen in both parenchymal encephalitis and acute psychotic episode. Bechter (2004) introduced the term `mild localized chronic encephalitis` in attempt to denote the small degree but rather chronic inflammatory process seen in schizophrenia. The microvascular system was identified as a site of inflammation with progressive damage after every new inflammatory psychotic episode (Hanson and Gottesman, 2005) (see in Figure 1). It seems that mild localized inflammation in perivascular spaces of the brain could be considered in schizophrenia. Maybe these events could further be explored as a basis for soft neurological signs that were observed and explored in patients with schizophrenia (Miljevic et al., 2018).

## **Asthma and Schizophrenia**

Considering similarities of asthma and schizophrenia it is very interesting that antipsychotic chlorpromazine was discovered incidentally during the testing as an antihistamine agent in subjects with schizophrenia (Shen, 1999). Our data suggests similar immune patterns in schizophrenia and atopic disorders. Others have also confirmed the high co-occurrence of asthma and schizophrenia (Pederson et al., 2012). It is known that asthma is a prototype of Th2 mediated disease, with inflammation of blood vessels and smooth muscles immediately after exposure to an allergen that could lead to fibrosis after repeated attacks (Abbas, 2009). Our results suggest that the immune response in schizophrenia may be similar to that of atopic diseases and that the cytokine imbalance can be corrected by antipsychotics. IL-4 cytokine that triggers a type-2 immune response has been shown to have a role in asthma (Koyasu and Moro, 2011) and also in our experimental group in psychotic exacerbation (Borovcanin et al., 2012).

After allergen challenge in asthma, an increase in bronchoalveolar lavage fluid BDNF levels was observed, and IL-6 and TNF- $\alpha$  induced neuronal hyperactivity showed to be mediated by BDNF-secreting monocytes (reviewed in Minic Janicijevic et al., 2018). In asthmatic patients IL-23 may regulate Th2 response by enhancing antigen induced Th2 cell differentiation (Li and Hua, 2014) and was elevated in sera of patients with schizophrenia (Borovcanin et al., 2015). IL-33 stimulates the expansion of IL-13-producing innate lymphoid cells, participates in induction of airway contraction in asthma (Lu et al., 2015) and has been overproduced in psychotic episode (Borovcanin et al., 2018). Gal-3 facilitates type-2 immune response (Fermin et al., 2013), which is in accordance with our findings of predominance of type-2 immune response in patients with schizophrenia (Borovcanin et al., 2012; Borovcanin et al., 2013). All these cytokine alterations observed in patients with psychosis that are similar to those observed in asthma could point out further directions in developing new therapeutical strategies.

The similarities in immune changes in asthma and schizophrenia have been presented in the Figure 2.

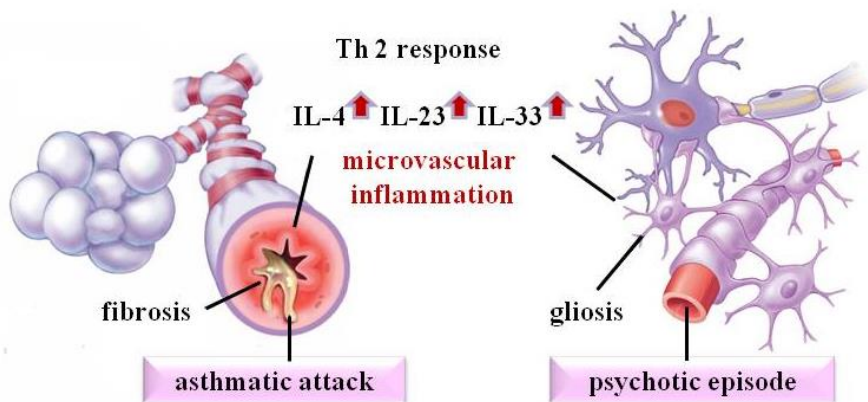


Figure 2. Similarities of immune responses in asthma and schizophrenia.

In every repeated asthmatic attack and psychotic episode possible microvascular inflammation could be considered, with elevated levels of type-2 immune response cytokines, such as IL-4, IL-23 and IL-33, which could consequently lead to pulmonary fibrosis or maybe even brain gliosis.

## **Cardiometabolic Changes in Schizophrenia**

Life expectancy in patients with schizophrenia is 10-25 years shorter than the general public (Crump et al., 2013). Patients with schizophrenia are three times more likely to have sudden cardiac death (Davidson, 2002) and these events have been related to cardiovascular diseases and strongly correlated to aggressive behavior (Hou et al., 2015). Recent research in the field of immunometabolism of mental disorders has revealed that metabolic abnormalities including obesity, impaired glucose tolerance, type 2 diabetes and cardiovascular disease are associated with schizophrenia and could be interpreted by specific immune disbalance (Greenhalgh et al., 2017; Misiak et al., 2017).

Numerous studies have confirmed that both metabolic syndrome and schizophrenia have underlying chronic low-grade inflammation with elevated cytokines important in glucose utilization and insulin sensitivity in both conditions. Our data suggests that decreased levels of IL-6 after antipsychotic therapy could predispose the obesity and obesity-disorders development in schizophrenia (reviewed in Borovcanin et al. 2017).

Both innate immunity markers IL-33 and Gal-3 have been included in the therapeutical guidelines of American College of Cardiology Foundation & American Heart Association and are useful in prognosis of one-year mortality of patients with acute heart failure (Nayor et al., 2015). Although IL-33 has been shown to have a protective role in atherosclerosis (Miller et al., 2008), increased levels of IL-33 and sST2 were measured in cardiac diseases (Dieplinger and Mueller, 2015) and metabolic syndrome (Celic et al., 2016).

This was confirmed by us in patients with schizophrenia when positive correlation of CK-MB levels with serum sST2 was established, but also negative correlation with cholesterol and LDL (Borovcanin et al., 2018). Serum Gal-3 levels were elevated in remission of schizophrenia and its protective function in obesity and diabetes was suggested (Jin et al., 2013; Pejinovic et al., 2013).

## Mammary Carcinoma in Schizophrenia

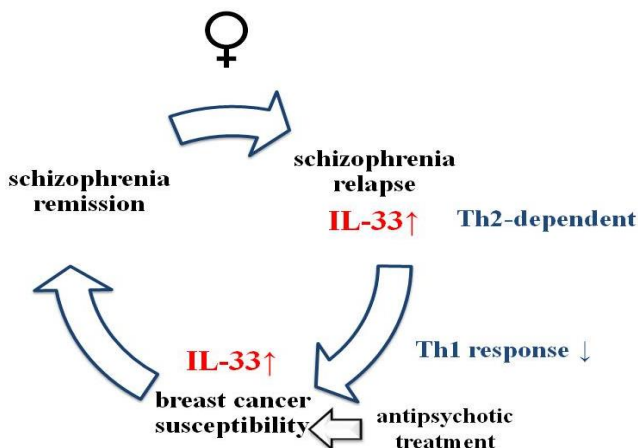


Figure 3. IL-33/ST2 axis as a link between schizophrenia and breast tumor comorbidity. Every psychotic episode and excessive secretion of IL-33 promotes the Th2 response and, with antipsychotic treatment, could predispose females with schizophrenia to breast cancer development. Thus, schizophrenia relapse characterized by an increase in IL-33 may be a facilitating factor leading to more frequent occurrence of breast carcinoma in female schizophrenia patients. More frequent exacerbations do not only have an impact on cognition but could be considered as a new somatic perturbation and lead into somatic deterioration.

There is recent report that female schizophrenia patients have a higher risk of breast cancer compared to female patients without any serious mental illnesses (Wu Chou et al., 2017). We argued that IL-33 participates in this link between schizophrenia and breast cancer. The IL-33 and sST2 could affect development of various tumors (Jovanovic et al., 2012). Animal studies demonstrated the role of IL-33 in breast cancer progression by ability to promote type-2 immune response (Jovanovic et al., 2014). Clinical data indicated that IL-33 promotes breast cancer development (Milosavljevic et al., 2016). Further, a crucial function of IL-33 seems to be in endocrine resistance in patients with breast cancer (Hu et al., 2017). It is possible that this mechanism could be potentiated in patients with schizophrenia, dependent on antipsychotic profile. Long-term use of prolactin-inducing antipsychotics was associated with an increased risk of breast cancer,



particularly with estrogen receptor positive breast cancers (Pottegård et al., 2018).

IL-33 is a member of the IL-1 family and has a protective role in atherosclerosis, obesity, bone loss and experimental fulminant hepatitis by downregulating Th1-mediated response (Milovanovic et al., 2012), but it is pathogenic in allergen-specific type-2 immune response seen in asthma (Salimi et al., 2013) and possibly in schizophrenia (Borovcanin et al., 2018).

In the Figure 3 we proposed potential link between schizophrenia, IL-33/ST2 and breast tumors.

## **Osteoporosis in Schizophrenia**

In a review article by Koricanac et al. (2018), we presented the possible mechanisms of osteoporosis onset in patients with schizophrenia that could be caused by antipsychotics. Considering the immune changes that were observed even before antipsychotics were applied and also after their use, this imbalance may be involved in the onset of bone metabolism disorders in these patients. It was already shown that regulatory T cells, by secreting TGF- $\beta$  and IL-4 cytokines, are included in bone remodeling and osteoporosis (Bozec & Zaiss, 2017), and our results pointed out that the serum levels of these mentioned cytokines are elevated in schizophrenia early phase exacerbation (Borovcanin et al., 2012). Macari et al. (2018) pointed out that IL-33/ST2 have a bimodal role in bone remodeling, and could be site and estrogen dependent, so they must be considered in the context of the phase of schizophrenia and antipsychotic therapy.

## **CONCLUSION**

We established differences in the cytokine profile of patients in first psychotic episode and patients with schizophrenia in relapse, as well as after one-month and three-month therapy. Considering the average duration of the disorder, our research involved primarily patients in the early stages of

the disease. It is obvious that cytokine profiles may vary, both due to the duration of the disease and the effects of antipsychotics. We can assume that in the central nervous system of the patients with schizophrenia pro-inflammatory activity is predominant. Antinflammatory activity on the periphery seems to be an attempt to limit the inflammatory process and to prevent the development of progressive chronic inflammation (Meyer et al., 2011). Despite an enhanced pro-inflammatory response, its severity is modest in relation to significant chronic inflammation in rheumatoid arthritis or atherosclerosis (Serhan & Savill, 2005), and is often referred to as `lower inflammation` (Fan et al., 2007; Meyer et al., 2011). A weakened type-1 immune response was observed in the early stages of schizophrenia, while chronic pro-inflammatory status with prevalence of type-2 responses and high levels of IL-6 may be dominant in later stages of schizophrenia progression (Müller & Schwarz, 2010). Since IL-6 induces autoimmunity, it may also be possible to develop an autoimmune process in schizophrenia at later stages (Müller & Schwarz, 2010). Gal-3 sera levels were elevated in remission, and IL-33 and its soluble receptor sST2 levels were elevated in acute phase. It is probable that the immune profiles of patients with schizophrenia vary depending on the stage of the disorder and the applied therapy.

Neuroinflammation in psychosis is widely explored, but maybe it is not a predominant underlying mechanism in all of patients with schizophrenia. It is possible that schizophrenia, in the immunological sense, is a heterogeneous disorder, so that different types of schizophrenia have different immune profiles and responses. The patterns of changes in immune mediators could reflect disease progression, be used in patient stratification or even in drug side effects evaluation (Prata et al., 2014). Similarly, with those proposals for treatment of subgroups of patients with depression (Leighton et al., 2018) the subgrouping of patients with schizophrenia in higher inflammatory state and different treatment should be considered (Pillinger et al., 2018).

New Genome Wide Association Studies (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and many meta-analyses of serum cytokines in schizophrenia, have also emphasized the role of immune

molecules in schizophrenia. The thorough and integrative analysis of cytokines interplay through schizophrenia continuance is still lacking. The summarized understanding of specific peripheral and central cytokine production could reveal new possibilities for schizophrenia treatment and prevention of somatic comorbidity.

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*Chapter 3*

**IMMUNE ACTIVATION AND COGNITION:  
COGNITIVE CHANGES ASSOCIATED  
WITH IL-6 IN PATIENTS WITH  
SCHIZOPHRENIA, VERSUS OTHER  
PSYCHIATRIC AND MEDICAL DISORDERS**

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**ABSTRACT**

A wealth of data exists, implicating an altered immune response in the aetiology of Schizophrenia. In this chapter, we review evidence that immune activation, measured in terms of cytokine response, is associated with variation in cognitive performance in schizophrenia, other psychiatric and non-psychiatric disorders, and healthy participants, including older healthy participants. Our purpose in carrying out this review was: (1) to

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examine whether altered cytokine response resulted in functionally relevant changes in schizophrenia, and (2) to examine whether any association observed was different in patients versus other groups. Because of the volume of research published in this area we focused our study on one inflammatory marker – interleukin 6, the cytokine most reliably associated with schizophrenia. To achieve this we conducted a search on Pubmed to June 2017. Studies which measured serum or plasma levels of IL-6 and which examined their relationship to cognitive test scores were included. In total 88 studies were identified as meeting our criteria for inclusion. The picture which emerges from this review is that, in general, there is consistent evidence for an association between IL-6 and cognitive function, depending on the participant group. Most studies controlled for a wide range of confounders in their analysis, and multiple cognitive domains were implicated, including executive function, processing speed and verbal and visual memory. Where significant associations were observed, the vast majority of studies found higher IL-6 levels to be associated with cognitive impairment.

## **1. INTRODUCTION**

### **1.1. Inflammation in Schizophrenia**

There is now a wealth of data implicating an altered immune response in the aetiology of SCZ. Prenatal and childhood infection studies (Brown et al., 2010; Khandakar et al., 2014), elevated inflammatory markers in peripheral blood and CSF (Fineburg et al., 2013), as well as genetic (Sekar et al., 2016), post-mortem (Fillman et al., 2013; Trepanier et al., 2016), and neuroimaging (Doorduyn et al., 2009) studies have all pointed to increased inflammation and altered immune system functioning as associated with SCZ risk. In animal models, maternal immune activation models have further enhanced our knowledge of the mechanisms by which inflammation might relate to pathophysiology related to SCZ (Meyer et al., 2011).

For 50 years, the most influential hypotheses about Schizophrenia aetiology have focused on dopamine and glutamate (Howes et al., 2015), based on evidence of, for example, abnormal dopamine D2 and NMDA receptor function in the pre-frontal cortex (Laruelle et al., 2014). In recent years, altered immune activation has been suggested to contribute to these

abnormalities via altered kynurenine metabolism, resulting in turn in altered dopamine and glutamate levels (Watkins & Anderson, 2015, Ribeiro-Santos et al., 2014), as well as changes other neurotransmitters such as serotonin and noradrenaline (Muller et al., 2015). Elucidating the precise mechanism by which altered immune function results in this cascade of changes is the focus of much current research. One line of enquiry is testing whether immune activation during critical neurodevelopmental stages (e.g., via maternal immune activation during second trimester) leads to microglia (the resident macrophages of the brain) being ‘primed’ to have exaggerated responses with deleterious effects on brain structure and function. For example, Meyer et al. (2013) have proposed a ‘Prenatal cytokine hypothesis’ based on evidence from animal models that abnormal cytokine function prenatally leads to abnormalities in cognition and behaviour into adulthood, similar to those reported in Schizophrenia. This is one of a number of such models proposed during the last 20 years (Smith & Maes, 1995; Monji et al., 2009; Yolken & Torrey, 2008; Anderson & Maes, 2012; Kneeland et al., 2013).

## **1.2. Elevated Peripheral Cytokine Levels in Schizophrenia**

Cytokines have a wide range of roles in both the innate and adaptive immune system. At a neural systems level, cytokines play a role in synaptic plasticity, synaptic transmission and neurogenesis (McAfoose & Baune 2009). Elevated peripheral levels of inflammatory markers, including cytokines, have been consistently reported in patients with SCZ (Rodrigues et al., 2017; Bergink et al., 2014). Potvin et al. (2008) found IL-1RA, sIL-2R and IL-6 to be consistently increased in patients with SCZ across studies. Miller et al. (2013) found that a number of these markers, including IL-1b, IL-6, TGF-b, appeared to be responsive to anti-psychotic treatment. Others, including IL-12, IFN- $\gamma$ , TNF-a and sIL-2R appeared more stable or ‘trait-like’, with elevated levels in both acute stages and after anti-psychotic treatment. In a study of first episode psychosis and medication naïve

patients, Upthegrove et al. (2011) and found that cytokines were elevated in this population also.

Among these cytokines, Interleukin-6 (IL-6) is involved in numerous fundamental processes of the CNS. It is a pleiotropic cytokine and plays a role in homeostasis, astro-gliogenesis and neuronal differentiation (Spooren et al., 2011). IL-6's role in CNS function was identified when it was observed to be up-regulated in neurodegenerative disorders, such as in Alzheimer's disease, Parkinson's disease and Multiple Sclerosis (Spooren, 2011). It is upregulated in many other pathophysiological states also (Wolf, 2014). IL-6 is produced by multiple cells in the CNS, including neurons and microglia but is mainly released by astrocytes (Groul et al., 2015). It can be rapidly upregulated in response to inflammatory states but also to psychosocial experiences such as stress (Atzori et al., 2012). While IL-6 is normally classified as a pro-inflammatory cytokine, it actually plays a dual role in the CNS where it can also have anti-inflammatory properties and can act as a neurotrophin (Wolf, 2014).

### **1.3. Focus of the Review**

In this chapter, we review the evidence that immune activation, measured in terms of cytokine response, is associated with variation in cognitive performance in schizophrenia, other psychiatric and non-psychiatric disorders, and healthy participants, including older healthy participants. Our purpose in carrying out this review was: (1) to examine whether altered cytokine response resulted in functionally relevant changes in schizophrenia.

We focus on cognition because, unlike clinical symptomatology, cognitive deficits remain reasonably stable across the life span and are strongly predictive of level of function (Green et al., 2015); (2) to examine whether any association observed was different in patients versus other groups. We did this in the context of neurodevelopmental theories that the brain might be influenced in specific ways by altered immune response, which may differ from, for example, immune activation during adults

following illness, or as part of neurodegenerative processes. Because of the volume of research published in this area we focused our study on one inflammatory marker – interleukin 6, the cytokine most reliably associated with schizophrenia, and the evidence for which is discussed next.

## **2. METHODOLOGY FOR SYSTEMATIC REVIEW**

### **2.1. Search Strategy**

We conducted a search on Pubmed to June 2017. Studies which measured serum or plasma levels of IL-6 and which examined their relationship to objectively measured cognitive test scores were included. The search terms were 1. Interleukin-6 (search terms- interleukin-6 OR interleukin 6 OR IL-6 OR IL6 OR IL 6) 2. Cognition (search terms- cognition\* OR cognitive\* OR executive function OR attention OR memory OR working memory OR episodic memory OR verbal memory OR non-verbal memory OR declarative memory OR non-declarative memory OR IQ OR intelligence OR processing speed OR neuropsychological test). See Figure 1.

### **2.2. Inclusion and Exclusion Criteria**

Included Studies were screened and selected according to the following criteria: (1) Original and peer-reviewed article, (2) Measured serum or plasma levels of IL-6, in its own single independent measurement, (3) Well-established objective cognitive test(s) scores used and their relationship to peripheral IL-6 levels reported, and (4) Cross-sectional and/or longitudinal study designs were included. Exclusion included studies where (1) Only subjective verbal self-report of cognitive symptoms available, (2) Brief screening tool measure of cognition (MMSE (Mini-Mental State Exam) or Moca (Montreal Cognitive Assessment only)), (3) Studies which did not measure peripheral IL-6 independently but as a combined inflammation

score, (4) only salivary or CSF levels of IL-6 was measured, (5) Only a genetic marker of IL-6 was reported, and (6) the study did not explicitly report finding between IL-6 and objective cognitive test and/or just used IL-6 as a co-variate in other analyses, (7) only Neo-Natal participants were included study, or the study was (8) an Intervention or administering an inflammatory agent or IL-6 itself for a reaction.

### 2.3. Data Extraction

The data extracted for the review were the following: First Author and Year of Publication, Study Design, Study Population, Sample Size, Objective Cognitive Tests Used and the Significant Associations reported between peripheral IL-6 levels (serum or plasma) and the cognitive tests.

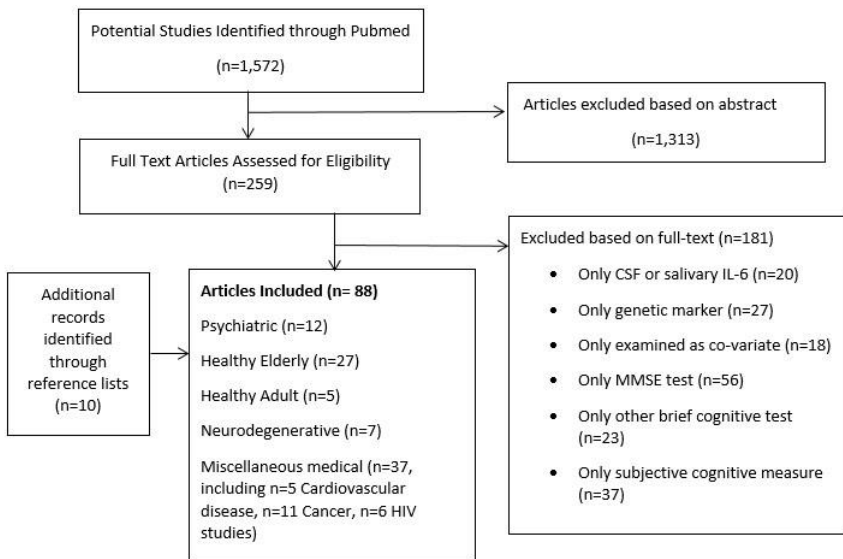


Figure 1. PRISMA Flow chart for Included Studies.

### **3. RESULTS**

In total 88 studies were identified as meeting our criteria for inclusion, and organized into five broad categories; Psychiatric (n = 12), Healthy Elderly (n = 27), Healthy Adult (n = 5), Neurodegenerative (n = 7), and studies of miscellaneous medical conditions (n = 37, including n = 5 Cardiovascular disease, n = 11 Cancer, n = 6 HIV studies).

#### **3.1. Psychiatric Disorder Results**

Twelve studies were identified which looked at peripheral IL-6 levels and cognitive function in psychiatric disorders. Five studies were included which examined persons with schizophrenia, and of these five studies, two studies also included a group with bipolar disorder. Four studies were found for major depressive disorder (MDD), and three additional studies looked at MDD in elderly population samples.

##### **3.1.1. Schizophrenia**

Five studies were identified which investigated persons with schizophrenia and the possible relationship between peripheral IL-6 levels and performance on objective measures of cognitive function. Frydecka et al. (2015) tested a large cognitive battery with a large sample size (n = 151 persons with schizophrenia n = 194 healthy controls). They found before Bonferroni correction that all tasks correlated with IL-6 while after Bonferroni correction higher IL-6 was still associated with worse performance in working memory, executive function and verbal memory.

None of the other four identified studies found an association between cognition and individual measurement of peripheral IL-6 levels. Hoseth et al. (2016) used two common tests, the Wechsler Logical Memory test and also used the California Verbal Learning test and found no association with IL-6. Hope et al. (2015) used four subtests of the Wechsler cognitive battery assessing both performance and verbal cognitive domains and found no association with IL-6. Fillman et al. (2016) used a large battery assessing a

range of cognitive domains, and found no association with individual IL-6 levels, although the study did find association with cognition when combining inflammatory markers. Hori et al. (2016) used only a brief cognitive battery and found no association with IL-6.

Overall, while the study with the largest sample size and breadth of cognitive testing did find an association of cognition with IL-6, all other studies looking at cognition in patients with schizophrenia did not find an association. One reason may be that the participants were tested at different stages of the illness.

In a meta-analysis of studies, Miller et al. (2011) found that IL-6 was a 'state' as opposed to 'trait' marker as it was more strongly associated in acute states of psychosis rather than after medication treatment and stable periods. While Frydecka et al. controlled for PANSS scores, the sample included both stable outpatients as well as persons who had recently recovered from an acute episode which may explain the discrepant results.

### ***3.1.2. Bipolar Disorder***

Only two studies were found which looked at peripheral IL-6 levels and cognitive function in bipolar patients. Both Hope et al. (2015) and Hoseth et al. (2016) found no association between serum or plasma levels of IL-6 and cognitive function.

### ***3.1.3. Major Depressive Disorder***

Four studies were identified which looked at peripheral levels of IL-6 and their association with objective cognitive testing in persons with major depressive disorder. Only one study used a large cognitive battery that measured multiple cognitive domains (Krogh et al., 2013). Krogh et al. (2013) also had the largest sample size of the studies (n = 112 patients, n = 57 healthy controls) and they used an exercise intervention and measured all variables again 3 months later. Only the serial seven task was associated with IL-6 at baseline. The serial seven task is a short test measuring concentration and memory.



**Table 1. Psychiatric Studies Table**

First Author and Year	Sample Size and Study Design	Cognitive Tests	Results
<b>Depression</b>			
Krogh (2013)	n = 112 patients n = 57 HC Cross-sectional and longitudinal	TMT A and B, Digit Span, Digit Symbol, Letter and Category Verbal Fluency, Design Fluency, Serial Sevens, Buschke's Selective Reminding test, Rey Complex Figure test.	IL-6 was positively associated with Serial sevens At 3 months follow-up IL-6 did not significantly change from baseline and did not differ between the two patient groups. Combining the two groups, a decrease in IL-6 was associated to decreased verbal fluency
Grassi-Olivera (2011)	n = 30 with recurrent MDD Cross-sectional	Logical Memory (WMS)	Low performances in immediate verbal recall and delayed verbal recall in logical memory are associated with IL-6 levels in women with recurrent MDD
Goldsmith (2016)	n = 93 unmedicated patients with MDD Cross-sectional	TMT A, Wechsler DSST. CANTAB Reaction Time Task.	IL-6 was not associated with individual cognitive task scores Exploratory principle component analysis factor named as 'processing speed factor' was associated with IL-6.
Young (2016)	n = 35 unmedicated depressed patients n = 25 HC Cross-sectional	Autobiographical memory task.	No association with IL-6
<b>Late Life Depression</b>			
Naude (2014)	n = 369 Cross-sectional	Stroop, Digit Span, Rey Verbal Learning test.	No association with IL-6
Elderkin-Thompson (2012)	n = 42 persons with depression n = 45 HC	Wechsler test for Adult Reading scale, California Verbal Learning test, Visual Reproductions, Rey Osterrieth Complex Design, Matrix Reasoning, Stroop, Wisconsin Card Sort Test, Letter-Number sequence, TMT A and B, Digit Symbol Substitution test.	Encoding and Recall were inversely associated with IL-6 across diagnostic groups

**Table 1. (Continued)**

First Author and Year	Sample Size and Study Design	Cognitive Tests	Results
Charlton (2017)	n = 24 persons with depression n = 34 healthy elderly	California Verbal Learning test, Logical memory and Visual Reproductions WMS,	IL-6 associated with worse cognitive performance in persons with depression but not in healthy controls
Schizophrenia and Bipolar Disorder			
Frydecka (2015)	n = 151 persons with schizophrenia Cross-sectional	Rey Auditory Verbal Learning test, TMT A and B, Verbal fluency, Stroop Similarities, Digit Symbol Coding, Digit Span.	IL-6 correlated with worse performance on all constructs listed before Bonferroni correction. Still significant with correction-working memory, executive function and verbal memory.
Hori (2016)	n = 146 persons with schizophrenia chronic outpatient n = 51 HC Cross-sectional	NART, Brief Assessment of Cognition in Schizophrenia	No significant correlations between IL-6 and cognitive function.
Hope (2015)	n = 121 persons with schizophrenia, n = 111 persons with bipolar disorder n = 241 HC Cross-sectional	Similarities, Vocabulary, Matrix Reasoning, Block Design.	No association with IL-6
Hoseth (2016)	N = 109 persons with schizophrenia n = 121 persons with bipolar disorder n = 236 HC Cross-sectional	Logical Memory, California Verbal Learning test.	No association with IL-6
Fillman (2016)	n = 43 persons with schizophrenia n = 43 HC Cross-sectional	Letter Verbal Fluency, Logical Memory, Letter Number Sequencing test, Picture Completion, Digit Symbol Coding, Similarities, Arithmetic Subtest WAIS,	No association with individual IL-6 measurement

Two of the studies measured memory domain only. Young et al. (2016) used an autobiographical memory task while Grassi-Oliveira et al. (2011) tested verbal memory using the Wechsler logical memory task. Young et al. (2016) did not find any association with IL-6 and autobiographical memory. Grassi-Oliveira et al. (2011) study only included women and a relatively small sample of 30 but found IL-6 associated with the Wechsler logical memory (episodic verbal memory) in both immediate recall and delayed recall. The fourth study (Goldsmith et al., 2016) looked at psychomotor speed aggregated across different tasks. While no individual test used was associated with IL-6, aggregating the tasks using exploratory principle component analysis, the resultant psychomotor speed factor was associated with IL-6, with higher IL-6 predicting slower speed.

Overall there is some evidence that IL-6 may impact cognitive processes in depression, with three of the four studies finding higher IL-6 associated with lower cognition performance in psychomotor speed and memory. The studies measured different domains which makes comparison difficult. Krogh and Goldsmith both used the DSST and TMT A and did not find an association with the individual test, while in aggregating scores Goldsmith found the association with psychomotor speed. Had Krogh et al. used factor analysis the results would be more comparable. The negative finding with the autobiography task, while an objective cognitive test, it was designed for the fMRI experiment. Future studies are warranted to replicate these results.

### ***3.1.4. Major Depressive Disorder in the Elderly***

Three studies were identified which looked at the association between cognitive function and IL-6 levels in elderly populations with depression. Naude et al., (2014) had a large sample size of 369 elderly persons, with an average age of 70 years old, and used 3 brief cognitive tests, the Stroop, Digit Span and Rey verbal learning test. From a previous factor analysis these scores were turned into four cognition domains (verbal memory, processing speed, inference control and attention). No association was found for any of the domains with IL-6. The other two studies had smaller sample sizes, Elderkin-Thompson et al. (2012) (n = 42 with depression, n = 45 healthy controls) and Charlton et al., (2017) (n = 24 patients with depression,

n = 34 healthy controls) but both studies found an association between higher IL-6 levels and lower memory performance. In both studies the memory domain was measured using combined scores from both verbal and visual memory tests. The Elderkin-Thompson study found the association with both healthy controls and the depressed group while Charlton et al. study the association was only with the elderly with depression.

Overall in two independent samples a combined memory score was negatively associated with IL-6 levels in this population. The largest study did not find an association yet did use briefer test measures. The studies suggest that the use of briefer tests may not be sensitive enough to find associations with IL-6 levels. Both the Naude et al. study and Elderkin-Thompson study used measures of processing speed, including both using the Stroop test but did not find any association.

### **3.2. Healthy Elderly Results**

Inflammation is known to increase with age (Marsland et al., 2006) and much research has focused on whether this known increase in inflammation is related to normal age related cognitive decline or can function as an earlier marker and risk factor for such decline. Inflammation is thought to relate to neuro-degenerative disorders (Guoping et al., 2015) and longitudinal research in healthy elderly has also looked to see if inflammatory markers can predict subsequent risk of neurodegenerative disorders and thus severe cognitive deficit.

27 studies (Table 2) were identified which looked at normal age-related cognitive decline and its potential relationship to peripheral levels of interleukin-6. Overall, an association between IL-6 levels and cognitive performance was reported in 17 out of 27 studies of healthy older adults. Executive functioning and/or processing speed emerged as the cognitive function showing the most consistent link with IL-6 levels. 10 out of 17 studies which looked at executive function and/or processing speed found an association. Memory function assessed using word lists were also a common test used but most studies did not find an association. A strength of many of the studies for the healthy elderly was the very large sample sizes

involved. This of course was balanced with brevity of cognitive test batteries used, but despite this many studies with large sample sizes did test multiple cognitive domains.

Executive functioning and processing speed emerged as having a somewhat more consistent association with IL-6 levels than other cognitive domains tested. Two separate but similar studies with large cohorts, used factor analysis on a wide battery of cognitive tests administered. Both Tegeler et al. (2016) and Troller et al. (2012), in studies with sample size of  $n = 1,312$  and  $n = 873$ ) respectively, found that a factor measuring Executive function and processing speed factor was associated with peripheral IL-6 levels, with higher IL-6 levels associated with worse performance. No association with any of the other cognitive domains was observed. By comparison, other studies found that processing speed alone was associated with peripheral IL-6 levels. Bettcher et al. (2014) exclusively investigated processing speed, using and combining multiple measures in a cross-sectional design. Higher IL-6 levels were found to be associated with slower performance. Heringa et al. (2014) used a very large cognitive battery using 12 tests in all (see Table 2), which tested 6 cognitive domains which were organized a priori. The DSST, TMT A and Stroop processing speed factors were combined. IL-6 levels at baseline were found to predict worse processing speed performance at follow-up at five years, the only domain which was associated. Palta et al. (2014) measured psychomotor speed with TMT A and found that over a nine-year period IL-6 was associated with decline in performance. The TMT B measuring executive function and a verbal memory test had no association.

One of the most popular tests used was the Digit Symbol Substitution test (DSST). The DSST is thought to measure ‘complex attention’, along with motor speed and visuo-perceptual functions (Jaeger, 2018). Three studies used this test exclusively and were from the same cohort of patients (Newman et al., Jenny et al., and Sanders et al.), with two of the studies reporting IL-6 to be associated with decline in the DSST over a nine-year period and one finding no association. As these were equivocal results, they were not included in the 10 tests which found an association with executive function and/or processing speed as mentioned above.

**Table 2. Healthy Elderly**

First Author and Year	Sample Size and Design Study	Cognitive Tests Used	Results
Newman (2016)	n = 5,888 Cross-sectional and longitudinal Age at baseline: 72.8	DSST	No association between IL-6 and DSST over time
Singh-Manoux (2014)	n = 5,217 Cross-sectional and longitudinal	20 Word Free Recall test, Alice Heim test, phonemic and semantic verbal fluency, (MMSE)	Lower Reasoning scores (Alice Heim test) in high IL-6 versus low IL-6 groups, both in cross-sectional and longitudinal data (Higher IL-6 also associated with worse MMSE performance)
Schram (2007)	Cohort 1 n = 3,874 Cohort 2 n = 491  Cross-sectional and longitudinal	Two different cohorts measured  In Both- Stroop test part 3, Letter Digit Substitution test, (MMSE)  Additionally Group 1-Word Fluency Group 2-12 Picture Learning test	Cohort 1 higher IL-6 associated with worse global cognition and executive function but not in cohort 2 trend for CRP but not IL-6 Higher IL-6 related to steeper annual decline in memory function in cohort 2. Higher IL-6 steeper annual decline in global cognition in APOE 4 carriers only in cohort 1.
Jefferson (2011)	n = 1,878 Cross-sectional and longitudinal	WMS logical memory delayed recall, WMS visual reproductions delayed recall, TMT A and B, BNT, Hooper Visual organisation test, WAIS similarities test, WRAT-3 reading subtest.	No significant association with IL-6
Tegeler (2016)	n = 1,312 Cross-sectional Age Range: 65-71	10 word test with 3 trials (immediate recall, delayed recall, recognition), Phonemic and Semantic Verbal Fluency, Digit Symbol Substitution test.	Higher IL-6 and CRP was associated with worse performance in a composite score of executive function and processing speed.
Dik (2005)	n = 1,284 Cross-sectional and longitudinal Age Range: 55-85 years	Auditory Verbal Learning test, Raven's Coloured Progressive Matrices, Alphabet Coding task, (MMSE).	No significant association with IL-6

First Author and Year	Sample Size and Design Study	Cognitive Tests Used	Results
Chi (2017)	n = 1,159 Longitudinal	California Verbal Learning Test (delayed free recall), Block Design WAIS, Boston Naming test, TMT A, Stroop colour/word test (interference condition).	Individual measure IL-6 not associated with cognition. (Combined score was associated with memory and psychomotor speed decline)
Jenny (2012)	n = 1,051 Longitudinal	Digit Symbol Substitution test, (MMSE).	Doubling of IL-6 over time was associated with higher risk of cognitive impairment.
Troller (2012)	n = 873 Cross-sectional Mean age: 78	Logical Memory WMS, Rey Auditory Verbal learning test, Rey and Benton Visual Retention test recognition, TMT A and B, Stroop, Boston Naming tests, Semantic fluency, Digit Symbol Coding test, Block Design WAIS, Grooved Pegboard test.	Higher IL-6 associated with worse performance in executive function/processing speed factor
Alley (2008)	n = 851 Cross-sectional and longitudinal	Similarities WAIS, Geometric Figures, Span test, Boston Naming test, delayed verbal memory from incidental recall of naming items,	Cross-sectionally, there is a generally linear negative relationship between inflammation and cognition, after controlling for confounders, there was no relationship. (However, persons in the top tertile on IL-6 were at an increased risk of incident declines on the Short Portable Mental Status Questionnaire (SPMSQ).)
Weaver (2002)	n = 779 Cross-sectional and longitudinal	Boston Naming test, delayed verbal memory with Boston naming test, Delayed Recognition Span test, Similarities subtest of WAIS, copying geometric figures test	Those in highest IL-6 tertile marginally more likely to have lower baseline function. Those in highest IL-6 tertile more likely cognitive decline over 2.5 years and over 7 years follow-up. After extensive adjustments IL-6 was not associated
Sanders (2014)	n = 771 Cross-sectional and longitudinal	Digit Symbol Substitution test, MMSE.	Higher IL-6 associated with declines in DSST scores

**Table 2. (Continued)**

First Author and Year	Sample Size and Design Study	Cognitive Tests Used	Results
Rafnsson (2007)	n = 452 (men only) Cross-sectional and longitudinal	Logical Memory test WMS, Raven's Standard Progressive Matrices, phonemic Verbal Fluency test, Digit Symbol Coding test, NART.	IL-6 was negatively associated with performance on all cognitive measures. IL-6 turned inversely related to decline in information processing speed
Heringa (2014)	n = 377 Cross-sectional and longitudinal Mean Age: 73	Raven Advanced Progressive Matrices, Digit span WAIS, Corsi Block-Tapping task, Rey Auditory Verbal Learning test, Location Learning test, Rey Osterrieth Complex figure, TMT A, Stroop, Digit-symbol WAIS, Brixton Spatial Anticipation test, Semantic and Phonemic Fluency, Token test, NART.	IL-6 associated with information processing speed.
Baune (2008)	n = 369 Cross-sectional Mean Age: 72.6	Tulving and Colotla Word List, Semantic Fluency, Stroop, Letter Digit Substitution test, Purdue Pegboard test.	No significant association with IL-6
Palta (2015)	n = 336 (women only) Cross-sectional and longitudinal Every 18-36 months over 9 years Mean Age: 74	Hopkins Verbal Learning test (immediate and delayed recall), TMT A and B.	Higher IL-6 associated with greater decline in psychomotor speed over 9 years.
Jordanova (2007)	n = 290 Londitudinal	Consortium to Establish a Registry for Alzheimer's disease battery (CERAD) word list (immediate, delayed recall, recognition), TMT A.	Higher IL-6 associated with cognitive decline in orientation and immediate verbal recall and also a weaker association with decline in delayed recall and psychomotor speed.
Lekander (2011)	n = 298 (women only) Cross-sectional	Episodic recall (12 word list, 16 sentence commands), Episodic recognition (16 colour photographs, word list), Semantic Knowledge (word comprehension/vocabulary task) Semantic Fluency, Prospective Memory.	Interaction effect, negative association between IL-6 and cognitive function evident at higher ages only



First Author and Year	Sample Size and Design Study	Cognitive Tests Used	Results
Goldstein (2015)	n = 219 Caucasians n = 59 African Americans Cross-sectional	Computerized tests developed by Aharonson (2007)-Identify the Odd Pattern, Recall a Pattern, Digit Symbol Substitution task, Digit Span.	IL-6 associated with DSST score and Digit Span.
Bettcher (2014)	n = 151 Cross-sectional	Multiple Processing Speed tasks (animal matching, word rhyming, word judgment, and word pronunciation tasks).	Higher IL-6 was related to worse processing speed
Metti (2015)	n = 135	NART, Raven Coloured Progressive Matrices, California Verbal Learning test, Rey Osterrieth figure, Boston Naming test, Verbal fluency test, Block Design, copy of Geometric figure, Stroop.	No association between IL-6 and cognitive decline Variability in IL-6 was associated with worse cognitive function
Segerstrom (2017)	n = 120 Age Range: 60-93 Mean Age: 74	Wechsler	Higher IQ associated with lower IL-6 levels
Krabbe (2009)	n = 112 Cross-sectional Age Range: 80-85 Mean Age:	Wechsler Full Adult Scale	Higher IQ associated with lower IL-6 levels
Fabregue (2016)	n = 96 Cross-sectional	Stroop	No association with IL-6
Elwan (2003)	n = 94 Cross-sectional	Paced Auditory Serial Addition test, Intentional Memory test, Incidental Memory test, Digit Symbol Substitution test, TMT A and B.	Higher IL-6 associated with significant impairment in attention and sensory memory.
Teunissen (2003)	n = 92 Cross-sectional and longitudinal	Auditory Verbal Learning test (immediate and delayed recall), Letter-Digit Coding test, Stroop.	No association with IL-6
Dev (2017)	n = 24 Cross-sectional	n-back working memory task.	No association with IL-6

Two studies using the DSST analyzed on its own and not combined with other factors, found worse performance was associated with higher IL-6 levels. Goldstein et al. (2015) found DSST, as well as Digit Span as a test of working memory to be associated with IL-6 in a cross-sectional study. In their two other short tests in recalling patterns no association was found. Their analysis was carried out using quartile analysis of IL-6. Rafnsson et al. in a longitudinal study looking at cognitive decline over 4 years, found

higher IL-6 to be related to decline in the DSST. They also found IL-6 to be associated with decline in verbal fluency, reasoning in Ravens matrices and in general cognitive factor but in fully adjusted models higher IL-6 was only associated with worse performance in the DSST.

Two studies found an association between IL-6 and multiple measures of cognition, with association found in both memory and psychomotor assessments. Jordanova et al. (2007) ( $n = 290$ ) was one of the few studies which found that decline over 3 years in verbal recall was associated with IL-6. They also found that IL-6 was associated with a decline in psychomotor speed although the association was relatively weak. Jordanova used the TMT A test as a measure of psychomotor speed. Schram et al. (2007) had two cohorts. One cohort found higher IL-6 to be associated with worse decline in memory function. In their other cohort they found higher IL-6 to be associated with worse global cognition and with executive function. Memory was assessed with a picture learning test, while executive function was measured with a combined the Stroop and a version of the DSST, but a letter-digit substitution and not a symbol substitution. Lekander et al. (2011) in a cross-sectional study, tested over a wider age range (45-90 years old) and found an interaction effect with age, such that at higher age ranges IL-6 was associated with verbal fluency and a prospective memory test.

Two studies examined the link between IQ and IL-6. Krabbe et al. (2009) tested 112 individuals in an octogenarian cohort with the full Wechsler scale. IL-6 was correlated with IQ tested at two time-points, with a stronger correlation at age 85 than at age 80, although both were significant. Segerstrom et al. (2017) used an estimate of IQ using the NART measure (North American Adult Reading test). Higher IQ predicted lower IL-6 levels over five years, with participants aged 74 at baseline.

Elwan et al. examined the DSST, as well as TMT A and B and did not find an association with IL-6, while they did find IL-6 to be associated with attention (using PASAT) and also with a measure of intentional memory. Metti et al. (2015) ( $n = 135$ ) tested many domains and did not find any linear associations with cognitive function and IL-6.

They did however analyze the results by looking at variability of the IL-6 measure overtime and found that greater variability resulted was associated with cognitive impairment. None of the other studies analyzed the results in this way. Dev et al. (2017) had the smallest sample size ( $n = 24$ ) and used a short working memory task and found no association with peripheral IL-6 levels.

Singh-Manoux et al. (2014) included over five thousand participants and was part of the famous Whitehall studies. Participants in this study were assessed and analyzed over ten years. Results were stronger in the cross-sectional analysis, where those in the highest tertile of IL-6 performed worse on all of the cognitive measures. The associations in both the cross-sectional and longitudinal analysis remained significant with Bonferroni correction for the reasoning test only which used the Alice-Heim reasoning test which was not used by any of the other studies.

Although many studies found evidence of an association between IL-6 and executive function and/processing speed, seven studies did not find such an association. Chi et al., Teuisen et al., and Fabregue et al., all used the Stroop task and found no association. Teuisen et al. and Dik et al. also used a modified simpler version of the DSST and did not find an association with IL-6. Baune et al. used a composite score of cognitive speed and did not find an association with IL-6. Jefferson et al. used the TMT A and B test and did not find an association with IL-6. Elwan et al. as mentioned above also did not find an association with DSST or the TMT A or B.

Dik et al. (2005) had a very large sample size ( $n = 1,284$ ) and found no association with IL-6 with any of the tests used. They tested memory with a word list task, used Ravens Matrices for fluid intelligence and a version of the Digit Symbol Substitution task using alphabet coding task for processing speed. A weakness of the Dik et al. study was the detection limits for IL-6. The assay they used only had a lower limit of detection at 5pg/ml so that for most of the sample IL-6 was not sensitively measured and was just defined as below 5pg/ml.

The sample was split between high and low IL-6, with  $n = 1,140$  below 5pg/ml compared with a small sample of  $n = 147$  for the 'high' IL-6 group, with IL-6 above 5pg/ml. It is still an important non-significant result for IL-

6 as they used a large sample size and had a negative finding for the coding task which is similar to the DSST, while many other studies using this same task did find an association.

Both Alley et al. (2008) and Weaver et al. (2002) were two studies which tested a large range of cognitive domains and had large sample sizes ( $n = 851$  and  $n = 779$ ), respectively, that did find associations with IL-6, but after adjustment for confounders associations were no longer significant. Jefferson et al. (2011) had a very large sample size ( $n = 1,878$ ) and tested a very large battery of cognitive tests and found no association with IL-6. Chi et al. (2017) with a very large sample size ( $n = 1,159$ ) and found no association of single measure of IL-6 with cognition although in combined inflammation scores there were some significant findings.

Teunissen et al. (2003) ( $n = 92$ ) found no association of IL-6 with any task measured including the letter coding task. They found no association with the two other short measures they had used, a word list memory task and the Stroop task. In a study where the only cognitive measure was the Stroop task, Fabregue et al. (2016) found no association with IL-6. Baune et al. (2008), ( $n = 369$ ) found no association of IL-6 with any of the measures used.

### **3.3. Healthy Adults**

Five studies were identified which looked at cognitive function and peripheral IL-6 levels in middle age. Gimeno et al. (2008) had a very large sample size ( $n = 4,362$ ) with a larger male sample ( $n = 3,093$ ) and analysed the data separately for men and women. IL-6 was measured when the sample was an average age of 50 and followed-up five and ten years later. IL-6 was associated with cognitive function in all tests measured for and for all but the memory test in women. In fully adjusted models only semantic fluency was significant in the male sample and phonemic fluency and the Mill-Hill test in women.

**Table 3. Healthy Adults**

First Author and Year	Sample Size and Study Design	Cognitive Tests	Results
Jimeno (2008)	n = 3,093 men n = 1269 women Total n = 4,362 Longitudinal Average Age at baseline: 50	Short term verbal memory word list, Alice Heim 4-1, Mill Hill vocabulary test, Phonemic and Semantic Verbal Fluency.	In men, in age-adjusted analyses IL-6 were associated with all cognitive measures. After extensive adjustment IL-6 was associated with decline in semantic fluency in men and in women with decline in phonemic fluency and the Mill Hill Vocabulary test.
Marsland (2006)	n = 500 Cross-sectional Age Range: 30-54 Average Age: 44	Logical Memory, Verbal Paired Associates, Faces subtest, Family Pictures, Visual Reproductions, Letter-Number Sequence test, Digit span, Mental Control, Spatial span (all WMS), TMT A and B, Stroop.	Inverse relationship of IL-6 and performance on clusters of tests assessing auditory recognition memory, attention/working memory, and executive function.
Marsland (2015)	n = 408 Cross-sectional Age Range: 30-54 Average Range: 43	Block design, Matrix Reasoning, Digit Span, Spatial span, Vocabulary, Similarities (all from WAIS), TMT A, Stroop, Four Word Short Term Memory test, Rey Verbal Learning test.	Higher peripheral inflammation was associated with poorer spatial reasoning, short term memory, verbal proficiency, learning and memory, and executive function.
Stenfors (2017)	n = 214 Cross-sectional Age Range: 25-67 Average Age: 48	Face Recognition test, Letter Digit Substitution, Word List (immediate and delayed recall), TMT A and B, Reading span, Stroop, Reading span task, 2 back task.	IL-6 associated with poorer executive cognitive functioning. These associations co-varied with age especially and were not present after adjustment for demographical factors.
Wang (2017)	n = 30 Cross-sectional Average Age: 30	Internet based cognitive battery 'IntegNeuro', Immediate, short and long delay memory recall-12 word list,	IL-6 showed a positive correlation with long-delay recall.

Marsland et al. ran two similar studies (2006, 2015), using similar procedures in two different cohorts. They found strong results for an association between IL-6 and cognitive function across numerous cognitive domains and the studies largely replicated each other. The sample sizes

included were large ( $n = 408$  and  $n = 500$ ) and a comprehensive battery of test were used. Higher IL-6 was found to be associated with worse performance in auditory recognition memory, attention/working memory, and executive function in the 2006 study and with poorer spatial reasoning, short term memory, verbal proficiency, learning and memory, and executive function in the 2015 study. A range of factors had been controlled for. Stenfors et al. (2017) measured a number of cognitive domains, also in a cross-sectional design. They found that higher IL-6 was associated with worse performance in executive function but this association became non-significant after extensive adjustment. In the final study reported, by Wang et al. (2017), higher IL-6 was associated with better performance in delayed recall in a younger sample (mean age = 30); however, the small sample involved ( $n = 30$ ) limits the conclusions that can be drawn.

### **3.4. Neuro-Degenerative Disorders and Mild Cognitive Impairment Results**

Seven studies were identified which looked at individual with a neurodegenerative disorder or mild cognitive impairment, with one identified study with persons with dementia, three studies in Parkinson's disease and three studies were included which looked at mild cognitive impairment (MCI).

#### ***3.4.1. Mild Cognitive Impairment***

Three studies examined peripheral levels of IL-6 and their association with neuropsychological performance in persons diagnosed with MCI. Roberts et al. (2009) examined a large cognitive battery testing several cognitive domains and had a large sample size of  $n = 313$  persons with MCI as well as a very large sample of healthy elderly ( $n = 1,570$ ). No association between IL-6 and cognitive performance was found. Karim et al. (2014) looked at memory as well as verbal fluency and found no association with IL-6 at baseline or at 12-month follow-up. Zhou et al. (2012) only looked at

one objective cognitive test, the Auditory Verbal Learning Test, and found a weak but significant negative association with IL-6.

**Table 4. Neuro-degenerative and Mild Cognitive Impairment Table**

First Author and Year	Sample Size and Study Design	Cognitive Test	Results
<b>Mild Cognitive Impairment</b>			
Roberts (2009)	n = 313 subjects with MCI n = 1,570 HC Cross-sectional Age: 70-89 years old.	TMT B, Digit Symbol Substitution test, Boston Naming test, Category Fluency, Logical Memory, Visual Reproduction 2, Auditory Verbal Learning test, Picture Completion, Block Design.	No association with IL-6
Karim (2014)	n = 70 MCI follow-up with 62 MCI No HC Cross-sectional and Longitudinal	Free and Cued Recall Selective Reminding test, Phonemic Verbal Fluency, Cognitive Estimation test, NART, Cambridge Cognitive Examination Revised, MMSE.	IL-6 no association with any cognitive measure
Zhou (2012)	n = 150 2 groups APOE carriers versus non-carriers,	Auditory Verbal Learning test	Weak significant association of AVLT with IL-6
<b>Dementia</b>			
Guoping (2015)	n = 61 vascular cognitive impairment patients (n = 28 with dementia, n = 33 without dementia) n = 25 controls with normal cognitive function	V-DAS Cog (modified version of Alzheimer's Disease Assessment scale, only executive function scale used), (Moca and MMSE)	Higher IL-6 associated with better performance in executive function
<b>Parkinsons Disease</b>			
Menza (2010)	n = 52 PD patients also with depression Cross-sectional	Digit Span, Word List Recall and Recognition (WMS), Boston Naming test, Verbal Category Fluency, Stroop, (MMSE). (Used composite cognitive score using all measures)	Higher IL-6 associated with better composite cognitive score in unadjusted model
Selikhova (2002)	n = 27 PD with depression n = 18 without depression n = 15 HC Cross-sectional	Tower of London test, (MMSE).	Higher IL-6 was associated with worse performance in Tower of London task
Dufek (2009)	n = 29 persons with Parkinson's Disease	Verbal Fluency test, Wechsler Word List 1 and 2.	No association with IL-6.

### **3.4.2. Dementia**

Only one study of cognitive performance and IL-6, by Guoping et al. (2015), was identified, in which Executive function was measured using the VDAS-cog measure. It was found that higher IL-6 levels were associated with better scores in executive function.

### **3.4.3. Parkinson's Disease**

Three studies were identified which looked at peripheral IL-6 levels and their association with objective cognitive test performance in persons diagnosed with Parkinson's disease. Menza et al. (2010) tested persons with PD who also had depression. They tested a large battery of tests but only used a composite cognitive measure using all scores. Higher IL-6 was correlated with better performance on the composite cognitive score but in the full adjusted multiple regression model the IL-6 association became non-significant. Selikhova et al. (2002) tested persons with Parkinsons with (n = 27) and without (n = 18 depression) and only used one cognitive, the Tower of London test. IL-6 was associated with worse performance on the Tower of London task. Dufek et al. (2009) tested 27 persons with PD and tested verbal fluency and the Wechsler Word List 1 and 2 and found no association between these tasks and peripheral levels of IL-6.

## **3.5. Miscellaneous Medical**

### **3.5.1. Cardiovascular Disease Results**

Five studies were identified which looked at persons with cardiovascular disease or its risk factors and the possible relationship between cognitive function and peripheral IL-6 levels. Many longitudinal studies have been carried out looking at cardiovascular risk factors over time and which biomarkers may predict risk. Inflammation is known to play a significant role in cardiovascular disease and is associated with cognitive decline and increased risk for dementia. These studies assessed objective measures of cognitive function and peripheral IL-6 levels. An advantage of many of the



studies is very large samples sizes, but this also means brevity of cognitive tests used in many studies.

**Table 5. Cardiovascular Results Table**

First Author and Year	Sample Size and Study Design	Cognitive Tests	Results
Mooijaart (2013)	n = 5,653 (with cardiovascular disease or its risk factors.) Cross-sectional and longitudinal Age 70-82	Stroop, Letter Digit Coding test, Picture Learning test (immediate and delayed recall), (MMSE)	In the cross-sectional higher IL-6 was associated with worse executive cognitive function independent of cardiovascular disease status and risk factors. In the prospective analysis, higher IL-6 concentration was associated with an increased rate of cognitive decline in both executive function and memory function also independent of cardiovascular disease status and risk factors.
Windham (2014)	n = 1,965 (with African American (AA) and European American (EA)) Cross-sectional	Digit Symbol Substitution task, TMT A and B, Rey Auditory Verbal Learning test, Semantic and Phonemic Verbal fluency, MMSE.	Higher IL6 was associated with poorer executive function in AA. No association between cognitive tests and either IL-6 or CRP were found in EA.
Lin (2012)	n = 747 Cross-sectional	Word List, Digits Backward, Category Fluency, Number Series, Backward Counting, Stop and Go Switch Task Factor analysis- two constructs- 'Episodic Memory' and 'Executive Function'	IL-6 did not mediate the effect between cardiovascular risk scores and cognitive function.
Burkauskas (2015)	n = 483 Cross-sectional	Digit Span test, Digit Symbol test, TMT A and B.	Higher IL-6 associated with lower scores in Digit Symbol Test. Higher IL-6 also associated with longer completion time in Digit Symbol Test.
Hoshi (2010)	n = 381 Cross-sectional	Stroop, Frontal Assessment battery, (MMSE).	The FAB score was negatively correlated with IL-6.

Mooijaart et al. (2013) had a very large sample size ( $n = 5,653$ ) and measured IL-6 at baseline and then 4 additional times over 39 months (at 9, 18, 30 and 39 months). Executive function was measured with a combined score of Stroop test and Letter Digit Substitution task and a memory score used visual memory with picture learning, with both immediate and delayed memory tested.

At baseline IL-6 was associated with executive function but not with memory tests. Over time IL-6 predicted decline in both executive function and memory tests. Both the cross-sectional and longitudinal findings controlled for cardiovascular disease and risk factors.

Windham et al. (2014) had a large sample size ( $n = 1,965$ ) and tested multiple cognitive domains and divided the sample between African Americans and European Americans. Executive function was associated with IL-6 levels but only in the African American samples and not European Americans. This is an intriguing finding and many studies did not differentiate results by race.

Burkaukas et al. (2015) ( $n = 483$ ) tested participants after acute cardiac events and found that higher IL-6 was associated with lower scores and longer completion time in the Digit Symbol test. Hoshi (2010) et al. found in people with CVD risk factors that higher IL-6 was associated with a worse score in a frontal assessment battery. Lin et al. (2012) found that IL-6 did not mediate the effect between cardiovascular risk scores and cognitive function.

### **3.5.2. Cancer Studies Results**

Eleven studies were identified which looked at patients with different forms of cancer and the possible relationship between cancer related cognitive deficits and peripheral IL-6 levels. IL-6 is known to be elevated in several cancers and cognitive deficits are associated with cancer treatment as well as studies showing cognitive deficits before treatment.

The studies were very heterogeneous as they assessed the relationship at these different stages both before treatment, and then after radiotherapy, chemotherapy, before and after surgery. Breast cancer was the most studied

(8 of 11) of the total papers. Most studies (7 of 11) found no relationship between objective cognitive test performance and IL-6 levels (see Table 6).

Shibayama et al. (2013) looked at the effects of radiotherapy in breast cancer patients and its association with cognitive function and inflammation levels. They used the full Wechsler Memory Scale (WMS-R). Elevated levels of IL-6 were associated with radiotherapy and with lower delayed recall index of WMS-R.

They had a relatively large sample size of 105 patients, with breast cancer with (n = 51) and without radiotherapy (n = 54). Jehn et al. (2015), looked at persons with metastatic cancer (n = 59) and also with a subset also diagnosed with depression (n = 30). It was found that short term memory in the depressed cohort was associated with IL-6 levels. Meyers et al. (2005) had a sample size of 54 with patients with acute myelogenous leukemia and tested a range of cognitive domains. They found that IL-6 was associated with poorer executive function. Kesler et al. (2013) had the smallest sample of the identified cancer studies and looked at chemotherapy treated breast cancer patients (n = 20) and also had a control group (n = 23). They tested verbal memory, as well as Matrix Reasoning and Information subsets of Wechsler and found higher IL-6 to be associated with worse performance in verbal memory.

Six of the eight breast cancer studies found no association between IL-6 levels and cognitive function. Patel et al. was the largest study (n = 174 patients, n = 88 controls) and measured multiple cognitive domains and found no association. Ganz et al. also had a relatively large sample size (n = 94 patients) and used a very comprehensive battery of tests and found no association.

Three of other breast cancer studies all used a short computerised cognitive battery (two called 'Headminder' and one 'CNS vital signs) and all three found no association. An additional study administered computerized CANTAB measures and found no association. The sole study investigating testicular cancer used a wide battery of tests and found no association.

**Table 6. Cancer Study Results Table**

Author and Year	Sample Size and Study Design	Cognitive Tests	Results
Patel (2015)	n = 174 breast cancer patients prior to surgery n = 88 controls Cross-sectional	Trails 4, Colour Word Inhibition and Inhibition Switching (all from Delis Kaplan Executive Function battery), Hopkins Verbal Learning test, Processing speed index (from WAIS).	No association with individual levels of IL-6 on any test
Vardy (2017)	n = 126 patients with breast cancer (n = 44 who received chemotherapy and self-report cognitive difficulties, n = 52 who received chemotherapy and no self-report cognitive symptoms, n = 30 did not receive chemotherapy) Cross-sectional	CANTAB test battery, modified Six Elements test. WRAT Reading test, FACT-Cog Self Report	No association between IL-6 and any cognitive test.
Chae (2016)	n = 125 breast cancer patients post chemotherapy cognitive impairment 3 time-points (CACI-chemotherapy associated cognitive impairment)	Four tasks on Headminder™ (Attention, Memory, Processing Speed, Response speed).	No association between Headminder tasks and plasma IL-6. (self perceived result)
Shibayama (2014)	n = 105 breast cancer surgical with (n = 51) and without radiotherapy (n = 54) Cross-sectional	Full Wechsler Memory Scale-Revised.	Elevated levels of IL-6 were associated with radiotherapy and with lower delayed recall index of WMS-R
Cheung (2015)	n = 99 Patients with Breast Cancer No HC Cross-sectional and Longitudinal 3 time-points, baseline before chemo, and at 6 and 12 weeks after chemo initiation.	A computerized neuropsychological assessment (Headminder™) (assesses memory, attention, response speed and processing speed). (FACT-Cog self perceived cognitive disturbances)	No association with IL-6 and any objective cognitive tests. (Higher IL-6 and worse self-reported cognitive disturbances.)
Ganz (2013)	n = 93 Breast Cancer patients after treatment. Measured at baseline, 6 months and 12 month later	Wechsler Test of Adult Reading, California Verbal Learning Test, Wechsler Logical Memory scale, Brief	No association with IL-6 levels with any cognitive measure.

Author and Year	Sample Size and Study Design	Cognitive Tests	Results
		Visuospatial Memory Test, Rey Osterreith Complex Figure, Trailmaking Test, Parts A and B, Digit Symbol test, Stroop, letter number sequencing test, grooved pegboard, verbal fluency,	
Lyon (2016)	n = 75 Breast Cancer Longitudinal	CNS Vital signs test (Psychomotor speed, complex attention, executive function, verbal memory, cognitive flexibility, composite memory and visual memory.)	No association with IL-6 levels
Amidi (2015)	N = 66 testicular cancer N = 25 healthy controls	Wechsler Symbol Coding, TMT- A and B, Digit span, PASAT, Rey Auditory Verbal Learning Test, Verbal Fluency, WCST, WAIS vocabulary test,	No association with IL-6 levels (Subjective cognitive complaints associated with IL-6)
Jehn (2015)	N = 59 Patients with Metastatic Cancer (n = 30 with depression, n = 29 without depression)	Verbal Learning and Memory test.	Short term memory deficit was associated with IL-6 levels
Meyers (2005)	n = 54 patients with Acute Myelogenous Leukemia at baseline (n = 27 also evaluated 1 month later) Cross-sectional and longitudinal	Digit Span, Digit Symbol, Hopkins Verbal Learning test, Controlled Oral Word Association, TMT A and B, Grooved pegboard.	IL-6 associated with poorer executive function.
Kesler (2013)	n = 20 chemotherapy treated breast cancer survivors n = 23 HC Cross-sectional	Hopkins Verbal Learning test revised, Matrix reasoning and Information subtests of Wechsler combined for measure IQ.	Higher IL-6 associated with worse performance in Verbal Memory

### 3.5.3. HIV Studies Results

Six studies were identified investigating HIV and cognitive dysfunction and its possible relationship to peripheral IL-6 levels. Four of the six studies found an association.

Lake et al. (2015) used two cognitive tests, TMT A and B and DSST and had the largest sample size of 509 persons with HIV and also 271 healthy controls. They found within the HIV group only that IL-6 was associated worse cognitive performance. Pederson et al. (2013) tested several cognitive domains and found a weak association with learning and memory score. Cohen et al. (2011) had a relatively smaller sample size and found IL-6 levels to be associated with reduced performance in TMT B. Rubin et al. (2017) was the only longitudinal study and looked at women only with HIV (n = 72) and found IL-6 levels to predict subsequent cognitive decline.

**Table 7. HIV Studies**

Author and Year	Sample Size and Study Design	Cognitive Tests	Results
Lake (2015)	n = 509 HIV+ n = 271 HC Cross-sectional	TMT A and B, Symbol Digit test.	In HIV+ only IL-6 was associated with worse cognitive performance.
Imp (2017)	n = 253 (women only) Cross-sectional	Hopkins Verbal Learning Test– Revised, Stroop, TMT A and B, the Symbol Digit Modalities Test, the Phonemic Verbal Fluency, Semantic Verbal Fluency, the Letter Number Sequencing test, and the Grooved Pegboard test.	IL-6 not associated with worse cognitive performance.
Kapetanovic (2010)	n = 89 children with HIV Cross-sectional	Full Wechsler Intelligence scale for children.	No association between the cognitive measures IL-6
Pedersen (2013)	n = 53 HIV patients n = 31 HC Cross-sectional	Information (WAIS), NART, Rey Auditory Verbal Learning test, Phonemic and Semantic Verbal fluency, TMT A and B, Digit Symbol Modalities test.	Weak negative association IL-6 and learning and memory
Rubin (2017)	n = 72 women with HIV Longitudinal	Hopkins Verbal Learning test, Letter Number Sequencing, TMT A and B, Stroop, Symbol Digit Modalities test, Controlled Oral Word Association test, Category Verbal Fluency test, Grooved pegboard.	IL-6 predicted cognitive impairment
Cohen (2011)	HIV and Hep C coinfection n = 30 HIV patients n = 37 HC Cross-sectional	TMT A and B, Stroop, Letter Number Sequencing, Digit Symbol Coding, Symbol search, Grooved Pegboard test.	Elevated IL-6 associated with reduced performance of TMT B.

Imp et al. (2017) in  $n = 253$  considered women with HIV. They tested a large cognitive battery (Table 7) but found no association between IL-6 and cognition. In a study with HIV positive children, Kapetanovic et al. (2010), the full Wechsler IQ test was used and no association was found with IL-6. Overall there is some evidence to suggest IL-6 to be connected with cognitive function in HIV as four of the six studies found associations, with higher IL-6 associated with poorer performance.

#### **3.5.4. Diabetes**

Two studies were identified which looked at cognition and IL-6 levels in persons with diabetes. Both studies had very large sample sizes and were cross-sectional in design. Marioni et al. tested a very large cognitive battery (Table 8) and had a sample size of over a thousand ( $n = 1,066$ ). Higher IL-6 associated with worse performance in general 'g' factor as well as all individual cognitive tests except for Logical Memory. After controlling for many co-varieties, the general g factor as well Digit Symbol test, TMT B and Matrix Reasoning remained significant. Murdock et al. (2016) used a smaller battery of cognitive tasks with a large sample size ( $n = 835$ ). IL-6 was found to be associated with all cognitive measures with better inhibition was associated with lower levels of IL-6. These studies suggest that elevated IL-6 levels may be associated with cognitive function in diabetes.

#### **3.5.5. Kidney Disease**

One study investigated chronic kidney disease and cognitive function (Tamura et al., 2017) with a very large sample size ( $n = 757$ ) and looked at two cognitive tasks, the TMT A and B and Buschke Selective Reminding test.

Chronic kidney disease patients have an increased risk for cognitive decline and dementia and it is thought this may be connected to the increased inflammation associated with the disorder. IL-6 levels were measured at a median of 1.2 years before the first cognitive assessment. Higher IL-6 was associated with each cognitive score in age-adjusted analysis at baseline, however in fully adjusted models there was no association with IL-6. IL-6 was not associated with decline in cognitive function.

### **3.5.6. Stroke**

One study was identified looking at ischemic stroke patients (Narasimhalu et al., 2015). A very large battery of cognitive tests were used (Table 8) with a sample size ( $n = 243$ ).

The cognitive tests were assessed 3 months post-stroke and annually for 5 years. IL-6 levels were not associated with the baseline cognitive scores or with decline, although other inflammatory markers in the study were associated.

### **3.5.7. Epilepsy**

One study was found which looked at epilepsy and the possible link between cognition and IL-6 levels in the disorder (Hermann et al., 2017). The study specifically looked at older people who had suffered with chronic epilepsy. The study only cross-sectional in design and used a very large battery of tests, looking at several cognitive domains (Table 8). Forty patients were included with 152 healthy controls. No association with IL-6 was found.

### **3.5.8. Hepatitis C**

Two studies were found which looked at Hepatitis C and cognitive function and its possible association with IL-6 levels, one in an adult sample and one in a child sample. Hilsabeck et al. (2010) looked at veterans with chronic Hep C and a computerized battery looking at several cognitive domains.

IL-6 was associated with worse performance in the continuous performance test and the Sternberg memory search test. Abu Faddan et al. (2015) looked at children with Hep C and used the Stanford-Binet test. Higher IL-6 was associated with worse performance in abstract visual reasoning, quantitative reasoning test and IQ.

### **3.5.9. Lupus and Rheumatoid Arthritis**

Two studies were found which looked at lupus, with one also assessing rheumatoid arthritis. Kozora et al. (2001) tested a very large battery of tests,



but only had a very small sample size with only 15 Lupus patients, 15 with Rheumatoid Arthritis and 15 controls.

Higher IL-6 was associated with better performance in learning domains (learning tests defined as Story and Figure memory test and California Verbal Learning test). Kozora et al. (2012) also tested a large battery of tests and had a much larger sample with 84 patients with Lupus.

These patients were also selected for those Lupus patients without any neuro-psychiatric disorders and had 37 controls. The results were largely negative with composite scores of various conditions were negative. In the analysis with individual test scores, TMT-A was the only test that was significantly associated with IL-6, while there was a trend result for the California Verbal Learning test.

### ***3.5.10. Sleep Disorder Results***

Two studies were identified which looked at sleep apnea and the possible role of increased IL-6 impacting on cognitive function. Haensel et al. (2009) tested a very large cognitive battery (see Table 8), and had a sample size of 39. Participants had an overnight stay to confirm the sleep apnea diagnosis.

Blood was taken upon waking in the study. IL-6 was not found to be associated with any of the cognitive tests, although other inflammatory markers, such as TNF-a, were found to be associated. The average age in the study was 47 years old. In the second study, Huang et al. (2017) had a larger sample size of 79 and was focused on children with sleep apnea, aged 4 to 12 years old.

They looked at just two cognitive tests, the Wisconsin Card Sorting test (WCST) and the Continuous Performance test. There was a significant relationship between IL-6 and three of the WCST measures (total error standard scores, total error T scores and also with conceptual level response scores) in a regression model controlling for many other factors. No relationship with the CPT measure was found.

**Table 8. Miscellaneous Medical Studies Table**

First Author and Year	Sample Size and Study Design	Cognitive Tests	Cognitive Results
<b>Diabetes</b>			
Marioni (2010)	n = 1,066 elderly Cross-sectional	Faces and Family Pictures, Logical Memory (WMS), Letter Number Sequencing, Matrix Reasoning, Digit Symbol test (WAIS), Verbal Fluency, TMT A and B, (Mill Hill Vocabulary test as co-variate)	Higher IL-6 associated with worse performance in general g factor as well as all individual cognitive tests except for Logical Memory. After controlling for many co-varieties general g factor as well Digit Symbol test, TMT B and Matrix Reasoning remained significant.
Murdock (2016)	n = 835 Cross-sectional	Digit Span, Stop and Go Switch task, Backwards Counting, Number Series task.	Higher IL-6 associated with worse performance in all cognitive measures. Better inhibition associated with lower levels of IL-6.
<b>Lupus</b>			
Kozora (2001)	n = 15 Lupus patients without neuropsychiatric symptoms n = 15 patients with rheumatoid arthritis n = 15 HC Cross-sectional	WAIS-R, Digit Vigilance test, Paced Auditory Serial Addition test, Category test, TMT A and B, Story Memory test, Figure Memory test, California Verbal Learning test, Controlled Oral Word Association test, Ruff Figural Fluency test, Complex Material test, Reading Comprehension-PIAT, WAIS Vocabulary, Block Design and Object Assembly.	Higher IL-6 associated with better performance in learning domains (learning tests defined as Story and Figure memory test and California Verbal Learning test).
Kozora (2012)	n = 84 Systemic Lupus Erythematosus without neuropsychiatric disorders n = 37 Healthy Controls Cross-sectional	American College of Rheumatology SLE battery WAIS Digit Symbol Substitution, TMT B, Stroop, California Verbal Learning Test, Rey Osterrieth Complex Figure test, WAIS Letter Number Sequence task, Semantic and Phonemic Verbal Fluency, Finger Tapping test, WAIS Block Design, Paced Auditory Serial Addition test, Digit Vigilance test, Category test, Wechsler test of Adult Reading	IL-6 not associated with any of the composite scores. For each individual test performance only TMT-A was significant. Trend significance for CVLT.

First Author and Year	Sample Size and Study Design	Cognitive Tests	Cognitive Results
<b>Kidney Disease</b>			
Tamura (2017)	n = 757 patients with chronic kidney disease Cross-sectional and Prospective	TMT A and B, Buschke Selective Reminding test, (MMSE).	Higher IL-6 was associated with each cognitive score in age-adjusted analysis at baseline, however in fully adjusted models there was no association with IL-6. IL-6 was not associated with decline in cognitive function.
<b>Hep C</b>			
Hilsabeck (2010)	n = 78 patients with chronic Hep C patients (77 were men) Cross-sectional	-Automated Neuropsychological Assessment Metrics (Code Substitution, Continuous Performance test, Matching to Sample, Math Processing, Spatial Processing, Simple Reaction Time, Sternberg Memory Search).	Higher IL-6 was associated with poorer cognitive functioning, with Continuous Performance test and Sternberg memory test.
Faddan (2015)	n = 35 children with Hep C n = 23 HC Cross-sectional	Stanford Binet-test.	Higher IL-6 associated with worse performance in abstract visual reasoning, quantitative reasoning test and IQ in children with Hep C.
<b>Stroke</b>			
Narasimhalu (2015)	n = 243 Cross-sectional and longitudinal First assessment 3 months post stroke and then annually for up to 5 years	Digit Span, Visual Span, Auditory Detection, Boston Naming, Category Fluency, Symbol Digit Modality test, Digit Cancellation, Maze task, Visuo-construction (WMS), Visual Reproduction Copy task, Clock drawing, Block Design, Word list recall, Story recall, Picture recall. (Composite score used).	No association with IL-6, with baseline or decline
<b>Epilepsy</b>			
Hermann (2017)	n = 40 patient with epilepsy, n = 152 HC Cross-sectional	Vocabulary, Similarities (WAIS), WRAT reading test, Boston Naming test, Block Design, Matric Reasoning, Benton Judgement of Line Orientation, Clock Drawing test, Digit span, Arithmetic, Letter Number sequencing, Stroop, TMT A and B, Faces (WMS), Rey Auditory Verbal Learning test.	No association with IL-6

**Table 8. (Continued)**

First Author and Year	Sample Size and Study Design	Cognitive Tests	Cognitive Results
<b>Sleep Disorders</b>			
Huang (2017)	n = 79 Paediatric Obstructive Sleep Apnea Cross-sectional	Wisconsin Card Sorting test, Continuous Performance task.	IL-6 associated with worse performance in WCST.
Haensel (2009)	n = 39 patients obstructive sleep apnea Cross-sectional	Digit Symbol, Digit Span, Symbol Search, Letter Number Sequencing, Brief Visuospatial Memory test, Hopkins Verbal Learning test, TMT A and B, Digit Vigilance test, Stroop, Controlled Oral Word Association test.	No association with IL-6
<b>Substance Use</b>			
Leclercq (2012)	n = 40 Alcohol Dependent persons n = 16 Controls Cross-sectional and longitudinal over 3 weeks	Selective Attention Reaction Time task (computerized 'Batterie d'Attention de William Lennox' (BAWL) in its version 4.0).	No association with IL-6.
Hanak (2017)	n = 24 alcohol dependent persons.	Stroop, Brown-Peterson procedure	No association with IL-6
Levandowski (2016)	n = 42 crack cocaine addicted women n = 52 HC Cross-sectional	Wisconsin Card Sorting task. Wechsler Matrix Reasoning and Vocabulary	Higher IL-6 was associated with worse performance on the WCST, in percent conceptual levels response and non-perseverative errors. IL-6 also associated with IQ in zero order correlation
Keen (2014)	n = 161 African American adults and self-report marijuana use Cross-sectional	Symbol Digit Modalities test, TMT A and B, Stroop, WCST.	In zero order correlations, higher IL-6 was associated with worse performance in TMT A and B, Stroop, Symbol Digit and total correct responses in WSCT. In a regression model controlling for various confounders, IL-6 was still significantly associated with worse performance on the Stroop task.

### **3.5.11. Substance Use Studies**

Four studies were identified which looked at alcohol and drug use and the possible connection with increased IL-6 levels and cognitive function. Two studies looked at alcohol dependent subjects at the beginning and end of a detoxification program. Two studies dealt with drug use, one with women with crack cocaine addiction and another study looking at persons with long term cannabis abuse.

Postmortem studies as well as animal models have indicated that increased neuro-inflammation may be associated with alcohol dependence (Hanak et al., 2017). Two studies were identified looking at alcohol use, cognition and IL-6 levels. Leclercq et al. (2012) used a very short selective attention task looking at reaction time, in a study of people with alcohol dependence. The study examined the participants before and after a 3 week withdrawal program. IL-6 was not associated with the selective attention task although other inflammatory markers such as CRP were associated. Hanek et al. (2017) also looked at alcohol dependent persons at the beginning and at end of a 3 week program.

Twenty-seven subjects were included, and subjects were further divided in Lesch topology, which separated the groups into three different types of alcohol dependence. They used the Stroop test to assess executive function and the Brown Peterson procedure to assess working memory. While there was a trend negative association with IL-6 and the Brown Peterson score, it did not reach significance and there was no association between IL-6 and Stroop.

Levandowski et al. (2010) used the Wisconsin Card Sorting test (WCST), to examine executive functioning in 42 women with crack cocaine addiction and also included 52 controls. They also included an IQ estimate measure using two subtests of the Wechsler. IL-6 was found to be associated with worse executive performance within the crack cocaine group, being associated with percent conceptual response and with non-perseverative errors. IQ was also found to be associated with IL-6 in a zero order correlation.

In a full regression model controlling for several co-variates, IL-6 could predict percent conceptual levels response but not the non-perseverative errors in the WCST.

Keen et al. (2014) looked at long-term self-reported marijuana use in 161 African Americans and possible links between inflammation and cognitive function. Part of the interest in the study was that marijuana use has been linked to having anti-inflammatory effects and the study wanted to examine inflammation and its effects in long term users. Non-marijuana users were found to have higher levels of IL-6.

They assessed cognition in four tests using the Symbol Digit task, TMT A and B, Stroop and WCST. In zero order correlations, higher IL-6 was associated with worse performance in TMT A and B, Stroop, Symbol Digit and total correct responses in WCST. In a regression model controlling for various confounders, IL-6 was still significantly associated with worse performance on the Stroop task. There was an interaction between IL-6 and lifetime use, such that those with high levels of IL-6 who were not life time users of marijuana had worse neurocognitive performance than life time users with high IL-6 levels.

## **4. DISCUSSION**

A large body of research covering numerous disorders have investigated the role IL-6 may play in cognition. There has been an explosion of research examining the role inflammation plays across CNS disorders and cytokines have been found to be involved in basic CNS processes of learning and memory, outside of 'neuro-inflammation'. Eighty-eight clinical studies were identified in this systematic review.

The picture which emerges from this review is that, in general, there is consistent evidence for an association between IL-6 and cognitive function, depending on the participant group. Most studies controlled for a wide range of confounders in their analysis, and multiple cognitive domains were implicated, including executive function, processing speed and verbal and visual memory. Where significant associations were observed, the vast

majority of studies found higher IL-6 levels to be associated with cognitive impairment.

#### **4.1. IL-6 and Cognition in Schizophrenia and Other Psychiatric Disorders**

For schizophrenia, the focus on this review, alternative models have been proposed for how immune function may contribute to risk. For example, following on a wealth of evidence from genetic studies association Schizophrenia risk with a region of Chromosome 6 known as the multiple histocompatibility complex (MHC), a complex region long been associated with autoimmune function, it has been proposed that variation at this locus leads to increased risk via altered synaptic pruning (Schatz et al., 2003; Sekar et al., 2017). Here, independent of immune activation resulting from, e.g., infection during neuro-development, changes in expression of autoimmune proteins many result in abnormal changes to neurodevelopmental processes such as synaptic pruning. In these alternative models, IL-6 may or may not serve as part of the immune or autoimmune related mechanisms by which risk is mediated. Even if IL-6 is an aspect of the mechanism, IL-6 may or may not have a role in mediating variation in cognition.

Based on the schizophrenia studies reviewed, the evidence that IL-6 is consistently associated with cognitive deficits is somewhat weak. Only one of five studies reviewed found evidence of a significant correlation between IL-6 levels and cognitive performance. It is noteworthy the quality of studies varied and that the single significant association was observed in the largest of the studies reported. It is also noteworthy that the association was influenced by clinical state (Miller et al., 2011), and that stage of illness was not included as a covariate in most analyses. Similarly, in students of bipolar patients a consistent association was not observed.

By contrast a more consistent association between IL-6 and cognition was observed across the depression studies reviewed. These findings are in contrast to findings from studies in patients with neurodegenerative disorder and those treated for other medical conditions, discussed next. A review of

the table of psychiatric results versus study in healthy participants, degenerative disorders and other medical disorders suggests that these other studies often had samples 3-10 times larger than the schizophrenia studies. It may be that the case that studies carried out until now have been underpowered to detect association between IL-6 and cognition. Low sample size is particularly likely to result in issues of power in studies of schizophrenia given the well-known heterogeneity in profile of cognitive deficits observed. This, together with evidence of genetic contribution to cognitive deficits in schizophrenia may have obscured the impact of IL-6 on cognition in these studies.

#### **4.2. Association between IL6 and Cognition in Health Aging and Neurodegenerative Disorders**

By far the largest category of studies identified were in the healthy elderly studies. 27 studies were identified and in many of the studies, there were very large sample sizes. While there were 9 studies with no association found, 17 studies did find an association and the executive function and processing speed domains emerged as a more consistent finding, with 10 of the 17 looking at this domain observing an association with IL-6. Verbal memory was a common measure used with much less evidence for an association with IL-6. Higher IL-6 levels were associated with impairment in cognitive function in all studies. The next category which had the strongest association were in the cardiovascular disease and risk factor studies. Five studies were identified and similar to the healthy elderly population studies, there were very large sample sizes involved (the lowest study with 381 participants and the largest with 5,653). Four of the five studies found an association and all were with executive function/processing speed domains.

Results were also mixed in the neurodegenerative studies. In the MCI studies, only one out of three studies reported a relationship between IL-6 and cognitive performance. In studies of Parkinson's disease, both better and worse cognitive performance have been associated with higher IL-6 levels.



Finally, only one study of dementia was identified, which reported association between poorer cognitive performance and IL6.

Collectively, these findings suggest a more complicated picture of the relationship between IL-6 and cognitive function than simply higher levels leading to impairment. Animal models have previously shown equivocal findings where IL-6 can be associated with improved or impaired performance. IL-6 has been shown to have both neuroprotective and neurotoxic properties within the CNS. Cytokines have been shown to be involved in learning and memory processes outside of neuro-inflammation. The relationship may not be linear, with studies for IL-1b showing that both high and low levels were associated with impairment, and presenting with a u-shaped curve. Cytokines may be necessary for learning and memory processes where low levels also result in impairment (Goshen et al., 2007). These results suggest that IL-6 relationship with cognition may be disorder specific.

#### **4.4. IL-6 and Cognition in Other Medical Disorders**

Overall there is consistent evidence for an association between IL-6 and cognitive function in patients with cardiovascular disease or with cardiovascular disease risk factors. In four of the five studies, higher IL-6 was associated with worse cognitive performance. One study found an association with the DSST task, while three of the additional studies found an association with executive function tasks. One of the studies found an association of IL-6 with decline in visual memory. The studies controlled for numerous CVD risk factors as well as other confounders.

In studies of patients with cancer the results were more mixed. Four of the studies found an association, two looking at breast cancer patients, one metastatic cancer and one in leukemia. Three of the four studies identified deficits in verbal memory, with one finding a deficit in executive function. Seven studies did not find an association, including six of the eight breast cancer studies. While some of the cancer studies used a relatively brief computerized test, two of the studies used more comprehensive battery and

found no association. Among the studies which did find an association, one was only in cancer patients with depression and one was associated with radiotherapy. One of the studies which found an association also had the lowest sample size (Kesler et al.;  $n = 20$  patients,  $n = 23$  controls).

Two studies investigated Hep C and both found an association, one with IQ and the other study with memory and the continuous performance task. The two diabetes studies both found an association with higher IL-6 and worse cognitive performance and both studies used composite cognition scores. Two studies investigated Lupus. IL-6 was found to be associated with a learning domain in one study and the other found an association with the TMT A which measures processing speed. Two studies investigated sleep apnea. One of the studies found higher IL-6 associated with lower scores in the Wisconsin Card Sorting test (WCST) (which is a test of executive function), while examined a large battery, testing multiple cognitive domains and found no association.

In the substance use studies, no association was found in the two studies looking at alcohol dependence. In the study investigating crack addiction, higher IL-6 was associated with worse performance in the WCST, which is an executive function task. In the cannabis study, higher IL-6 was associated with worse performance in Stroop, which is also a test of executive function. In disorders with only one study identified, no association was found; in the kidney disease study, the epilepsy study, or stroke study.

## CONCLUSION

This review suggests that peripheral interleukin-6 levels are associated with variation in cognitive function. While this was seen across a range of studies of healthy and older healthy participants, as well as patients with neurodegenerative and other medical disorders, the picture was perhaps least clear of all for patients with schizophrenia. A variety of reasons for this are discussed, including the size of the studies carried out to date and the heterogeneity of both the samples and range of cognitive performance typically observed in patients with psychotic disorders. Both can be

compared with patients with depression which, as with other groups, showed a more consistent pattern of association. Among the studies review, most investigated peripheral IL-6 levels in isolation, in either plasma or serum. A single cytokine measure may be very limiting as an assessment of chronic low-grade inflammation. With the advent of accurate multiplex systems which can measure multiple inflammatory measures at a time, these global inflammation assessments may be advantageous to assess the link with chronic low-grade inflammation and cognition, which could be a focus of future studies. Based on the current data for schizophrenia however, one important conclusion is for future intervention studies targeting IL-6, with the implication that changes in cognition are unlikely to represent a useful primary outcome measure against which to estimate efficacy. Instead, it may well be that other outcome variables, including psychotic symptoms are, at least in this instance, likely to be more sensitive to changes in IL-6.

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*Chapter 4*

**INTEGRATED NEUROCOGNITIVE THERAPY:  
AN INNOVATIVE APPROACH TO  
REHABILITATION OF PATIENTS  
WITH SCHIZOPHRENIA**

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**ABSTRACT**

Schizophrenia is considered one of the most disabling of mental illnesses affecting the population. It is characterized not only by the presence of positive symptoms, such as delusions and hallucinations, but also by the presence of cognitive deficits that have a strong impact on the psychosocial functioning of patients. It is for this reason that cognitive enhancement interventions were developed, which led to improvements in global functioning. Recently, experts from the MATRICS project (Measurement and Treatment Research to Improve Cognition in Schizophrenia) identified the cognitive areas that are altered in patients by

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dividing them into seven separate cognitive domains: Processing Speed, Attention/Vigilance, Working Memory, Verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition. Most cognitive enhancement interventions do not integrate all seven of these MATRICS identified cognitive domains. Recently however, a group of experts from the University of Bern developed such an approach, called Integrated Neurocognitive Therapy (INT), which combines neurocognition and social cognition by developing specific interventions for each MATRICS domain.

The aim of this chapter is to describe this new type of intervention, clarifying its benefits in light of recent studies conducted to evaluate its effectiveness.

**Keywords:** cognition, rehabilitation, Integrated Neurocognitive Therapy

## INTRODUCTION

Cognitive impairment is one of the fundamental characteristics of schizophrenia. In fact, beyond the peculiar symptoms of the disease there is a high percentage of schizophrenic patients (about 98%) presenting with impairment in a wide range of cognitive abilities (Keefe et al., 2005). According to some studies (Davidson et al., 1999; Cornblatt & Erlenmeyer-Kimling, 1985), cognitive deterioration starts before the emergence of the hallmark positive symptoms of the illness. In fact, moderate to severe impairments across most cognitive domains are detectable at the time of the first episode (Bilder et al., 2000; Saykin et al., 1994) and appear stable from emergence of the first episode until middle age (Rund, 1998). Two recent meta-analysis confirmed that a minor cognitive impairment is present at the onset of the disease (Woodberry et al., 2008; Aylward et al., 1984).

Schizophrenia is associated with impairments across a number of cognitive domains and the breadth of this impairment has led some to conclude that it is a disease with a global profile of neuropsychological impairment (Blanchard & Neale, 1994; Dickinson et al., 2004).

A meta-analysis (Heinrichs & Zakzanis, 1998), based on 204 studies confirms previous suggestions that any selectivity of deficit in schizophrenia occurs in the context of a background of a very general impairment in

cognitive brain function. Some evidence, however, suggests that there are discrete domains of cognitive impairment. For example, Bilder and colleagues (Bilder et al., 2002) found mild to moderate deficits in attention, verbal fluency, working memory, and processing speed, with superimposed severe deficits in declarative verbal memory and executive functioning. Other work suggests that discrete cognitive domains have differential correlates with symptom and functional domains. That is, most individuals with schizophrenia demonstrate at least some cognitive impairment, but, like other aspects of the illness, the severity and breadth of these impairments vary across patients. A rather unique feature of cognitive deficits, as compared to other characteristics of schizophrenia, is that they remain relatively stable within the same patient over time; they are generally consistent in severity and topography across changes in a patient's clinical status (Harvey et al., 1990; Bowie & Harvey, 2006).

Relative to the positive, negative, and disorganization symptom domains, cognition is the strongest predictor of functional outcome (Green, 1996; Green et al., 2000). Cognitive deficits in schizophrenia have been shown to interfere with various aspects of daily functioning, including employment, independent living, and quality of life (Bell & Bryson, 2001; Twamley et al., 2002; Perlick et al., 2008; Mohamed et al., 2008). In particular, a negative correlation between cognitive deficit and global functioning of the subjects has been found (Bowie & Harvey, 2006). As such, it is important to consider the inclusion of rehabilitative activities aimed at cognitive recovery within the patient's therapeutic path.

## **COGNITIVE REMEDIATION TECHNIQUES**

In recent years, there has been an increasing interest in the development of new pharmacological agents to improve cognition. However, to date, the use of antipsychotic drugs has shown an effect on the main symptoms of the disease but not on specific cognitive domains, which explains the increasingly widespread use of cognitive remediation (CR) for schizophrenia (Bon & Franck, 2018). Cognitive remediation techniques are

defined as interventions based on behavioral training that aims to improve cognitive processes in a long-lasting and generalizable way.

These interventions can be classified according to two models: compensatory and reparative. Compensatory interventions try to bypass the deficit and compensate for it by relying on intact cognitive skills and environmental resources, promoting an adaptation of the context in which the patient lives and an adaptation of his behavior to the specific situation, while restorative interventions try to correct and improve the deficit by drill and practice exercises.

The restorative techniques are based on neuroscientific knowledge according to which the neuronal processes compromised can be repaired through repeated exercise, which leads to a restoration of those neuroanatomical connections linked to neuropsychological abilities. This particularly concerns the white matter pathways, which, as known through many studies on imaging and MR techniques, play an important role in the neuropathology of schizophrenia, and are likely related to clinical symptoms observed in this disorder (Kubicki et al., 2007).

In recent years, structured protocols of cognitive training specific for schizophrenia have been developed and used in various randomized controlled trials published in international scientific literature. They can be distinguished by the mode of application (individual or group; computerized or paper and pen; presence or absence of therapist) or by whether they are primarily based on repeated execution of specific tasks, or on the development and learning of new strategies (Vita et al., 2014).

One example of a recent CR program is that published by McAvinue and colleagues in 2013; an online program specifically targeting Working Memory (WM) (McAvinue et al., 2013). This web-based program targeted both auditory and visual WM modalities following Baddeley's (2000) model and consisted of a mixture of psycho-education on the nature of working memory, strategy-based learning, and practice of nine working memory focused training exercises that were gradually introduced (Baddeley, 2000). A recent study by Hargreaves et al., (2015) sought to ascertain the effectiveness of this novel 8-week WM training program on neuropsychological performance in patients with schizophrenia and related

psychosis. Based on a comparison of patients who received CR versus treatment as usual (TAU), some improvements in working and episodic memory were observed. Even though the cognitive benefits observed in this preliminary study indicate that internet-based working memory training could be an effective cognitive remediation therapy, the improvements remained limited to the target cognitive domain mainly (Hargreaves et al., 2015). From the literature, only three cognitive domains have been reported to be positively impacted by WM training: episodic memory (Hargreaves et al., 2015); attentional ability (Kundu et al., 2013; Lilienthal et al., 2013) and fluid reasoning (Rudebeck et al., 2012; Jaeggi et al., 2008). Anyway, improvements in memory related tasks did not generalise to general cognitive functioning. This suggests that an approach targeting multiple cognitive domains may be more of benefit, since according to Wykes et al., (2011), one of the fundamental concepts of CR is that any cognitive benefits be generalizable across cognitive domains (Wykes et al., 2013).

Thus, an important concept is that the change in cognitive performance is a primary goal of cognitive remediation techniques, but the main goal is to improve the overall functioning and quality of life of the patient (Vita et al., 2014).

On this basis, some innovative approaches have been developed. One of them is a new form of CR, action-based cognitive remediation (ABCR), which aims to optimize traditional CR to promote cognitive flexibility and to transfer skills acquired during treatment sessions to patients' everyday lives. It involves individual goal setting, an intense training program combining computerized training with practical in-session activities, and cognitively challenging tasks between sessions, covering the following cognitive domains: meta-cognition, verbal and visual working memory, memory, attention, and executive functions (organization, shifting attention, and planning) (Ott et al., 2018).

To address the issue that cognitive remediation programs often have larger effects on cognition compared with everyday outcomes, this new CR program was examined and compared across cognitive, functional competence, and vocational domains with traditional CR (tCR) programs and has shown promising results. Specifically, Bowie et al., (2017)

compared ABCR to tCR in a patient group with severe mental illness. Significantly more ABCR participants were retained in the intervention compared with tCR and reported greater increases in perceived competence with cognitively challenging tasks. They also were marginally more likely to be competitively employed and, among those employed, experienced less job-related stress. While both treatments improved cognition, ABCR had a greater effect on functional capacity than traditional CR (Bowie et al., 2017). This converges with a meta-analysis on CR trials in schizophrenia showing that the combination of CR and skills training had larger effects on patients' functional capacity than CR alone (McGurk et al., 2007).

Overall, the data reported in the literature highlight the favorable effects of various techniques on cognitive performance and problem solving skills, with a persistence of the effect even after the interruption of treatment and a generalization of the effects to social and work functioning (Genevsky et al., 2010; Kern et al., 2009; Pfammatter et al., 2006).

Furthermore, some recent meta-analyses have shown that cognitive remediation interventions have positive effects not only on cognitive performance, but also on psychosocial functioning and, to a small degree, on symptoms that tend to improve on the first follow-up. The apparently limited impact of cognitive remediation on symptoms is consistent with numerous studies showing that cognitive impairment is relatively independent of other symptoms of schizophrenia. Cognitive remediation may have some beneficial effects on symptoms by providing positive learning experiences that serve to bolster self-esteem and self-efficacy for achieving personal goals, thereby improving depression (Wykes et al., 2011; McGurk et al., 2007). Several studies have reported that cognitive remediation improved mood (McGurk et al., 2005; Wykes et al., 1999).

Either way, the positive effects of cognitive remedies on schizophrenic disorder are visible through specific tests that show improvements and changes within neural networks in some areas of the brain. To support this, Mothersill and Donohoe (2019) conducted a systematic review and meta-analysis of 31 neuroimaging studies, which examined brain activation in response to cognitive training in schizophrenia. The most common finding among the studies was an increase in activation of the left prefrontal cortex,



indexed as an increase in cerebral blood flow that can be interpreted as a “normalization” of the activation of this region in schizophrenia, such that the cortical activation of the patient approaches that observed in healthy post-treatment controls. At the same time, however, changes in neural activation have been reported in a wide range of other brain areas. Indeed, the activation likelihood estimation meta-analysis conducted by Mothersill and Donohoe (2019) did not reveal any specific brain regions showing consistent effects across studies but rather suggested a broader, more distributed pattern of effects resulting from the interventions tested. This suggests that the effects are widely distributed in many brain regions, including parietal, occipital, temporal and limbic regions. As such many important areas for cognition and emotions may be sensitive to training, probably due to the variety of therapy programs used (Mothersill & Donohoe, 2019).

## **THE MATRIX PROJECT**

The recognition of the importance of cognitive functioning in schizophrenia has encouraged the development of different therapeutic approaches and assessment tools. For this reason, it is important that there is agreement on which cognitive domains are relevant in schizophrenia and how they can be reliably evaluated for the study and development of new therapeutic programs. In this context, the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative of the National Institute of Mental Health (NIMH) set itself the goal of finding a consensus about defining the main areas of cognitive functioning in schizophrenia and then developing a battery of standardized neuropsychological tests (Marder & Fenton, 2004).

The other objective was to evaluate the possible methods of intervention, initially mainly pharmacological, for the improvement of cognitive deficits (Green & Nuechterlein, 2004; Nuechterlein et al., 2004; Kern & Horan, 2010). Therefore, based on expert interviews and various factorial analyzes, six main dysfunctional neurocognitive domains,

relatively independent of each other (Nuechterlein et al., 2004; Roder et al., 2010; Roder et al., 2011) were identified in subjects with schizophrenia: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving (Nuechterlein et al., 2004).

### **Speed of Processing**

This domain measures the time it takes a person to do a mental task. It is related to the speed in which a person can understand and react to the information they receive, whether it be visual (letters and numbers), auditory (language), or movement. Both motor and perceptual skills are required.

### **Attention/Vigilance**

Selective attention is the ability to select and focus on relevant stimuli, while ignoring non-relevant ones. It indicates the ability to maintain a certain level of attention over time in situations where there is a low frequency of stimuli.

### **Working Memory**

Working memory is the function of storing relevant verbal and spatial information long enough to enable completion of a task. The stored information is constantly adapted to the contingent situation and allows behavior to be guided in a planned manner.

### **Verbal Learning and Memory**

The perception and preservation of verbal information.

## **Visual Learning and Memory**

The perception and preservation of non-verbal information.

## **Reasoning and Problem Solving**

This domain includes cognitive flexibility and the construction of concepts, the ability to plan and solve problems, as well as the ability to control one's behaviors, inhibiting them, when useful, in favor of new goals (Vita & Comazzi, 2015).

Initially, the MATRICS initiative focused exclusively on the differentiation of neurocognitive domains in schizophrenia. Only later, due to its growing importance, the domain of Social Cognition was recognized.

## **Social Cognition**

Given the critical role of functional outcome in schizophrenia, there has been growing interest in factors that may underlie it. If the nature of these factors can be delineated, interventions may be devised to ameliorate them, which, in turn, may have a concomitant impact on long-term outcome. As mentioned above, neurocognition is one such factor. More recently, social cognition has been identified as a likely contributor to functional outcome. Given the preliminary evidence that social cognition does have functional significance in schizophrenia, there has been growing interest in devising interventions aimed at improving functional outcomes via remediation of social cognitive deficit (Couture et al., 2006).

Brothers (1990) defined social cognition as the “mental operations underlying social interactions.” The theory implies a close association between social cognition and functional outcome because the ability to process social stimuli is essential for social interactions and problems in this area can affect peer, romantic, and family relationships as well as work/school behavior.

In addition, social cognition may influence the functional outcome of independent living skills because accurately assessing social cues from the environment, and having the social opportunities necessary to learn skills such as home and financial care may be a prerequisite for making improvements in daily living skills.

Therefore, social cognition can be considered a cognitive construct that includes a wide range of social and emotional knowledge and skills, which mature during the evolution of the individual allowing him to modulate his behavior in reference to the social organization to which he belongs (Brothers, 1990).

Social cognition includes five different functions, that were all included in the standardized neuropsychological test battery developed by MATRICS project experts, in addition to the six neurocognitive domains.

The five social cognition domains are:

- 1) The processing of emotions (recognition, understanding and management of emotional states);
- 2) Social perception, as an understanding of the roles and rules of socio-relational contexts;
- 3) Social schemas, which are long-term memory awareness structures containing declarative or procedural information about the roles, rules and objectives that characterize certain social situations. For this reason, they play a decisive role in the codification of incoming information and have a guiding function for the completion of actions.
- 4) The style of attribution, understood as an individual tendency to attribute the causes of events to oneself (to one's own abilities, commitment, intelligence) or to external circumstances (luck, chance, situations, people);
- 5) The theory of the mind (ToM, Theory of Mind), defined as the ability to understand the mental states of others (Penn et al., 1997; Green & Leitman, 2008; Penn et al., 2006). In particular, ToM is a complex construct that incorporates both "mental state reasoning" (cognitive ToM) and "mental state decoding" (affective ToM) with

different associations to social functioning (Bora et al., 2006; McGlade et al., 2008). About the first one, reasoning means being able to interpret intentions, perspective and beliefs of others and it is usually measured on tests that include false belief and hinting tasks. The Hinting Task (Greig et al., 2004), specifically, is a test of ability of subjects to infer real intentions behind indirect speech utterances. The second one concerns the ability to decode mental states on the basis of immediately available information such as facial expression or tone of voice. This kind of competence does not only involve decoding basic emotions, but also more complex concepts including detection of sarcasm from prosodic cues and identifying whether, based on their facial expressions, someone is serious. Unlike recognition of basic emotions, recognition of these mental states depends on context; different meanings may be inferred from identical facial expression in different situations.

Both abilities, reasoning about intentions and decoding of mental states, are essential in identifying social cues. Since recognition of social cues has substantial importance in social skills, both abilities may be critical for social functioning (Bora et al., 2006).

The impairment of social cognition leads to an inability to build appropriate relationships with others, problems in social life and difficulties in adapting to the continuous and multiple demands of a complex and heterogeneous social context (Roncone et al., 2013). Moreover, studies reported that social cognition (comprising emotional perception and social knowledge), is related to both neurocognition and functional outcome (Schmidt et al., 2011), hence the importance of including it in rehabilitative interventions.

Although all that has been said up to now suggests using a global approach and, that an integrated treatment of neuro- and social cognition may produce better generalization effects on functional outcome than neuro- or social-cognitive therapy alone, only a few interventions that combine the rehabilitation of both cognitions have been developed.

Furthermore, as there is no evidence that boosting one cognitive domain might improve functional outcome more than another (Wykes & Huddy, 2009), an approach targeting multiple cognitive domains may be of benefit for most schizophrenia patients. Nevertheless, none of the contemporary approaches integrates all cognitive domains identified by the MATRICS project experts (Mueller et al., 2015).

Only recently did a group of experts from the University of Bern develop such an approach—called Integrated Neurocognitive Therapy (INT)—which combines both neurocognition and social cognition by developing specific interventions for each MATRICS domain (de Mare et al., 2018).

## **INTEGRATED NEUROCOGNITIVE THERAPY**

This recent intervention is an evolution of the previous cognitive remedy intervention called Integrated Psychological Therapy (IPT) that aimed to improve specific cognitive functions and the acquisition of social skills through five sub-programs: Cognitive Differentiation, Social Perception, Verbal Communication, Social Skills and Interpersonal Problem-solving (Mueller et al., 2013). Indeed, an empirically based starting point for the development of INT came from IPT evaluation: a combination of the neurocognitive and social cognitive IPT subprogram yielded superior effects in proximal and distal outcome compared to neurocognitive remediation alone (Mueller & Roder, 2008; Roder & Mueller, 2006).

The INT includes all the eleven neurocognitive and social cognition domains defined by the MATRICS initiative and therefore extends the first two IPT subprograms.

It is a new cognitive remediation group approach that incorporates neuro and social cognitive domains into four therapy modules. Each module focuses on different cognitive domains and on social cognition: Module A takes into account the processing speed, attention and perception of emotions; Module B concerns verbal and visual learning and memory, social perception and theory of mind; Module C is about reasoning, problem

solving and “social schemes”; and Module D trains working memory and the ability to attribute appropriate meanings (Vita & Comazzi, 2015).

INT is partly computer based (particularly the Cogpack computer program) and intends to reconstitute and compensate neuro- and social cognitive (dys-)functions, using both an approach based on learning strategies and an approach based on repeated practice. It is a structured cognitive remedy, complete with manual, which consists of 30 sessions. It involves the presence of a therapist and a co-therapist working with groups of 6-8 patients.

Sessions are held twice a week, each lasting approximately 90 minutes and the therapeutic contents are proposed in a sequential way, so that the complexity of the proposed exercises and the emotional content of the same increase progressively, while the level of structuring of the sessions decreases (Roder et al., 2007).

Neurocognitive therapy is fast emerging as an effective treatment for schizophrenia because it turns out to be the most complete treatment method that, next to the primary objective of cognitive remedy, aims to modify also the other deficit areas of the schizophrenic patient. What differentiates the INT from other interventions of cognitive remedy and that makes it innovative and unique, is the ability to use different tools to target different areas, cognitive and non-cognitive, that still appear to be well integrated within a unified and coherent program.

The therapeutic objectives of the intervention aim primarily to improve neurocognition, as described by the MATRICS domains, whilst simultaneously improving social cognition and the ability to cope with emotional and interpersonal stressful factors. As a result, INT intends to be both a neurocognitive and socio-cognitive remedy, which is why it decisively differs from laboratory-based traditional cognitive remediation approaches (Roder & Mueller, 2015).

Based on an integrated model (Roder et al., 2010; Roder & Mueller, 2015) confirmed by recent empirical data (Vauth et al., 2004; Brekke et al., 2005; Sergi et al., 2006; Bell et al., 2009; Brune et al., 2005; Addington et al., 2006; Pinkham & Penn, 2006; Sergi et al., 2007), social cognition mediates the relationship between neurocognitive capacities and the

acquisition of social skills as well as a generalization to the broad level of social functioning. Consequently, the inclusion of social cognitive therapy tools and the reference to patients' experience of their cognitive functioning during daily living increase the emotional relevance and additionally support the generalization of proximal treatment effects to the level of social functioning. Furthermore teaching patients cognitive functions and their relevance in real-life situations within a vulnerability-stress-coping framework of schizophrenia enhances their insight into individual cognitive capacity. Individualized coping strategies (compensatory approach) are derived to compensate difficulties in daily life. Therefore, INT places a strong emphasis on fostering patients' intrinsic therapy motivation (Roder & Medalia, 2010). The reinforcement of the cognitive resources in repeated practice exercises using errorless learning principles as well as new experiences of successful coping in daily life enhances self-efficacy expectancy in terms of creating a sense of self-empowerment. Intrinsic motivation represented a strong mediator of improved functional outcome (Medalia & Lim, 2004; Medalia & Richardson, 2005; Nakagami et al., 2008).

Following the IPT tradition, the sequence of the INT subparts follows explanatory models describing mechanisms of interaction between basic and more complex cognitive skills with higher emotional strain (Brenner et al., 1992; McGurk & Mueser, 2004). In accordance with the IPT program, the level of structuring group processes decreases during therapy. This 'bottom up' and 'top down' approach puts a strong focus on the patients' daily life context to promote transfer and generalization. Enhancing insight into (illness-specific) cognitive resources and deficits, as well as possibilities of coping represents a further aim of treatment (Roder & Medalia, 2010).

Through all these strategies and some innovative tools (like simulated workplace situations, goal setting and an orientation to patients' individual resources rather than their deficits), INT aims to promote the factors that could contribute to improving general functioning:



- 1) awareness: recognition and understanding of both problems secondary to cognitive deficits and available resources in everyday life;
- 2) knowledge: of the disease and coping possibilities;
- 3) motivation;
- 4) self-efficacy: awareness of being able to dominate specific activities, situations and events;
- 5) patient's involvement;
- 6) generalization: transfer of acquired competences in everyday life (Roder & Mueller, 2015).

## **APPLICATION**

Each of the four modules begins with a neurocognitive therapeutic area followed by a therapeutic area of social cognition. There are two therapeutic phases: introductory sessions and work sessions.

The introductory sessions aim at a self-perception with respect to one's own resources and deficits and optimization of one's own possibilities in daily life. It aims to help patients understand the basic cognitive skills of the current session, how these skills are experienced in everyday life and how they can be managed. Knowledge and understanding of one's cognitive abilities in situations relevant to everyday life is another goal of the intervention.

The work sessions are subdivided into 3 sub-phases: compensation (elaboration of coping strategies and use of them in the group), restoration (training, through the repetition of exercises in groups and at the PC/rehearsal learning) and in vivo exercises (exercises to be performed autonomously to promote transfer and generalization).

In summary, after a short overview of the contents of the INT procedure, information-processing models are used to elucidate the impact of cognitive functioning on daily living. In this context, patients are asked about their own perceived resources and deficits in general cognitive functioning for the first time. Then, INT starts with the introduction of the basic neurocognitive

domains of speed of processing and attention, followed by the social cognitive domain of emotion perception. In the beginning, the INT procedure is very structured and the cotherapist is working as a model in each new exercise.

### **Module A - Neurocognitive Therapeutic Area: Speed of Processing Information and Attention**

In module A, the neurocognitive focus is on speed of information processing and attention/vigilance. For both domains there is an introductory phase in which the terms are explained and patients are encouraged to recognise their available resources. Then there are computer exercises that the patient will have to use for a comparison between the subjective perception of resources and potential and objective results.

Work sessions, on the other hand, focus firstly on the learning of coping strategies that concern the speed of processing information, activating attention and maintaining vigilance (compensation phase). This is followed by exercise of the strategies learned through computer and group exercises (restoration phase). Finally, in vivo exercises are employed, involving the transfer of coping strategies to everyday life.

### **Module A - Therapeutic Area of Social Cognition: Perception of Emotions**

In module A, the social cognitive focus is on the perception of emotions. The term is explained with reference to the patients and to everyday life. The basic emotions are presented, alongside related functions, and patients are asked to discuss the emotions in relation to their own experience or that of others. For a better understanding of emotional impact, the relationship between emotional feeling and neurocognitive functioning, somatic reaction and behavior is explored. The compensation phase involves the learning of coping strategies for the decoding of emotions, in particular of: facial

expressions, mimicry, emotional sequences. Patients then express their emotions in groups and built emotional understanding. The restoration phase and in vivo exercises involve the practice of strategies learned through group exercises and their transfer to everyday life. In the group exercises, patients have to reach solutions to problems via group consensus. If this is not possible, two solutions are accepted. Finally, the impact of the emotional state on cognitive functioning in daily life in terms of the use of speech is discussed in the group.

### **Module B - Neurocognitive Therapeutic Area: Verbal and Visual Learning and Memory**

In module B, the neurocognitive focus is on learning and memory. In the compensation step, patients are instructed on memorization and memory enhancement techniques, alongside specific coping strategies. Both visual and verbal memory are addressed. Attention is paid to perspective memory, since it constitutes a very important factor for achieving independent living.

Work sessions provide learning and individualization of coping strategies through:

- written media for memory;
- use of the senses as memory support;
- stratagems to memorize numerical sequences;
- conservation of textual information;
- stratagems to memorize numerical sequences and shopping lists;
- follow a conversation;
- stratagems to memorize appointments;
- stratagems to use visual memory.

The compensation strategies are exercised in the repetition of the PC tasks. Additionally, there are group exercises to simulate real-life situations and to force group processes.

## **Module B - Therapeutic Area of Social Cognition: Social Perception and Theory of Mind**

On the basis of the issues addressed in the introductory sessions, coping strategies are discussed for the improvement of skills related to social perception and to the assumption of perspective (social cognition). In this regard, participants have the opportunity to experiment with these strategies through group exercises. The goal is that each participant can build an individual repertoire of strategies useful for implementing the skills of social perception.

During these tasks, two series of standardized and validated images are utilised, portraying different emotions on human faces. Patients learn to identify and decode these emotions. The image processing takes place in three phases:

- 1) Collection of information
- 2) Interpretation and discussion of information
- 3) Assignment of a title

The assumption of perspective (theory of the mind) focuses on the perception of the emotions learned from module A. Some of the contents of these ToM exercises are also transferred into role-play. This enables understanding of emotional impact, and comparison of individual daily life experiences.

## **Module C - Neurocognitive Therapeutic Area: Reasoning and Problem Solving**

In module C, the neurocognitive focus is on the executive functions of reasoning and problem solving. The reasoning includes cognitive flexibility and the construction of concepts, which are, accordingly, the object of intervention of the module.

The concept of problem solving also includes planning skills. The prerequisite for a successful intervention in this area is the acquisition of coping capacity, discussed in the previous modules.

A definition of terms is therefore given: cognitive flexibility and construction of a concept. They refer to the semantic network, as the goal is that the participants will face an improvement in the classification of semantic information (construction of a concept, construction of categories).

The compensation phase involves the identification of coping strategies. We discuss the obstacles to successful reasoning and problem solving and discuss their implementation in daily life. For example, when discussing the planning of the actions necessary to reach an objective we start from concrete examples of everyday life.

Once the necessary steps to goal achievement have been identified, patients proceed with implementing them until they reach their goal. Unlike the more complex social objectives (such as social schemes), which will be treated in the therapeutic area of social cognition, here the examples are limited to purely cognitive contents.

The last part of the compensation phase involves the construction of a concept (find the right words). In practice, the goal is that each participant describes concrete situations of daily life to illustrate their strengths and weaknesses in the search for the right words. Patients improve their ability to find the right words during a communication and to summarize in their own words what they have experienced.

Groups and computer exercises are utilised here.

## **Module C - Therapeutic Area of Social Cognition: Social Schemas**

This module of social cognition starts with the definition of some terms: social patterns and rules, social roles, prejudices. The session begins with patients' self-perception of their resources from which they create their own individual profile, with references to everyday life and to themselves. In work sessions, the focus is on recognizing the social roles and social rules at

play in a given situation, and not on the reasons why another person does or says something.

To better illustrate and to allow participants to experiment with the functioning of social rules and roles, role-play can be proposed to make it clear that bad social rules can lead to inadequate behavior and unnecessary emotional stress. Subsequently participants are helped to identify coping strategies to defend themselves from the stigma situations in which they can be found and, for each coping strategy, each individual identifies and notes the possible advantages and disadvantages deriving from the application of each single strategy. At the end of the compensation step, attention is paid to the consequences that the sequences of actions can have in the social context.

## **Module D - Neurocognitive Therapeutic Area: Working Memory**

In the neurocognitive therapeutic area of the module, the focus is on working memory. It is necessary for decision-making processes, goal setting, problem solving and targeted selective perception. Learning of coping strategies with the help of PC-based exercises and role-playing games is planned. The latter stimulates the use of cognitive flexibility skills in a social context and allows learning on how to deal with distraction and over-stimulation problems. Subsequently a discussion is held regarding rituals and behavioral changes. In other practices when talking about coping strategies for the management of hyperstimulation and concentration problems, therapists also include the rituals often used by participants in everyday life. Through them, patients address the need for security and cohesion, both in their life and in their behavior, as well as the need to control daily situations. In order to foster a sense of autonomy and control, it is important to avoid offering too many therapy-oriented interventions, which might lead to an over reliance on the therapy itself. The goal in this case is to promote understanding and evaluation of any “benefits” (control,

safety) and any “costs” (inflexibility, removal from the norm, etc.) of the rituals.

Other objectives of the module are learning the ability to move from one action to another and strategies to prevent distraction during a conversation.

## **Module D - Therapeutic Area of Social Cognition: Style of Social Attribution and Regulation of Emotions**

Many schizophrenia (out-)patients suffer from persistent positive symptoms associated with negative life experiences. The social cognitive domain of attribution is often strongly related to positive symptoms. In appraising a situation, schizophrenia patients often jump to conclusions without gathering all the information or show an overgeneralized attribution. Thus, intervening in attribution can lead to a high emotional strain for the patients. This is the reason why INT addresses this theme at the end, when the group has established high cohesion (friendship and confidence).

Social attributions are defined according to the MATRICS initiative (Green et al., 2005) as individual explanations of the causes that have led to the success or failure of an experience and contribute to the understanding of social situations and events. As in the previous intervention units, the abstract concept of style of social attribution is first defined and then the resources of the participants are identified. The introductory sessions also comprise a discussion about the ability to regulate emotions, and the vulnerability-stress model is introduced first and then the strategies of coping to better adjust your emotions. Emotion regulation includes the processes by which individuals participate in determining the emotions they experience and how to experience and express them.

The work sessions focus on verifying our attribution style and its consequences. Thus, the goal is to develop alternative attribution styles to the inadequate ones.

Then there is the learning of strategies for the management of stress and for the regulation of emotions. The ‘learned coping strategies’ exercises

involve repetitive group exercises followed by individual exercises which focus on transfer to life.

At the end of this module, all compensation strategies from across the four modules are integrated and applied to situations in daily life (Roder & Medalia, 2010).

## CONCLUSION

There is now evidence that an integrated treatment aimed at improving the general functioning of patients with schizophrenia, both cognitively and in terms of quality of life, is more efficacious than treatments which focus on only one domain. Even though neurocognitive deficits play an integral role in undermining the functioning of patients, other decisive elements must also be taken into account when drawing up therapeutic interventions for those with schizophrenia.

The results of a study developed by Beck et al., (2018) pointed out the contribution of attitudinal/motivational factors in schizophrenia. In particular, seven non-neurocognitive factors have been identified that contribute significantly to the performance of neurocognitive tests: avolition, dysfunctional attitudes, effort, stress, negative emotions, asociality and disorganized symptoms (Beck et al., 2018).

Although it is not clear how much variance of the neurocognitive performance of individuals with schizophrenia would be explained if all the elements examined above were evaluated, this influence does not seem to be trivial. In this regard, it is useful to note that a common feature of all these “confusion” factors is the role of beliefs. Beliefs are impacted by emotion (Grant & Beck, 2009; Smith et al., 2006), low effort (Granholm et al., 2016; Reddy et al., 2018), stress (Palmier-Claus et al., 2011), asociality (Grant & Beck, 2010), and disorganization (Grant & Beck, 2009b).

A recent meta-analysis of 10 studies found that defeatist beliefs were significantly associated with negative symptoms and functional results (Campellone et al., 2016), which suggests that cognitive remediation treatments that counteract negative beliefs, can have a significant effect on



neurocognition test scores and on real-world functioning (Wykes et al., 2011; Medalia & Saperstein, 2013; Best & Bowie, 2017). An intervention of this kind aims to improve the positive attitudes that are activated following positive experiences, thus increasing the patient's motivation, a factor that would seem to give a strong contribution to functional outcome (Beck et al., 2018).

In summary, given the complexity and pervasiveness of a condition such as schizophrenia, the INT fits into this context as an ideal treatment, as it seems to possess all requisites, according to the evidence set out above. It is an effective cognitive remediation intervention, which is not exclusively based on cognitive training, but rather consists of a multi-pronged approach which is at the same time integrative. INT, is an approach based on commitment, the definition of objectives, and collaboration with the individual to achieve goals and draw conclusions on success. In so doing, it impacts attitudes, beliefs, motivation, emotions, sociability, and other crucial factors for a positive functional outcome.

Although the Integrated Neurocognitive Therapy has enormous potential, few clinical studies have been conducted to date. In effect, whilst there are many studies on various cognitive remediation approaches, only two studies and one systematic review with meta-analysis (Mueller et al., 2015; De Mare et al., 2018; Mueller et al., 2017) have been conducted specifically on INT, in an attempt to test its effectiveness.

The two randomized clinical trials were conducted by the same team of experts who developed the IPT and consequently the INT. Both studies included patients diagnosed with schizophrenia or schizoaffective disorder who were subsequently randomized into either an experimental group (to which INT was applied) or a control group. The results of both trials have shown that INT leads to significant improvements in global neurocognition and in the various domains of social cognition, sometimes maintained even at the first follow-up. Also noted, was a significant reduction of negative symptoms in patients undergoing treatment and an improvement in overall functioning.

The conduct of a systematic review led to the acknowledgment of the presence of these unique clinical trials conducted on the subject. The result

of the qualitative analysis, however, led to the conducting of a quantitative synthesis to verify the effectiveness of the treatment in statistical terms adding the present studies. The data were shown in favor of the treatment both in considering the impact of the INT on the negative symptoms and positive symptoms of schizophrenia and on the functional outcome. Further studies are required in order to enable meta-analyses, which would constitute stronger scientific evidence.

These studies provide evidence that INT may be effective in treating cognitive impairment in patients with schizophrenia. It decreases negative symptoms, and improves functional outcome (Mueller et al., 2017), none of which can be achieved using pharmacological interventions. Given the current scarcity of RTCs, further studies are needed to compare patient populations and to produce stronger evidence in this specific rehabilitative setting.

It would be important to have access to a greater amount of data to conduct a meta-analysis and thence, a more exhaustive synthesis. This would allow the creation of stronger evidence than that deriving from the clinical studies, which is important considering the impact this type of intervention could have on the functional recovery of patients with schizophrenia (De Mare et al., 2018).

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*Chapter 5*

**COGNITIVE IMPAIRMENT IN PATIENTS  
WITH SCHIZOPHRENIA IN FORENSIC  
MENTAL HEALTH SERVICES**

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**ABSTRACT**

To date the importance of cognitive impairments for patients hospitalised within forensic mental health services has scarcely been examined. Over the course of four years, I conducted three studies, seeking to address this knowledge gap in two ways. First, by clearly describing the problem, namely investigating the mean level of cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder amongst a national cohort of forensic mental health patients, as well as clarifying the significance of these deficits for explaining social and occupational functioning in general, and violent behaviour in particular. Second, by exploring what can be done to improve cognitive functioning;

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specifically, whether anticholinergic burden arising from polypharmacy is associated with cognitive impairments and ability to benefit from psychosocial treatment programmes, and whether CRT may be useful for improving cognitive functioning. This chapter delivers a background on what we understand from the literature regarding the role of cognition in forensic mental health service patients, and culminates with a brief description of the 3 studies undertaken, which significantly add to that knowledge base.

## **FORENSIC MENTAL HEALTH SERVICES**

Forensic Mental Health Services (FMHS) can be defined as those services that provide care and treatment for a minority of patients with mental illnesses such as schizophrenia who come into contact with law enforcement agencies as a consequence of their mental disorder, or who cannot be safely managed within another service and require specialised secure care (Kennedy, 2002; McFadyen, 1999). The offences carried out by forensic patients are heterogeneous in nature and range from public order offences to acts of very serious violence including multiple homicide. Consequently, FMHS have a dual role in providing patients with care and treatment, whilst simultaneously protecting the public from further harm through involuntary detention and risk management (Kennedy, 2002; O'Reilly et al., 2015). Notwithstanding some international variation (Jansman-Hart et al., 2011), this dual role is frequently codified into law as is the case with the Republic of Ireland's Criminal Law (Insanity) Act, 2006 Section 11(2).

Internationally, many psychiatric patients are now managed within specialised Forensic Mental Health Services (FMHS), which interact with the criminal justice system (Fakhoury & Priebe, 2002; de Tribolet-Hardy & Habermeyer, 2016). One explanation for the international demand for forensic services is the deinstitutionalisation of psychiatric care (O'Neill et al., 2002; Priebe et al., 2008; Jansman-Hart et al., 2011; Chow & Priebe, 2013; O'Reilly et al., 2019). This shift to less restrictive community-based mental health care has occurred in many countries including the United Kingdom, Germany, Austria, Italy, the Netherlands, Denmark, Spain,

Switzerland, Canada, New Zealand, Australia and the United States (Jansman-Hart et al., 2011). Whilst the move to community-based care was welcomed in principle its implementation has been criticised. The primary criticism is that where community-based care models have been implemented, they have frequently been insufficiently resourced to provide an appropriate range of levels of care for patients with serious mental disorders (Jansman-Hart et al., 2011; Sharma et al., 2015). Crucially the architects of the deinstitutionalisation movement did not attempt to determine the amount of beds required to prevent or reduce adverse outcomes like suicide or homicide; a defining feature of a well-functioning mental health care system (O'Reilly et al., 2019). It has been argued that an unintended consequence of deinstitutionalisation, in addition to stricter laws regarding involuntary detention, is that many patients' first therapeutically meaningful contact with mental health services occurs via the criminal justice system (O'Neill et al., 2002; Crocker et al., 2011). Like for example, being assessed by a forensic psychiatrist during a prison clinic. Whereas previously violent assaults or problematic behaviour, like destruction of property, or fire setting, arising out of mental illness led to an involuntary admission to a psychiatric hospital they now lead to criminal charges (Hodgins, 2001; Crocker et al., 2011; Jansman-Hart et al., 2011). The criminal justice system therefore has become a pathway for accessing mental health care and treatment for some patients incapacitated by their mental illness, who fail to appreciate and understand their circumstances or recognise a need for treatment (Gray et al., 2000).

In keeping with the movement to community-based care models and stricter laws regarding involuntary detention the demand for forensic beds continues to increase internationally (de Tribolet-Hardy & Habermeyer, 2016). Within England and Wales, the number of forensic inpatients rose by 45% from 1996 to 2006 (Jansman-Hart et al., 2011). It has been estimated that across Western Europe there are approximately five forensic beds per hundred thousand inhabitants (Priebe et al., 2008).

Forensic patients are typically hospitalised for longer periods compared to general psychiatric patients (Fazel et al., 2016). The mean length of stay within FMHS within a European context is approximately five years

(Davoren et al., 2015; Fazel et al. 2016; Vollm et al., 2017). However, it would not be unusual for forensic patients to be detained for periods greater than five years (Buchanan et al., 2011). It is likely that the dual role played by FMHS regarding protecting society on the one hand and the needs of the patient on the other is a contributing factor to lengthy admissions (Shah et al., 2011; Davoren et al., 2015). Notwithstanding international variations in legal and administrative frameworks governing admission and discharge, in most countries involuntary detention is reviewed periodically by independent legal authorities (Jansman-Hart et al., 2011). For example, within the Republic of Ireland the need for continued involuntary hospitalisation is independently assessed by mental health review boards or mental health tribunals, in accordance with criminal or civil mental health law (Criminal Law Insanity Act, 2006 & 2010; Mental Health Act, 2001). Length of stay is in part a function of patient ability to participate, engage, and benefit from psychosocial treatment programmes targeting violence risk and mental health needs, as scrutinised by mental health review boards or tribunals (Richter et al., 2018).

Internationally, most patients hospitalised within FMHS suffer from schizophrenia or schizoaffective disorder with estimates ranging from 50-60% (Jansman-Hart et al., 2011; de Tribolet-Hardy & Habermeyer, 2016). For the Republic of Ireland, however, the vast majority of forensic mental health patients (approximately 90%) have a diagnosis of schizophrenia or schizoaffective disorder (O'Reilly et al., 2015). Within the Republic of Ireland only a small minority of patients would have other diagnoses such as a bipolar affective disorder, major depressive disorder, intellectual disability, or autism (O'Reilly et al., 2015).

## **SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER**

Schizophrenia and schizoaffective disorders are currently classified as psychotic disorders within psychiatry's two major nosological systems, DSM-5 and ICD-10 (American Psychiatric Association, 2013; WHO, 1993). Both disorders are characterised by behavioural, cognitive, and emotional



dysfunction (American Psychiatric Association, 2013; WHO, 1993). For a patient to be diagnosed with schizophrenia they must present with symptoms such as delusions, hallucinations, or disorganised speech, for a one-month period, which in addition to other symptoms are associated with a marked decline in social and occupational functioning (DSM-5; American Psychiatric Association, 2013).

The diagnosis of schizoaffective disorder can be distinguished from schizophrenia by the presence of a major mood episode (depressive or manic) concurrent with psychotic symptoms, and a decline in social and occupational functioning may not necessarily be present (DSM-5; American Psychiatric Association, 2013). There has been a longstanding debate within academic psychiatry about whether schizoaffective disorder is a valid diagnostic category (Malhi et al., 2008). Clear distinctions between schizophrenia and schizoaffective disorder have not been found using neuropsychological or neurocognitive tests, neuroimaging, molecular neurobiology, or genetic epidemiology studies (Malhi et al., 2008). There is some evidence however that those patients with schizoaffective disorder have a better prognosis, but this can probably be explained by the diagnosis itself not requiring a patient to experience social and occupational dysfunction. Despite these findings, both the American Psychiatric Association and the World Health Organisation (WHO, 1993) continue to support the distinction between the two disorders.

The prognosis for the majority of patients with schizophrenia is poor and meta-analytic studies indicate that only one in seven patients with schizophrenia achieve functional and symptomatic remission sustained over time (Jääskeläinen et al., 2013; American Psychiatric Association, 2013). One explanation for the rate of recovery is the degree of cognitive impairment associated with these disorders (Kahn & Keefe, 2013). However, to date the importance and prevalence of cognitive impairment for forensic patients with schizophrenia and schizoaffective disorder has scarcely been examined (O'Reilly et al., 2015). Moreover, the significance of these cognitive impairments for patients with schizophrenia even within general psychiatric settings has been marginalised (Kahn & Keefe, 2013).

## **COGNITIVE PROBLEMS AMONGST PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER**

Although not a core diagnostic feature of DSM-5 (American Psychiatric Association, 2013) or ICD-10 (WHO, 1993), cognitive impairment has a long history of being associated with schizophrenia and schizoaffective disorder (Kraepelin, 1893; Bleuler, 1950; Kahn & Keefe, 2013; Green, 2006). Up to 85% of patients with schizophrenia experience some form of cognitive impairment, where impairment is defined as scoring two standard deviations (SD) below the nonclinical population mean on a cognitive test (Kontaxaki et al., 2014). The cognitive tests on which patients perform poorly include not only neuropsychological or neurocognitive tests of attention, memory, and executive functioning, but also tests of social cognition such as perception of affect, emotional awareness, theory of mind, context sensitive processing, and emotional reasoning (Ochsner, 2008). Both neurocognitive and social cognitive impairments represent a major source of disability for patients with schizophrenia and schizoaffective disorder, accounting for more of the variance of functional outcome than psychotic symptoms (Kahn & Keefe, 2013). Patients with severe cognitive impairments have difficulties functioning day to day, finding meaningful employment, and living independently (Kahn & Keefe, 2013). Importantly, the cognitive impairments associated with schizophrenia and schizoaffective disorder are present prior to the onset of psychosis and found in medication naïve patients (Kahn and Keefe, 2013).

The cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder is hypothesised to arise in part because of neurodevelopmental processes like synaptic pruning, which lead to a lag in development, or presents as a decline in cognitive ability (Keshavan et al., 1994). Consistent with this hypothesis, certain forms of crystallised cognitive ability, like verbal intelligence, do not appear to be seriously affected by the illness and remain relatively unimpaired (Keefe, 1995; Kahn & Keefe, 2013; Joyce, 2013; Aylward et al., 1984). Presumably because information associated with verbal intelligence was acquired prior to the lag

in development or decline in cognitive ability. However, preserved verbal intelligence may mask less apparent but debilitating cognitive impairments like attention, memory, and executive functioning (Keefe, 1995; Aylward et al., 1984).

Standardised batteries have now been developed to assess the specific cognitive impairments associated with schizophrenia, of which the MATRICS Consensus Cognitive Battery (MCCB) is one example (Nuechterlein et al., 2008). The MCCB assesses the following seven cognitive domains: processing speed, attention and vigilance, verbal memory, visual memory, working memory, reasoning and problem solving and social cognition (Nuechterlein et al., 2008). The magnitude of cognitive impairment is particularly pronounced when measured using composite scores derived from instruments like the MCCB, which aggregate deficits across cognitive domains affected by the illness (Joyce, 2013). This general impairment, which is observed on the composite score of test batteries may underpin performance across cognitive domains and is likely to be the major source of functional impairment (Joyce, 2013; Dickinson et al., 2011).

## **VIOLENCE AND SCHIZOPHRENIA**

There is robust evidence consisting of multiple meta-analyses and systematic reviews indicating an association between schizophrenia and violence and homicide in particular (Fazel et al. 2009). The rate of homicide amongst patients with schizophrenia is ten times the rate of homicide within the general population (Fazel et al., 2009). Also, violence towards caregivers is more common than has previously been believed. Within one study examining the prevalence of violence against caregivers by patients with schizophrenia, of 277 caregivers 76% reported they had experienced a violent assault from their relative (Kageyama et al., 2018). The relationship between major mental illnesses and violence may historically have been downplayed in part for fear of increasing stigma (Torrey, 2011). Paradoxically the most effective way of decreasing stigma may be ensuring that those patients who are at greatest risk of acting violently receive

appropriate care and in some cases involuntary psychiatric treatment (Torrey, 2011).

Violent acts carried out by patients with schizophrenia are complex and cannot always be explained by psychotic symptoms. Some individuals with schizophrenia or schizoaffective disorder are violent at a young age prior to the onset of psychosis, others become chronically violent after the first psychotic episode even when receiving medication, and there are those who commit a single act of violence during their lifetime (Fazel et al., 2009; Nielssen et al., 2010; Tengström et al., 2001; Hodgins, 2008). Violent acts amongst this population appear to be driven in part by some of the same risk factors as violence in general (Fazel et al., 2009; Witt et al., 2013; Webster et al., 1997).

Risk prediction schemes such as the Historical-Clinical- Risk-20 (HCR-20; Webster et al., 1997) take advantage of this and assess violence proneness or propensity by including several equally weighted items (Dawes, 1979), many of which are not specific to schizophrenia or mental disorder but are associated with suboptimal functioning (Witt et al., 2013). Many of these functional difficulties are likely to be underpinned by the cognitive decline or lag in cognitive development experienced by patients with schizophrenia or schizoaffective disorder (Soyka, 2011; Kahn & Keefe, 2013).

Violence has been robustly associated with cognitive deficits in meta-analyses, systematic reviews, and large prospective studies, concerning brain injury, delinquency, intellectual disability, and prisoners (Fazel et al., 2011; Farrington and Welsh, 2007; Silver & Nedelec, 2018). In contrast, evidence concerning an association amongst patients with schizophrenia or schizoaffective disorder is contradictory and harder to interpret (Witt et al., 2013).

For patients with schizophrenia, some studies have found a positive relationship between impaired cognition and violence whereas others have not (Weiss et al., 2012). The causal nature of this relationship is therefore unclear. One challenge when interpreting this literature is that the studies typically assume that violence is a homogenous entity.

This may be a mistake. It is likely that the cognitive problems experienced by patients with schizophrenia and schizoaffective disorder are particularly relevant for unplanned reactive violence, but may be less relevant for instrumental violence, which is executively complex (Houston et al., 2003) and may be delusionally driven (Barratt & Felthous, 2003).

For some patients impaired cognitive ability may be a distal risk factor for violence, with psychotic symptoms like delusions being the proximal mediating factor (O'Reilly et al., 2015). Those patients whose delusions appear to be functionally linked or relevant to their violent act may not have the most pronounced cognitive impairments, but none the less experience more general and specific cognitive impairments compared to nonclinical controls (Bentall et al., 2009). The cognitive impairments that patients do experience may be relevant to the violent act but obscured within a sample of non-delusional patients also experiencing cognitive problems. For example, some patients may be impaired in their general ability to reason, whilst experiencing specific psychotic symptoms (Moynihan et al., 2018) at the time of the violent act.

Distal risk factors like general cognitive impairment may therefore be obscured by proximal risk factors like anger or delusions within uncontrolled samples of patients with schizophrenia and schizoaffective disorder. The distinction between unplanned reactive violence and premediated instrumental violence, in addition to the distinction between proximal and distal risk factors, may account for discrepancies amongst studies examining the relationship between cognition and violence. Identifying the kind of violence carried out by patients with schizophrenia and whether cognition is a distal or proximal risk factor may help elucidate whether there is a causal relationship between cognition and specific forms of violence.

Should this be so, it is possible that interventions for improving the cognitive impairments experienced by patients with schizophrenia or schizoaffective disorder may reduce risk of reactive violence or have an indirect effect on psychotic violence.

## **PHARMACOLOGICAL APPROACHES FOR IMPROVING COGNITION**

Currently, pharmacological attempts to remediate the cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder have been unsuccessful (Harvey & Bowie, 2012). However, there is emerging evidence that medications targeting cholinergic receptors may have some benefit. In a recent meta-analysis, Choi and colleagues found that for patients with schizophrenia, cholinergic medications led to marginal improvement in verbal memory and moderate improvements in spatial memory (Choi et al., 2013). The cholinergic system is a series of pathways from the basal forebrain radiating throughout the cerebral cortex and involved in regulating attention and memory (Chudasama et al., 2004; Sarter et al., 2005). For older adults it has been demonstrated that cholinergic antagonists impair memory whereas agonists enhance memory (Drachman & Leavitt, 1974). Also, for patients with Alzheimers disease cholinesterase inhibitor therapies have become an important treatment where they have been shown to induce significant symptomatic improvement (Summers et al., 1986; Hampel et al., 2018). Separate to medications targeting the cholinergic system there have been efforts to enhance glutamate transmission because of evidence suggesting a hypofunction of glutamatergic signalling via NMDA receptors (Kantrowitz et al., 2012; Falkenberg et al., 2014). Glutamate is the most widely distributed excitatory neurotransmitter in the brain and also acts as an intermediate in cerebral energy metabolism (Rothman et al., 2003). However, in contrast to cholinergic medications the recent meta-analysis conducted by Choi et al., (2013), did not support the use of glutamate agonists for improving cognition, although some benefit was observed for negative symptoms.

The reason why these medications are not more successful is unclear. Excessive synaptic pruning may limit the potential for improving cognition via neurotransmitters (Keshavan et al., 1994). The use and dose of concurrent medications may also be important (Harvey & Bowie, 2012). Concurrent medications may have a harmful effect on patients' cognitive

ability via the same mechanism as the cognitive enhancing agents, namely the cholinergic system (Nebes et al., 2005; Campbell et al., 2009). Many of the medications administered to patients with schizophrenia or schizoaffective disorder possess anticholinergic properties (Chew et al., 2006; Buchanan, 2005). Pharmacological treatments when aggregated may therefore create a considerable anticholinergic burden. Anticholinergic burden might impair ability to benefit from psychosocial treatments. No study has yet examined whether the effect of anticholinergic burden on ‘real world’ functioning is mediated via impaired cognitive ability. Anticholinergic burden may lead to increased cognitive impairment, which in turn might affect treatment progression. Several studies have been conducted that suggested that discontinuing anticholinergic medications had a positive effect on cognition amongst patients with schizophrenia (Baker et al., 1983; Mori et al., 2002; Drimer et al., 2004; Ogino et al., 2011; Desmaris et al., 2014). One pathway for reducing cognitive impairments experienced by patients with schizophrenia or schizoaffective disorder and for improving ‘real world’ functioning may be by minimising medications which have an anticholinergic burden.

## **PSYCHOLOGICAL APPROACHES FOR IMPROVING COGNITION**

Cognitive remediation training (CRT) is a psychological approach that has shown potential to improve cognitive impairments for patients with schizophrenia or schizoaffective disorder within non-forensic settings (Wykes et al., 2011; Cella et al., 2015). CRT is a behaviourally based training approach designed to help patients improve their cognitive abilities and ‘real world’ functioning.

A variety of therapies exist under the CRT umbrella but most aim to either strengthen patients’ basic cognitive capacities through a process of drill and practice, or to teach patients more effective ways to deploy cognitive resources using meta-cognitive strategies. CRT is also a

nonthreatening activity, which patients' report to enjoy, and focuses on experiences of success and mastery (Rose et al., 2008). A recent meta-analysis by Wykes involving non-forensic or general mental health patients demonstrated that CRT is an effective intervention for improving cognitive and functional outcomes for patients with schizophrenia or schizoaffective disorder (Wykes et al., 2011). Within the Wykes meta-analysis, the average patient who received CRT improved performance on cognitive tasks by an effect size of .5 (Cohens *d*) and .42 on patient functioning. However, the evidence base for CRT within a forensic mental health setting is limited.

To date only two randomised trials have been conducted within a forensic mental health setting. One was a small pilot study investigated the feasibility of improving social cognition amongst forensic mental health patients ( $n = 21$  Social CRT vs  $n = 15$  TAU; Taylor et al., 2016). The second study mixed forensic mental health patients with general mental health patients.

Mixing patient groups may undermine the confidence with which the findings can be generalised to forensic mental health patients (Ahmed et al., 2015). Of note within this study the forensic mental health patients were significantly more cognitively impaired on working memory and verbal learning than the general mental health patients. In addition to the limited evidence for CRT within a forensic setting there are also questions about the generalisability or transportability of psychological interventions like CRT from a non-forensic setting to a forensic setting.

In contrast to most community patients, forensic patients are involuntarily detained and consequently may not readily occupy the role of 'customer'. Many forensic patients may also have poor insight into their need for treatment and may be ambivalent or have negative attitudes towards participating or adhering to interventions, both of which are sometimes captured by violence risk measures (Webster et al., 1997). Therefore, there is a requirement that studies specific to the forensic mental health setting including RCTs be conducted to determine the transportability and effectiveness of non-forensic treatment programmes, in addition to developing forensic specific interventions (Tunis et al., 2003).



**BRIEF OVERVIEW OF STUDIES CONDUCTED WITH THE  
AIM OF UNDERSTANDING THE IMPORTANCE OF  
COGNITIVE IMPAIRMENTS FOR FORENSIC MENTAL  
HEALTH PATIENTS WITH SCHIZOPHRENIA OR  
SCHIZOAFFECTIVE DISORDER**

To date the importance of cognitive impairments for patients hospitalised within forensic mental health services has scarcely been examined. Over the course of four years, I conducted three studies, seeking to address this knowledge gap in two ways. First, by clearly describing the problem, namely investigating the mean level of cognitive impairment experienced by patients with schizophrenia or schizoaffective disorder amongst a national cohort of forensic mental health patients, as well as clarifying the significance of these deficits for explaining social and occupational functioning in general, and violent behaviour in particular. Second, by exploring what can be done to improve cognitive functioning; specifically, whether anticholinergic burden arising from polypharmacy is associated with cognitive impairments and ability to benefit from psychosocial treatment programmes, and whether CRT may be useful for improving cognitive functioning. The abstracts for these three studies are included below.

**Study 1: Prospective Cohort Study of the Relationship between  
Neuro-Cognition, Social Cognition and Violence in Forensic  
Patients with Schizophrenia and Schizoaffective Disorder  
(O'Reilly et al., 2015)**

This study involved recruiting patients from a national forensic cohort at the Republic of Ireland's Central Mental Hospital, which is part of National Forensic Mental Health Service; assessing cognitive impairments, and separately and independently assessing psychotic symptoms, patient

'real world' functioning, violence risk and actual violent assaults over a twelve-month period. The aim of the study was to determine the mean level of cognitive impairment within the national cohort and to determine the relationship between cognitive impairment and acts of violence prospectively over a twelve-month period.

It was hypothesised that a) neurocognitive and social cognitive deficits are determinants of reactive in-patient violence and b) that the relationship between neurocognitive deficits and violence would be mediated by risk factors such as deficits in social reasoning, increased symptoms, impaired social functioning and increased violence proneness.

## ***Abstract***

### **Background**

There is a broad literature suggesting that cognitive difficulties are associated with violence across a variety of groups. Although neurocognitive and social cognitive deficits are core features of schizophrenia, evidence of a relationship between cognitive impairments and violence within this patient population has been mixed.

### **Methods**

We prospectively examined whether neurocognition and social cognition predicted inpatient violence amongst patients with schizophrenia and schizoaffective disorder ( $n=89$ ; 10 violent) over a 12 month period. Neurocognition and social cognition were assessed using the MATRICS Consensus Cognitive Battery (MCCB).

### **Results**

Using multivariate analysis neurocognition and social cognition variables could account for 34% of the variance in violent incidents after controlling for age and gender. Scores on a social cognitive reasoning task (MSCEIT) were significantly lower for the violent compared to nonviolent group and produced the largest effect size. Mediation analysis showed that the relationship between neurocognition and violence was completely mediated

by each of the following variables independently: social cognition (MSCEIT), symptoms (PANSS Total Score), social functioning (SOFAS) and violence proneness (HCR-20 Total Score). There was no evidence of a serial pathway between neurocognition and multiple mediators and violence, and only social cognition and violence proneness operated in parallel as significant mediators accounting for 46% of the variance in violent incidents. There was also no evidence that neurocognition mediated the relationship between any of these variables and violence.

### **Conclusion**

Of all the predictors examined, neurocognition was the only variable whose effects on violence consistently showed evidence of mediation. Neurocognition operates as a distal risk factor mediated through more proximal factors. Social cognition in contrast has a direct effect on violence independent of neurocognition, violence proneness and symptom severity. The neurocognitive impairment experienced by patients with schizophrenia spectrum disorders may create the foundation for the emergence of a range of risk factors for violence including deficits in social reasoning, symptoms, social functioning, and HCR-20 risk items, which in turn are causally related to violence.

### **Study 2: Anticholinergic Burden in Schizophrenia and Ability to Benefit from Psychosocial Treatment Programmes: A 3-Year Prospective Cohort Study. (O'Reilly, 2016)**

This study also involved recruiting patients from a national forensic cohort at the Republic of Ireland's Central Mental Hospital, which is part of the National Forensic Mental Health Service; assessing cognitive impairment, and anticholinergic burden, participation, engagement, and benefit from psychosocial treatment programmes over a three-year period. The aim of the study was to determine if anticholinergic burden would be associated with cognitive impairments, which in turn would affect treatment progression, namely patient's ability to participate, engage and benefit from

psychosocial treatment programmes. If this is so, one possible future intervention to improve cognitive impairments within this patient group would be to reduce anti-cholinergic burden by discontinuing unnecessary medications.

It was hypothesised that a) the relationship between anticholinergic burden and ability to benefit from psychosocial treatment programmes would be mediated by cognitive ability, when controlling for age, gender, baseline performance on psychosocial treatment programmes, total antipsychotic dose, and symptoms, and b) that the 'mediation relationship' between medication, cognition, and programme completion would be specific to anticholinergic burden and not total antipsychotic dose; and that the mediation would be specific to cognition, and not to symptoms or functioning when cognition is controlled for.

## ***Abstract***

### **Background**

Many medications administered to patients with schizophrenia possess anticholinergic properties. When aggregated, pharmacological treatments may result in a considerable anticholinergic burden. The extent to which anticholinergic burden has a deleterious effect on cognition and impairs ability to participate in and benefit from psychosocial treatments is unknown.

### **Method**

Seventy patients were followed for approximately 3 years. The MATRICS consensus cognitive battery (MCCB) was administered at baseline. Anticholinergic burden was measured with the Anticholinergic Cognitive Burden (ACB) scale. Ability to benefit from psychosocial programmes was measured using the DUNDRUM-3 Programme Completion Scale (D-3) at baseline and follow-up. Psychiatric symptoms were measured using the PANSS. Total antipsychotic dose was measured using chlorpromazine equivalents. Functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS).

## **Results**

Mediation analysis found that the influence of anticholinergic burden on ability to participate and benefit from psychosocial programmes was completely mediated by the MCCB. For every 1-unit increase on the ACB scale, change scores for DUNDRUM-3 decreased by -0.27 points. This relationship appears specific to anticholinergic burden and not total antipsychotic dose. Moreover, mediation appears to be specific to cognition and not psychopathology. Baseline functioning also acted as mediator but only when MCCB was not controlled for.

## **Conclusion**

Anticholinergic burden has a significant impact on patients' ability to participate in and benefit from psychosocial treatment programmes. Physicians need to be mindful of the cumulative effect that medications can have on patient cognition, functional capacity and ability to benefit from psychosocial treatments.

## **Study 3: A Randomized Controlled Trial of Cognitive Remediation for a National Cohort of Forensic Patients with Schizophrenia or Schizoaffective Disorder (O'Reilly, 2018)**

This study involved delivering and evaluating the effectiveness of a cognitive remediation programme, involving forty-two individual sessions and fourteen group sessions for patients, fifty-six sessions in total, using an intention to treat (ITT) randomised controlled trial methodology with a national cohort of forensic patients with schizophrenia or schizoaffective disorder. The aim of the study was to discover if CRT would be an effective and valued intervention for forensic mental health patients.

It was hypothesised a) that patients allocated to cognitive remediation training (CRT) would improve on the primary outcome measure, cognition at the end of treatment, and at eight months follow up, b) That patients allocated to CRT would improve on specific neurocognitive and social cognitive domains at end of treatment and eight months follow up, c) that

patients allocated to CRT would experience improvements in negative and disorganised symptoms, d) That patients allocated to CRT would experience improvements in real world functioning, moves to lower level of security, and that patients' functional improvements or moves to lower levels of security would be mediated by cognitive gains, e) that patients would experience CRT as a satisfactory and efficacious intervention.

## ***Abstract***

### **Background**

Evidence is accumulating that Cognitive Remediation Training (CRT) is effective for ameliorating cognitive deficits experienced by patients with schizophrenia and accompanying functional impairment. There has been no randomized controlled trial of CRT using a nationally representative population of forensic patients, despite the significant cognitive deficits frequently present within this group.

### **Methods**

Sixty-five patients with schizophrenia or schizoaffective disorder were enrolled in a single blind randomized controlled trial of CRT versus treatment as usual (TAU); representing 94% of those eligible within a national forensic cohort. The primary outcome measure was the composite score of the MATRICS Consensus Cognitive Battery (MCCB). Secondary outcome measures included neurocognitive and social cognitive domains, symptoms, and 'real world' functioning. Patient satisfaction was examined using an exit interview. Participants were reassessed at 8 months follow up. All data were analyzed using an intention to treat design (ITT).

### **Results**

For the primary outcome measure, the MCCB composite score, there were significant differences between those who participated in CRT and those receiving TAU at both end of treatment and 8 months follow up (Cohen's  $d = 0.34$ ). Significant improvements were observed in visual and working memory. Mediation analysis found that those who cognitively

benefited from CRT had corresponding improved functioning, and more net positive therapeutic moves i.e., moves to units with lower security within the hospital. Ninety-six percent believed their cognitive gains positively affected their daily lives.

## Conclusion

CRT may be an acceptable and efficacious intervention for forensic patients with schizophrenia or schizoaffective disorder

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*Chapter 6*

**A PERSONAL RECOVERY NARRATIVE  
THROUGH RAP MUSIC IN MUSIC THERAPY**

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**ABSTRACT**

The following chapter provides a descriptive overview of music therapy and its potential benefits for supporting people experiencing severe and enduring mental illness to journey toward personal recovery. Music therapy is a health profession in which music is employed as the primary agent for therapeutic change. It has been increasingly recognised that the values underpinning music therapy practice are closely aligned with those of recovery in mental health. As a person-centred therapy, music therapy supports personal recovery by capitalising on protective factors and clients' individual resources. This chapter begins with a descriptive overview of music therapy and its role in mental health recovery, including a literature review outlining its clinical efficacy in alleviating the negative

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and global symptoms associated with schizophrenia. From a recovery perspective, exclusively pursuing quantitative outcomes when establishing evidence for music therapy provision is problematic, as it de-emphasises the role of service users' lived experiences in informing the therapeutic process. Accordingly, while presenting a comprehensive overview of supporting music therapy literature, this chapter means to delineate the emerging personal and clinical recovery discourses in the field. This is achieved primarily through the presentation of a case example outlining the personal recovery journey of a young man through his self-selected preference for Rap music. The development of a meaningful personal narrative has been identified as a particularly relevant component of the recovery process. Through this case example, the authors seek to illustrate this young man's use of Rap music in forging a narrative identity beyond his experience of illness. Overall, the authors hope to demonstrate music therapy's potential to provide experiences of mastery, personal agency, connection and vitality despite the presence of ongoing symptomatology, while offering a unique medium through which meaningful narratives can be formed.

**Keywords:** music therapy, schizophrenia, personal narrative, recovery

## INTRODUCTION

Music therapy is a health profession in which music is employed as the primary agent to elicit therapeutic change. Music therapy belongs to a family of therapies commonly referred to as arts therapies, which includes art therapy, dramatherapy and dance/movement therapy. These therapies share a similar underlying philosophy which acknowledges the capacity for creative engagement to facilitate therapeutic growth, while possessing distinct theoretical frameworks pertaining to the therapeutic application of their respective mediums. Unlike other allied health professions which target specific domains of functioning (e.g., occupational therapy, speech and language therapy, physiotherapy), the arts therapies are medium-specific (Silverman, 2015). This means that they draw on the unique possibilities afforded by their respective creative mediums to target goals across a range of clinical domains. The National Institute for Health and Care Excellence in the United Kingdom (2014) described the arts therapies as “complex

interventions that combine psychotherapeutic techniques with activities aimed at promoting creative expression” (p. 217). They summarised the shared principles of the arts therapies as follows:

- the creative process is used to facilitate self-expression within a specific therapeutic framework
- the aesthetic form is used to ‘contain’ and give meaning to the service user’s experience
- the artistic medium is used as a bridge to verbal dialogue and insight-based psychological development if appropriate
- the aim is to enable the patient to experience him/herself differently and develop new ways of relating to others (p. 220)

Music therapists are clinically trained health professionals who combine their mastery of music with their specialist clinical knowledge to facilitate personal growth. While music and sound have been applied for physical, emotional and spiritual healing since prehistory, the health profession of music therapy emerged in the 1940s when the United States Army began developing systematic music programs to promote health outcomes for veterans of World War II (Byers, 2016). In recent decades, the application of music therapy has extended to neurological conditions, physical and intellectual disabilities, neonatal intensive care, palliative care, substance abuse, trauma, and mental health across the lifespan. Music therapy is a person-centred intervention which supports individual clients to meet therapeutic goals in psychosocial, cognitive and physical domains. However, due to music’s unique capacity to put form on human experiences that lie beyond the tangible, the potential benefits of music therapy extend beyond functional domains to include emotional and spiritual well-being. These needs are often challenging to address through conventional dose-response treatment modalities as they represent highly nuanced and subjective qualities of the human condition.

Music is comprised of core elements which include pitch, timbre, rhythm, volume, texture and tone. When these elements are manipulated, even in the subtlest of ways, sound itself is altered and thus the nature of the

music we hear. The limitless possibilities afforded by the musical elements enable musicians to reflect moods and atmospheres effectually in real time, thus affording music its unique capacity to alter the emotional landscape of its recipients. One of the core assumptions underpinning the application of music as a therapeutic tool is the belief that all human interaction is intrinsically musical (Ansdell, 2014; Malloch & Trevarthan, 2010; Malloch & Trevarthan, 2018).

Our propensity for ‘communicative musicality’ is believed to be of fundamental importance to sustaining our vitality as human beings by strengthening our social resilience and capacity to recover from illness (Malloch & Trevarthan, 2018). Based on this assumption, musicality does not simply manifest as a talent gifted to the few but exists as a fundamental element of our very *being*. Music, therefore, is a vital resource for our well-being as it supports our connection to self and others, inspires motivation, and facilitates the expression of visceral human experiences.

The therapeutic relationship is a crucial component of music therapy, and all musical encounters are experienced within the context of this relationship. This is where the music in music therapy differs from recreational musical engagement. Creative engagement, when experienced as a solitary process, facilitates self-expression and emotional processing. However, creative engagement alone does not ensure progression towards recovery.

It is the experience of being witnessed and accepted in the creative process that transforms this process into one conducive to healing. The role of the music therapist is twofold: 1) to facilitate experiences conducive to personal growth by integrating their musical skill and therapeutic expertise with knowledge of clients’ individual circumstances, and 2) to provide a holding and reflective presence for any emotive responses that might arise during this process. In music therapy, music and sound are utilised as vehicles for self-expression. The emphasis is placed on the *process* of musical engagement as opposed to the musical output. In other words, facilitating genuine self-expression takes precedence over creating ‘pleasant’ music. The process of joint music-making functions as a means

of facilitating authentic experiences between client and therapist (Pavlicevic, 2000).

## **Music Therapy in Mental Health Recovery**

With a growing evidence base, music therapy has been establishing increasing recognition within the wider healthcare community as a therapy which supports the recovery goals of individuals living with mental health conditions. Recovery is grounded in two fundamental values: that people with mental health difficulties may lead productive lives in the presence of ongoing symptomatology, and that many people eventually recover from mental illness (Davidson, 2016). The concept of recovery from mental illness has typically been defined in dichotomous terms. Clinical recovery typically refers to the remission of clinical symptoms (Lieberman, Kopelowicz, Ventura, & Gutkind, 2002), while personal recovery presents the broader possibility of leading a meaningful life beyond limitations imposed by illness (Anthony, 1993). It has been suggested that personal recovery and clinical recovery should be viewed as complementary but not mutually exclusive (Roe, Mashiach-Eisenberg & Lysaker, 2011). For instance, it is common for patients who experience ongoing clinical symptomatology to simultaneously report subjective personal recovery outcomes (Chan, Mak, Chio, & Tong, 2018; Van Eck, Burger, Velinga, Schirmbeck & de Haan, 2018). Accordingly, researchers in the field of mental health recovery have argued for a more balanced discourse which promotes concepts of possibility and wellness rather than focusing solely on limitation and disability (Slade and Longden, 2015). Connectedness, hope, identity, meaning and empowerment (CHIME) have been identified as central components of the personal recovery process (Leamy, Bird, Le Boutillier, Williams, & Slade, 2011).

Over the past decade increasing attention has been given to the concept of personal recovery in the music therapy literature, as a growing body of research has recognised that the philosophies underpinning music therapy practice are closely aligned to that of the recovery model (Grocke, Bloch, &

Castle, 2008; McCaffrey, Carr, Solli, & Hense, 2018; McCaffrey, Edwards, Fannon, 2011; Solli, Rolvsjord, & Borg, 2013;). While the difficulties that accompany mental illness are very much acknowledged within music therapy practice, music therapy researchers have been advocating for a greater emphasis on well-being, personal resourcing, and strengths-based approaches to counterbalance the impact of hopelessness, stigma and low motivation that often accompany severe and chronic illness. Thus, the music therapy community has been collectively adopting a paradigm shift in their approach to working with people with mental health difficulties (McCaffrey et al., 2018).

Due to its capacity to promote motivation, self-expression and social engagement, music therapy has been recognised as a suitable therapy for people experiencing severe and enduring mental health difficulties, particularly where verbal therapies may be ineffective or deemed inappropriate (Gold, Solli, Krüger, & Lie, 2009; Grocke et al., 2008). As an adjunct to standard care, music therapy has demonstrated efficacy in improving symptoms of depression and anxiety, while also enhancing social, occupational and psychological functioning in adults with depressive illnesses (Aalbers et al., 2017). Music therapy has been observed to enhance mental health outcomes in adult populations when delivered in isolation or in addition to standard care (Lee & Thyer, 2013), producing similar benefits across a range of mental health conditions independent of formal diagnosis (Gold et al., 2009).

While music therapists bring a unique knowledge base to music therapy, the client's contribution to the relationship and the therapeutic process is valued as being of equal importance, and sessions are guided by the needs and desires of the client (Rolvsjord, 2010). Music is used in a variety of ways to support people living with or recovering from mental illness. Some of the most commonly employed music therapy methods in adult mental health care are musical improvisation, songwriting, and music listening (McCaffrey, 2014). Musical improvisation involves the spontaneous production of music by a client, or co-production between therapist and client. Songwriting can take a variety of forms which may include producing an original composition or personalising the lyrics of a well-known song.

Music listening may involve the client sharing personally meaningful song selections with the therapist and discussing the lyrical content; or engaging in mindfulness, relaxation, or movement to pre-recorded music, or live music performed by the therapist.

### ***Potential Considerations in Music Therapy***

Music therapy produces few negative side effects and is not reported to contraindicate the outcomes of standard treatments for mental health conditions (Aalbers et al., 2017). However, service users in mental health settings have reported experiencing frustrations at the absence of musical instruction (i.e., instrumental tuition) involved during musical improvisation. This points to a need for therapists to be aware of client expectations upon commencing therapy (Carr, 2014; McCaffrey, 2018). Although some therapists may include elements of skill acquisition in their practice for the purpose of supporting personal recovery goals, this is likely to rely on the preferred style of the music therapist. In addition, service users in mental health settings have reported experiencing triggering emotional reactions to music in group settings (Carr, 2014). Such findings highlight the importance of having a qualified music therapist present to support people in managing such reactions when they arise.

Furthermore, the music therapy literature has provided insights into the adverse consequences that can arise when people attempt to self-regulate with music outside of therapeutic contexts. For example, emotionally vulnerable young people may use music to engage in isolating and ruminating behaviours (McFerran & Saarikallio, 2014). While specific musical genres have traditionally been blamed for causing antisocial and risk-taking behaviours (Baker & Bor, 2008), the music therapy literature suggests that negative outcomes associated with music stem from the ways in which people engage with music, rather than the intrinsic qualities of the music itself (McFerran, Garrido, O'Grady, Grocke, & Sawyer, 2015; McFerran & Saarikallio, 2014). These findings suggest that music therapists have a responsibility to support clients in developing awareness around the ways they use music in their daily lives, particularly if clients are appropriating music in ways that enhance negative mood states (McFerran,

et al., 2015; McFerran & Saarikallio, 2014). Overall, music therapy is recognised as a therapy with few contraindications, although a client's desire to engage in therapy is considered fundamental to successful outcomes (Geretsegger et al., 2017; Mössler, Chen, Heldal, & Gold, 2005; Aalbers et al., 2017).

### ***A Clinical Overview of Music Therapy for Schizophrenia***

Although music therapists generally practice from a recovery-oriented perspective in mental health care, it has been equally important to establish a clinical literature which establishes its efficacy in relation to other specialities. While demonstrating efficacy as a therapy for mental health conditions more generally, music therapy has demonstrated particular benefits for people diagnosed with schizophrenia and related conditions. Perhaps one of the most compelling discoveries within the field of music therapy and mental health is that of music's therapeutic capacity to alleviate the negative symptoms associated with schizophrenia (Geretsegger et al., 2017; Mössler, Chen, Heldal, & Gold, 2005). Commonly recognised as some of the most persistent and debilitating clinical features associated with these conditions (Tandon, Nasrallah, & Keshavan, 2009), therapies which assist in remediating negative features are of fundamental importance to sustaining a person's quality of life outcomes over time. Affective symptoms, such as depression, have been associated with poorer personal recovery outcomes for people diagnosed with schizophrenia than the presence of positive symptoms (Roe, Mashiach-Eisenberg & Lysaker, 2011; Van Eck et al., 2018). Despite advances in treatments targeting the positive features of schizophrenia, there continues to exist a dearth of therapies which adequately restore feelings of vitality, meaning and personal agency to people experiencing persistent negative symptoms. In addition to standard treatment, music therapy has demonstrated beneficial outcomes for the emotional, affective and relational features of schizophrenia which impact most severely on a person's ability to lead a full, purposeful life. More specifically, there is evidence that music therapy assists in alleviating symptoms of depression and anxiety, while enhancing motivation, social functioning and quality of life (Geretsegger et al., 2017; Mössler et al.,



2005;). The arts therapies have been endorsed as “the only interventions (both psychological and pharmacological) to demonstrate consistent efficacy in the reduction of negative symptoms” (NICE guidelines, 2014, p. 220).

Cognitive impairment represents another feature which commonly impacts the capacity of people diagnosed with schizophrenia to participate in daily activities and community living (Aubin, Stip, Gélinas, Rainville, & Chapparo, 2009). A growing body of evidence indicates that music therapy yields positive benefits for global mental functioning in people with schizophrenia-like illnesses (Gold et al., 2009; Mössler, Chen, Haldal, & Gold, 2005). In practice, music therapists support people with cognitive impairment by adjusting their approach to meet the individual needs of each client rather than targeting specific features of cognition directly. However, research into neurodegenerative and neuropsychiatric conditions has begun to distinguish some of the particular cognitive benefits that music therapy offers, such as improved verbal fluency, memory and attention (Ceccato, Caneva, & Lamonaca, 2006; Fang, Ye, Huangfu, Calimag, 2017; Kwon, Gang, & Oh, 2013; Lyu et al., 2018). Improvements in this domain have been found to have a strong dose-response relationship and are likely to develop with regular engagement in music therapy (Gold et al., 2009).

Duration of treatment has been found to be a significant indicator of the effectiveness of music therapy for schizophrenia, with long-term therapy yielding greater effects than short-term interventions (Chung & Woods-Giscombe, 2016; Geretsegger et al., 2017; Gold et al., 2009; Mössler, Chen, Haldal, & Gold, 2005). While long-term therapy is generally recommended, some studies have demonstrated favourable outcomes when music interventions are delivered intensively over shorter durations. For example, participation in group music activities led to significant reductions in negative symptoms when delivered intensively over a two-week period (Peng, Koo, & Kuo, 2010). Relaxation techniques combined with receptive music listening have been shown to reduce depressive and psychological symptoms in people with a diagnosis of schizophrenia attending community health centres when delivered intensively over a four-week period (Kavak, Ünal, & Yılmaz, 2016). Adding music therapy to standard care led to greater

symptom reduction than standard care alone for individuals hospitalised with acute psychosis following a 12-week intervention (Gold, 2007), and improved psychosocial and global functioning in a short stay acute psychiatric ward (Volpe, et al., 2018). This research demonstrates that musical engagement can bring about short-term changes in mood which support individuals to transition from a phase of acute illness to a more stable state of well-being. Long-term therapeutic input may lead to more lasting changes by providing opportunities for deeper self-discovery and experiences of agency.

Music therapy generally yields high attendance rates and treatment compliance for people with a diagnosis of schizophrenia, indicating that it is a therapy which motivates participants towards engagement (Hannibal, Pedersen, Hestbæk, Sørensen, & Munk-Jørgensen, 2012; Talwar et al., 2006). In addition, studies have indicated that participation in music therapy may encourage individual clients to begin using music to support well-being in their daily lives (Solli et al., 2013). These motivations appear to arise organically rather than as a directive of the therapeutic process, which indicates that participation in music therapy alone is enough to prompt recreational engagement outside of the therapeutic environment. Such findings support the idea that music possesses intrinsic qualities which promote vitality and motivation.

Amidst the disorientation and disconnectedness that often characterise schizophrenia, the true benefits of music therapy are present in its potential to assist clients to form meaningful connections both internally and externally; fostering experiences of regulation, authenticity and connection to self. While outcomes-based studies contribute to our understanding of music therapy's overall clinical efficacy, an over-reliance on quantitative outcomes may overlook the beneficial contribution music therapy makes to peoples' subjective quality of life. Furthermore, it has been noted that outcomes-based studies may fail to recognise the advantages of process-oriented approaches which facilitate non-verbal expression (McCaffrey, Edwards, & Fannon, 2011). In recognition of this, the remainder of this chapter will focus more closely on the qualitative research which emphasises music therapy's role in supporting personal recovery.

***Supporting Personal Recovery through Music Therapy***

When supporting people with mental health difficulties, music therapists generally favour person-centred approaches which promote the client's agency within the therapy process. McCaffrey and colleagues (2018) proposed four ways that music therapy may facilitate individual recovery: 1) recognising and respecting expertise by experience; 2) awareness and integration of processes at the core of recovery; 3) being resource-oriented, and; 4) being community-oriented. By shifting the emphasis from deficits to personal resourcing, and promoting social participation and inclusion, music therapy has the potential to empower people to pursue goals beyond clinical remission and perceived dysfunction. Strengths-based approaches which support personal recovery have also been advocated for within the wider literature on schizophrenia and related conditions (Chan et al., 2018).

Music therapy affords incredible flexibility in terms of its application within a recovery paradigm. Given its position of value in many people's lives, music serves as a relatable medium through which therapeutic outcomes can be pursued in a variety of contexts. Not only can music therapy be offered to people seeking individual therapeutic support in acute and outpatient settings, but the communal elements of music-making can be harnessed to accommodate the needs of wider social settings through community music therapy (CMT). CMT practices capitalise on the health-promoting properties of participatory music-making in community settings (Stige & Aarø, 2012). The success of CMT in supporting people transitioning from hospital to community living has been documented in detail (Ansdell, DeNora, & Wilson, 2016). Such projects empower clients to become active agents in their own recovery process, while emphasising the power of creative communal spaces for fostering experiences of connectedness and shared identity. In addition, music is recognised as a medium which has the potential to instil hope (Ansdell, 2014) and facilitate transcendental experiences (Ansdell 2014; Moss, 2019). Music therapy has thus been positioned as a modality which naturally encompasses CHIME recovery concepts of connectedness, hope, identity, meaning and empowerment (McCaffrey et al., 2018).

Ansdell and colleagues (2016) introduced the concept of ‘recovering music’ as a noteworthy part of the recovery process, explaining that experiences of illness can cause people to become disconnected from the very resources that support their well-being, including music. They proposed that the process of ‘recovering music’s help’ is an important step towards wellness through reinitiating a connection with a “previously helpful resource” (p.221). The idea that losing our connection to music in some way represents a disconnection to self is a powerful indicator of music’s capacity to reignite qualities integral to the human experience. Irrespective of illness or disability, it is difficult to participate fully in life without the essential experiences of vitality, personal agency and self-esteem. Mediums that support these deeper human needs are of central relevance to a recovery philosophy that supports all people to live an enriching life.

Resource-oriented music therapy places an emphasis on capitalising on clients’ personal and musical resources in music therapy (Rolvsjord, 2010). This approach views the therapeutic process as a collaborative engagement between therapist and client rather than an ‘intervention’ delivered by the therapist. In resource-oriented music therapy, music is seen as a health resource that the client can access *through* therapy, while simultaneously taking into consideration the musical competences that the client *brings* to therapy. Such an approach encourages ongoing collaboration between therapist and client. In line with recovery principles, music therapists seek to draw on protective factors which will enhance quality of life despite the challenges posed by illness.

Service user perspectives have also begun to assume an important role within the field of music therapy and mental health research (Carr, 2014; McCaffrey, 2014; McCaffrey, 2018; McCaffrey & Edwards, 2016; Solli 2014). Within recovery-oriented practice, service user perspectives play an essential role in communicating the quality of life benefits of music therapy. To date, such research has revealed that music therapy is generally a positive experience for people which supports well-being (Carr, 2014; McCaffrey, 2018; McCaffrey & Edwards, 2016; Solli et al., 2013; Solli & Rolvsjord, 2015). Music therapy is a space where clients have reported feelings of agency, mastery, hope, and greater emotional regulation (Solli et al., 2013).

Moreover, clients bring skills, resources, and personal attributes which enable them to participate as active agents in the music therapy process (Rolvsjord, 2015). Crucially, these findings reveal that music therapy is experienced as a recovery-oriented process by clients themselves, not simply on a theoretical level. Clients have reported social benefits to attending music therapy (McCaffrey, 2018; Solli et al., 2013; Solli & Rolvsjord, 2015) as well as reductions in symptoms of psychosis (Carr 2014; Solli & Rolvsjord, 2015). Additionally, first-hand accounts by service users have illuminated some of the more challenging aspects of participation (Carr, 2014; McCaffrey, 2018). Such information is of crucial relevance to supporting reflective practice amongst music therapists working in mental health settings.

In addition to research detailing service user experiences, the qualitative case study literature has contributed to the understanding of music therapy processes from the perspective of music therapists working in mental health settings. Such examples have revealed insights into features of musical engagement believed to be characteristic of psychosis. For example, music therapists have described experiencing feelings of isolation, fatigue, disconnection, and loneliness during musical improvisations (where therapist and client co-create music together). Such experiences are thought to mirror the feelings of disconnectedness and isolation brought about by psychosis (Solli, 2008; Metzner, 2010). Similarly, music therapists have described the musical output of their clients as fragmented, repetitive, and/or chaotic in the early stages of therapy (De Backer & Van Camp, 2012; Metzner 2010; Solli 2008; Solli, 2014). As the therapeutic process evolves, the musical output becomes more coherent and organised, and music therapists note that they experience greater musical synchronicity when co-creating music with their clients. Such illustrations suggest that music offers a medium through which clients can safely externalise their distress by creating a soundscape that emulates their internal experiences. Case examples have also demonstrated the value of supporting a client's autonomy over the music therapy process, indicating that music therapy appears to work best when adapted to the preferences of the client (Solli, 2008; 2014).

## **Using Self-Selected Music to Establish a Personal Narrative**

In line with emerging resource- and recovery-oriented perspectives, the right to choose is considered a rudimentary element of the music therapy process which honours a client's right to feel empowered. One of the motivating factors for music therapists in providing opportunities for choice is to counteract the disempowerment often experienced by clients outside of the therapy room. Therefore, honouring an individual's musical preferences is of crucial importance to the therapeutic process. When clients are invited to share their own music, they are invited to share aspects of themselves and their experiences that are embedded in their associations with that music. By introducing music on their behalf, the therapist risks over-shadowing the client's personal, cultural and social identity by imposing their own assumptions on the client's experiences.

A client's self-selected music preferences are more likely to support the therapeutic process, as music that elicits emotional responses has been found to hold greater meaning for people (Craig, 2009). Accordingly, the music therapy literature is expanding to explore the impact of a diverse range of musical genres and their applications within therapy (Hines & McFerran, 2014; Viega, 2013). Specifically, an emerging body of literature describing the use of Rap in music therapy signals that it may have specific value within recovery-oriented music therapy practice due to its unique capacity to support the formation of personal narratives. The construction of a personal narrative (i.e., how a person makes sense of their story) may represent a meaningful aspect of recovery from schizophrenia which is independent of traditional recovery concepts such as hope and empowerment (Lysaker, Ringer, Maxwell, McGuire & Lecomte, 2010). Roe and Davidson (2005) observed that historical attitudes toward people diagnosed with schizophrenia distorted the belief that it is possible for such people to form coherent narratives about their lives, as the loss of self and inability to form insight were traditionally viewed as a core features of these illnesses. Conversely, they postulated that the process of creating a personal narrative is fundamental to moving beyond limiting definitions of illness. Recent paradigms have further emphasised the central role that personal meaning

plays in recovery from mental illness (Johnstone & Boyle, 2018). People with schizophrenia who develop a sense of meaning through the pursuit of personal recovery goals report better well-being than those who achieve clinical remission alone (Chan et al., 2017).

### ***Forging Narratives through Rap***

Rap music has its roots in the musical and storytelling traditions of Africa. As an art form, it evolved in response to a combination of musical, political and social influences affecting African Americans in the 1980s and is now embedded as a musical genre within mainstream culture (Frisch-Hara, 2012). Rap music is an artistic medium that has traditionally given voice to the marginalised by highlighting issues relating to poverty, oppression, injustice, and discrimination. Popular Rap songs have been identified to include a number of constructive themes broadly relating to social criticism, social empowerment, humanistic values, and criticism of negative behaviour (Tyson, Detchkov, Eastwood, Carver & Sehr, 2012). More specifically, these songs have been found to address themes of love, spirituality, perseverance, personal empowerment, and empathy; in addition to praising education, work and achievement; and condemning violence and substance abuse. Rap thus exists as a musical genre through which coherent, empowering narratives can be formed in the face of adversity.

The inherently improvised nature of Rap music makes it an idyllic medium for spontaneous self-expression, both musically and lyrically. Free-form songwriting and improvisation have been identified as the most commonly cited techniques in the music therapy literature (Stewart & McAlpin, 2016). Free-form songwriting often begins as a spontaneous improvisation which subsequently develops into a musical composition. It has been surmised that such artistic freedom within the songwriting process supports emotional expression (Stewart & McAlpin, 2016). Rap music naturally fits the criteria for free-form songwriting due to the verbal spontaneity it facilitates, although this often occurs within the context of a pre-determined musical structure (e.g., the beat of a backing track).

Rap music, and its associated Hip Hop culture, has been positioned as a musical genre which supports empowerment by providing a voice to those

who are drawn to this art form (Viega, 2016). Moreover, it has been observed that Rap music offers clients a context in which they can explore various roles and identities (Viega, 2013). Solli (2014) previously illustrated the benefits of freestyle rapping in helping a young man with psychosis to forge an identity in music therapy. This young man's identity as a rapper served as a musical resource which empowered him toward social recovery by promoting his awareness of his positive attributes. Freestyle rapping in particular provided him with a vehicle for articulating his thoughts and expressing himself emotionally. Thus, Rap music is well-situated to support the recovery goals of clients in music therapy who wish to engage through this genre.

### ***Facilitating the Therapeutic Process through Rap***

Rap has been characterised as a musical form that naturally supports the therapeutic process by offering innumerable possibilities for self-expression within a coherent structure (Frisch-Hara, 2012). For example, the steady beat provides a grounding rhythm which anchors the client as they engage in creative risk-taking (i.e., spontaneously producing lyrics). Service users have identified rhythm as both a stimulating and calming element of music, providing a grounding point from which mental clarity can be achieved (McCaffrey, 2014). It thus provides adequate safety while simultaneously allowing space for expansion.

Hadley and Yancy (2012) listed four ways that Rap can facilitate the therapeutic process through 1) listening and discussing, 2) performing, 3) creating, and 4) improvising. Used independently or in tandem, these processes serve a myriad of therapeutic functions, such as: stimulating in depth discussions about clients' life experiences, attitudes and beliefs; promoting self-expression and identity formation; providing opportunities for decision-making; and developing interpersonal skills. In music therapy, successful therapeutic process necessitates a balance between structure (which provides coherence and safety) and creative expression (which requires curiosity and an openness to explore). Viega (2016) outlined considerations for music therapists wishing to engage with Rap music in their practice, emphasising the importance of cultivating an awareness



around the cultural, technological and multi-modal components of this art form.

### ***Potential Considerations When Using Rap in Therapy***

Some discourse exists in the music therapy literature as to the limitations, if any, that should be placed on the use of Rap music in music therapy sessions (Hadley & Yancy, 2012; Viega, 2016), specifically in relation to explicit verbal content (Short, 2013). Misguided societal perceptions of Rap music have caused issues for music therapists working in facilities that have prohibited the use of Rap music due to its associations with misogyny, profanity, violence and drug use.

Nevertheless, it has been argued that commercial Rap music reveals little about the rich cultural traditions underlying the art form (Viega, 2016). Furthermore, explicit content is not exclusive to Rap music and frequently features across a wide range of modern genres. Thus, it has been observed that if we reduce our understanding of Rap music to superficial judgements, we risk negating the depth and complexity intrinsic to this art form (Hadley & Yancy, 2012).

It is generally acknowledged within the music therapy community that by denying an individual's music choices, the therapist risks invalidating important aspects of the person's identity (Hadley & Yancy, 2012). Accounts of explicit content arising during the music therapy process has primarily been reported in the context of adolescents who have been exposed to extreme life circumstances. In such circumstances, music therapists have clarified that explicit content may serve a variety of functions for clients, which include testing boundaries and defending against emotional vulnerability (Frisch-Hara, 2012; Short, 2013). Rather than focussing on the content of a song, music therapists are interested in the meaning the song holds for the client: *why* did they choose this song; what are they trying to communicate *through* this song? When worked with appropriately the level of explicit content tends to decrease naturally and can even serve as a platform from which therapists can explore complex issues with clients (Frisch-Hara, 2012; Short, 2013).

## CASE EXAMPLE

The authors will now introduce a case example which outlines the personal recovery journey of a young man, named Paul, through his self-selected use of Rap music in music therapy. Paul's therapeutic process is presented in a series of stages which represented important periods of personal growth. Through this case example, the authors hope to demonstrate the unique potential of music therapy as a platform for supporting people to develop a coherent, meaningful personal narrative within a recovery paradigm.

### **Paul's Personal Recovery Journey through Music Therapy**

Paul is a man in his thirties who has been attending weekly music therapy at a day service for individuals with mental health difficulties for the past two years. He has been involved with mental health services since his teenage years and has a diagnosis of schizophrenia. Paul receives standard medical treatment for his condition, attending the day service for regular medication reviews. He had not been hospitalised for a number of years prior to commencing music therapy, however he experiences ongoing positive and cognitive symptoms associated with schizophrenia including paranoid delusions, disorganised speech and disordered thinking. In addition, he has experienced recurring depressive episodes and negative symptoms which have impacted on his ability to engage in routine daily activities. Paul lives alone and has no known family contact apart from a grandparent whom he visits once a week.

#### ***Stage 1. Assessment Phase: Connecting through Music***

Paul was verbally recommended for music therapy during a conversation I had with a staff member at the day service. This staff member noted that Paul had an interest in music, however it was considered unlikely that he would commit to engaging in ongoing therapy as he had exhibited prior difficulties engaging with staff members. For example, he would

occasionally walk out of meetings with professionals if he became distressed or uncomfortable. In addition, Paul generally made his visits to the day service brief, rarely interacting with staff or other service users. With this knowledge in mind, I decided to approach Paul with the aim of having a general conversation about his music interests. I approached him casually one day while he was having a cigarette outside the day service and enquired as to his music interests and whether he'd like to "try some music." Paul responded that he was into Rap music and agreed tentatively to come in to see the room. I located an instrumental backing track online and put it on to see if he would like it. When the track started, I was struck by Paul's immediate response to the music as he spontaneously began freestyling in time to the beat. I remarked on Paul's enthusiasm and flare for rapping and we agreed to meet again the following week. Subsequent sessions progressed in a similar manner. Each week I set up the therapeutic space with a microphone, bass amp and a loop pedal in preparation for Paul's arrival. I began the sessions by playing a backing track online to which Paul would freestyle along to the selected beat.

Paul had demonstrated a preference for Rap music since his adolescence, and this continued to be his genre of choice during sessions. My personal interest in the American rapper Tupak Shakur (better known by his stage name 2Pac) served as an immediate point of connection from which I began building a rapport with Paul, as this had been his favourite artist from a young age. At this early stage the primary goal of therapy was to support Paul's emotional expression through free-form Rap improvisations.

Within the first few weeks of therapy, a structure to the therapeutic process had begun to develop organically. Paul often arrived up to an hour before the session and would spend this time outside smoking a cigarette, contemplating what he was going to rap about that day. He began to request certain styles of instrumental backing tracks that corresponded with his mood on a given day, noting that he was "underground," for example. He would listen to up to 30 seconds of the track before deciding if it was suitable. The music therapy sessions lasted between 15 and 30 minutes, depending on how much Paul needed to express on a given day.

***Stage 2. Finding Coherence within the Music***

In the early stages of the therapy process, Paul regularly exhibited features of disorganised and incoherent speech during his rapping, rhyming through combinations of repeated nonsense syllables and fabricated words, for example. Nonetheless, I noticed that he consistently demonstrated an ability to orient to the beat of the track. To support this, I began to improvise percussively to the backing track to amplify the grounding properties of the music. This afforded me opportunities to form musical connections with Paul while respecting his need for autonomy within the music. Amplifying the grounding components of the music also appeared to aid Paul's clarity of thought. When moments of verbal coherence occurred, I would record Paul on the loop pedal. This gave us the opportunity to listen back to the music and reflect on the lyrical content together. This process provided opportunities for esteem-building as Paul had the chance to hear his own music and gauge his progress from week to week. It helped him to gain clarity on his thought processes by providing some perspective on his improvised lyrical output.

From the outset I noticed that Paul was particularly expressive in the way he moved to the beat of the music. This physical embodiment appeared to offer him a means of physical release, demonstrating that musical engagement was more than an internal process for Paul. Over time, I noticed a greater sense of coherence emerging in the thematic and lyrical content of Paul's improvisational compositions. Paul appeared to notice this too, rapping the words "my language skills are much better." As my relationship with Paul developed I also experienced deeper moments of interpersonal connection occurring during the music. For example, Paul commonly made eye contact with me when making lyrical reference to something we had discussed earlier in the session. These shared moments of recognition developed in tandem with the therapeutic relationship, occasionally introducing elements of humour into the therapeutic process. They signified purposeful efforts on Paul's behalf to form connection with me through his music, whereas previously his rapping had contained an inherent impulsivity. This marked a progression to the next stage of therapy where support around illness management became a focal point.

### ***Stage 3. A Supportive Space for Developing Insight***

As the therapeutic process unfolded, staff members at the day service began to remark on Paul's consistent level of engagement with music therapy. Recognising the trust established between Paul and I, staff members occasionally made requests of me to follow through with him around conversations relating to psycho-education and personal care. Paul found these discussions difficult and would often cut conversations short with other staff members by walking out of the room if a topic became too sensitive. He had also begun refusing to cooperate with simple medical procedures, such as having his bloods taken. Through the context of music, I was able to find ways to incorporate discussions around sensitive issues that proved challenging for Paul in other contexts. For example, I discovered that part of his reluctance to have his bloods taken stemmed from a misunderstanding about the effect this procedure would have on his body. Approaching this topic within the music therapy context, an environment which represented safety, trust and mutual respect for Paul, offered space for him to communicate something that he had been unable to express previously. As well as providing Paul with a means of self-expression, the music therapy environment became one in which life skills, knowledge around medical procedures and social awareness were incorporated as part of the therapeutic process. This improved Paul's capacity to access other healthcare interventions which were integral to maintaining his overall well-being. As Paul's personal awareness continued to develop, the goals of therapy naturally began to centre on supporting Paul to process personal experiences, as the thematic content of his rapping began to revolve more specifically around personal issues and his experience of illness.

### ***Stage 4. Forming a Personal Narrative through Rap***

This stage of therapy marked an important breakthrough for Paul as the thematic content of his raps began reflecting his life experiences more directly. The content he explored ranged from contemporary political topics to personal issues impacting his daily life. Paul's willingness to begin using Rap to process his personal experiences was indicative of the trust that had been established in the therapy relationship up to that point. As Paul entered

the latter half of his second year of music therapy, he began to address the theme of ‘schizophrenia’ through his lyrics, exploring his lived experience of mental illness in more depth. Subthemes of his raps included lack of education, feelings of marginalisation, experiences of stigma, and desire for connection with others. The steady rhythm and structure of the backing track appeared to provide the solid grounding necessary for Paul to create a coherent narrative from his disorienting experiences of illness. Over time, the improvisations began to progress beyond the confines of the backing tracks. When Paul was engaged in a particularly expressive Rap, I would continue to play a grounding rhythm after the track had ceased while he continued to rap along to the beat of the drum. These instances of Paul rapping to the sound of my solo drumming required unwavering trust in my ability to hold his story through my rhythms, and thus were meaningful indicators of the trust established within the therapeutic relationship. They simultaneously revealed that Paul was no longer relying on the structure of the backing track to remain synchronised, signifying a growing trust in his own ability to maintain a coherent narrative without the track. As he began making sense of difficult experiences, Paul also started to find space in the music to consider who he was beyond the confines of illness. In this regard, a prominent theme for Paul was his love of Rap music. His journey and identity as a rapper arose as an empowering narrative which gave meaning to his life.

### ***An Ongoing Process: Commitment to Music Therapy***

To date, Paul is still attending weekly music therapy, having attended 106 out of 113 music therapy sessions overall. On rare occasions when he has been unable to attend therapy he has arrived at the day centre to inform me in advance or has made apologies the following week. Paul did not miss a single session during his first year of therapy. This level of commitment and motivation is unparalleled in his prior engagement with services. Furthermore, his mood has stabilised, and he has not experienced a severe depressive episode since commencing music therapy. He takes greater care of his personal hygiene, and I have personally noticed improvements in his physical appearance when attending music therapy. Other staff have also

noted these developments. Paul has recently started to attend appointments with an occupational therapist at the day centre, which is further supporting his personal care, and represents a new willingness on his behalf to engage with services. Moreover, he has reconnected with some extended family relatives which has enhanced his social contact outside of the day service.

Paul still experiences some of the clinical symptomatology associated with his illness, including paranoid delusions, however his attendance at music therapy has enabled him to embark on a rich recovery journey guided by his personal aspirations. To date, Paul has recorded a CD as part of his music therapy process, which has given him a great sense of accomplishment and mastery in his craft. With his consent, recordings of Paul's music have been shared with service users and staff at the day centre which has validated his musical identity. This has prompted more opportunities for social interaction as other service users have expressed an interest in hearing his music. In addition to this, he participated in a public performance which proved validating for Paul as it revealed that people were interested in what he had to say through his music. These positive experiences prompted Paul to establish contact with music groups in the wider community. While ongoing relationships with these groups have not been sustained to date, this is the first time that Paul has been motivated to form such connections outside of the day service, representing potential points of contact for him in the future. He is currently exploring the possibility of recording and releasing some original compositions in the coming months.

## **DISCUSSION**

Paul's story was introduced with a brief clinical description which revealed very little about his personality, and even less about his lived experience of illness. Moreover, it revealed nothing about his lived experiences outside of illness. This was done in the hope of illustrating that defining Paul solely in terms of his clinical history failed to provide any insight into who he was outside of his diagnosis and relationship to mental

health services. As we progressed with him on his recovery journey we discovered that there were many more layers to Paul's story. Indeed, he was a young man with meaningful passions and interests which remained unnoticed in his case history. These resources were brought to the forefront during his participation in music therapy. The direction of Paul's therapeutic process grew organically from his musical preferences and was thus tailored to his personal aspirations, rather than expectations imposed by the music therapist.

Throughout his therapeutic journey, Paul maintained primary control over the song writing process, with the freedom to choose the beat, tempo, lyrical content and the mood of the music. Moreover, the client-led nature of the therapy sessions ensured that the structure of 'treatment' was guided by Paul's interests rather than his limitations. Rap was a multi-layered creative process for Paul which facilitated emotional expression, embodied movement, and cognitive processing in the form of spontaneous lyric formation. By putting outer structure on his inner world, the more fragmented, visceral elements of his experience had opportunities to become assimilated. Paul's motivation to engage through this medium illustrated the advantages of trusting clients to intuitively guide their own therapeutic process according to their needs.

Paul's personal development was described through a series of stages. The first stage of therapy, *connecting through music*, marked the assessment phase. During this phase the foundational rapport was established through music. Rather than a formal meeting between service provider and service user, the initial point of contact was established between two people who shared a mutual interest. This very human connection sparked the engagement of a young man who had previously experienced an aversion to engaging compliantly with his service provider. From the outset the music therapist was guided by Paul's personal music selections. Working through music that he felt personally connected to enhanced Paul's capacity for spontaneous self-expression. Through personally meaningful music, Paul's core personality was appropriately represented in the therapy room from the beginning, untainted by clinical judgements. The use of the therapeutic space was mutually established from the beginning, and the autonomy



afforded within the therapeutic environment appeared to dismantle barriers to engagement for Paul. There also appeared to be an inherent occupational benefit to the music therapy sessions, evidenced in the fact that he began arriving in advance of sessions to contemplate how he would use his time. This echoes previous service user accounts which identified music therapy as a form of meaningful occupation (McCaffrey, 2016; 2018).

The second stage of therapy, *finding coherence within the music*, marked the beginning of a shift toward improved mental clarity. Rap music offered a safe musical structure which contained any disjointed thoughts or experiences that arose for Paul. The grounding rhythm helped him to stay anchored in the midst of disorganisation. Free-form song writing enables therapists to support clients by guiding the musical elements of the composition (Stewart & McAlpin, 2016). Using rhythmic grounding techniques, the music therapist found ways to enter the music without disrupting the free-form nature of Paul's rapping. The rhythmic nature of Rap permitted Paul to physically embody the music, augmenting the expressive quality of his experience. Listening back to recordings of the music presented opportunities for Paul to reflect on his lyrics with the music therapist. As the spoken content of the raps became more articulate, the music therapist observed Paul making deliberate attempts to connect with him through subtle humour. The use of humour can be indicative of rapport and connection, reflecting the shared language that emerges between therapist and client during musical improvisation (Haire & MacDonald, 2019).

During the third stage of therapy, *a supportive space for developing insight*, the trust established within the therapeutic relationship afforded opportunities for the music therapist to facilitate important discussions around illness management at the request of other staff members. Music therapy has previously been positioned as a motivating medium through which psychoeducational knowledge and skills can be imparted (Silverman, 2015). Approaching sensitive topics within the context of a safe, mutually respectful environment supported Paul to access medical treatments which were imperative to his overall well-being. This highlighted the value of approaching difficult conversations within supportive spaces where clients

feel comfortable and in control. The safety that the music therapy environment represented for Paul neutralised the perceived threat he associated with clinical settings. Equally, the common language of music neutralised any perceived power dynamics between Paul and his therapist, enabling him to participate in these conversations from a position of empowerment.

As Paul progressed on his recovery journey the experiences of inner coherence and interpersonal connection achieved at earlier stages of the therapeutic process enabled him to begin exploring his life experiences in more depth. Stage four, *forming a personal narrative through Rap*, marked a significant period of growth for Paul as he began constructing a narrative around his experiences of ‘schizophrenia’, particularly in relation to lack of education, marginalisation, stigma, and wanting to connect with others. During this time, the music therapist observed that Paul was developing an improved ability to tell his story without relying on the structure of the backing track. The depiction of solo voice and solo drum illustrated a juncture of meaningful interpersonal connection for Paul in which he trusted his therapist to safely ‘hold’ his emergent narrative. The therapeutic relationship facilitated important human experiences of attunement, connection, belonging and understanding. Coupled with his pre-established love of Rap music, Paul found a unique space in which he could make sense of his personal story, forming a new identity that was both meaningful and empowering.

Paul’s recovery journey is ongoing. His journey illustrates the power that music can impart when experienced within the context of a mutually established therapeutic alliance. Throughout his time in music therapy, Paul was highly committed to the therapeutic process. Rolvsjord (2015) delineated the bi-directional nature of the therapeutic relationship in music therapy, identifying a mutual concern on behalf of both the client and the therapist to establish an equal partnership. Paul’s motivation towards upholding reciprocity was evident in his relationship with the therapist. As is the case for many people with severe mental illness, Paul requires ongoing support in managing the positive symptoms of his illness. However, if we focus solely on clinical outcomes we may risk overlooking the enhanced

quality of life that he achieved from attending music therapy. Paul's therapeutic process was highly individual, and his accomplishments defined within the sphere of his distinct life circumstances. Not only did music therapy serve as an ongoing support throughout his recovery journey, it was the opportunity to attend music therapy that assisted him to embark on this journey to begin with. Paul reconnected with music as a 'helpful resource' (Ansdell et al., 2016), and in doing so he accessed a deeper awareness of self. Furthermore, he created a meaningful narrative that was not defined by his experience of schizophrenia. Rap music became the conduit through which he found his voice.

## CONCLUSION

This chapter provided an overview of music therapy as a process which promotes personal recovery for people with severe and enduring mental health conditions. Music therapy has a robust evidence-base for alleviating the negative, affective and global symptoms associated with schizophrenia. However, the qualitative literature offers a richer insight into how participation in music therapy can help people to reconnect with personal qualities that may have been overshadowed or lost through their experiences of illness. This chapter detailed one such example, demonstrating how the use of self-selected music in music therapy helped to motivate a young man to discover an identity beyond the confines of his illness, thus restoring a sense of purpose to his life.

The unique application of Rap music in the present case example should serve to highlight the scope of music therapy's applicability within a recovery context, and the individuality that can be accounted for within the arts therapies more generally. By drawing on personal preferences as a point of connection in therapy, clients are invited to bring core attributes of their identity to the forefront from the outset. In the present case example, Paul's self-selected preference for Rap music served as the most efficient channel through which he could engage in therapy and develop his narrative through spontaneous lyric creation. However, there are many ways of forming

personal narratives that do not necessitate the use of words. In fact, the visceral dimensions of human experience often require channels outside the sphere of language to be communicated authentically, and the arts therapies are uniquely positioned to support that endeavour. The creative process offers people a myriad of ways to tell their stories while simultaneously presenting opportunities to evolve beyond them.

This case highlights the importance of providing ongoing therapeutic support to individuals experiencing enduring symptoms. While time-limited interventions may help to target specific areas of need, the ongoing nature of therapeutic processes such as that offered by music therapy supports people to aspire toward goals that supersede daily functioning. As personal recovery from serious mental illness is regarded as an ongoing and individual journey, music therapy provides a space where this process can be honoured within the sphere of each client's competencies and personal aspirations. For people with chronic and enduring mental illness, regular participation in music therapy offers a supportive environment where the therapeutic process is permitted to unfold at a pace determined by the client. It also ensures that consistency, trust and safety can be established within the therapeutic relationship; crucial elements which support progression toward recovery.

While symptom-reduction can form an important part of a person's individual recovery goals, people with mental illness have the right to aspire beyond this. Therapies that emphasise personal resourcing can be empowering for people who have experienced persistent negative consequences due to severe mental illness. In recognising and supporting the personal aspirations of each client, music therapy is an expansive process which honours the ever-evolving nature of human experience. Music possesses unique qualities as a creative and therapeutic medium. By altering our emotional landscape with such immediacy, it enables us to step *inside* the experience *with* the person creating the music. In therapy, this offers us an unparalleled opportunity to share in the lived experiences of people with mental illness. By sharing directly in peoples' experiences, the narratives take on a new meaning.

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*Chapter 7*

**COPING STRATEGIES IN ORAL HEALTH:  
PROBLEMS EXPERIENCED BY PEOPLE  
WITH SCHIZOPHRENIA**

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## ABSTRACT

Schizophrenia is a psychiatric disorder that affects approximately one percent of the population. Persons with schizophrenia (PWS) neglect their self-care and are particularly susceptible to medical illnesses, including cardiovascular disease and oral health problems. The neglect of self-care by PWS appears to be influenced by “denial of the body”, by the side effects of treatments, and by poor lifestyle habits; all of which may affect the ability and desire to perform preventive oral hygiene. In addition, mental disorders are accompanied by addictions to tobacco, alcohol and/or psychoactive substances (cannabis) that are common risk factors for tooth decay and periodontal diseases. Furthermore, schizophrenia interferes with a person’s ability to manage stress situations (e.g., dental pain) and, as such, PWS use more passive coping strategies to oral health management. Coping strategies are conscious efforts used by individuals to solve problems or needs in daily life, by using perceptible, emotional or behavioral processes to cope with stress. In this case, understanding an individual’s physiological reaction to, and perception of, various stressors, should be considered when assessing oral health care in PWS. Finally, clinical indicators or measurement in oral health related quality of life are insufficient to explain why PWS rarely consult dentists, are more likely to delay seeking care, and are less likely to adhere to or receive adequate treatment in comparison to the general population.

To better understand these issues we developed a self-administered questionnaire for PWS focused on oral health strategies and how they might contribute to improving Oral-Health-related Quality of Life (OHRQoL). This questionnaire was then utilized in a qualitative study, exploring the coping strategies in oral health for PWS. Better understanding of how individuals effectively manage and cope with adverse situations, thus preserving and improving their health, is an important issue. Early identification of coping strategies may facilitate the development of cognitive behavioral interventions to change the person’s perceptions of their own ability to improve oral hygiene.

**Keywords:** coping, oral health, quality of life, schizophrenia, mental health

## **1. INTRODUCTION**

### **1.1. The Relationships between Schizophrenia and Poor Oral Health**

The poor oral health of people with severe mental disorders such as schizophrenia is a major public health issue. Indeed, schizophrenia affects about 1% of the general population (Jablensky, 2000). People with schizophrenia (PWS) are particularly susceptible to a large number of somatic medical problems (Jablensky, 2000), they have at least one associated somatic condition, including cardiovascular, gastrointestinal, respiratory, neoplastic, infectious, endocrine, and oral disorders. About half of these comorbidities are undiagnosed (De Hert et al., 2011; Hennekens et al., 2005; Capasso et al., 2008; Joukama et al., 2006; Chafetz et al., 2005; Brown et al., 2000). The studies unanimously show that there is a gap between the oral health of PWS and that of the general population. Negative symptoms often affect both health behaviors and lifestyle, and may lead to poor oral health and dental diseases (Kwong et al., 2017; Khokhar et al., 2011). For instance, side effects due to medications to manage schizophrenia, antipsychotics, induce hyposalivation (xerostomia) or hypersalivation (clozapine) and/or oral dyskinesias with first-generation antipsychotics (Heliövaara et al., 2006). Indeed, mental disorders are accompanied by a carbohydrate rich diet (Lewis et al., 2001), by addictions to tobacco (Dalack et al., 1998), and alcohol/or psychoactive substances (cannabis) (Drake et al., 1998) that deteriorate oral health. In addition, these people have real difficulties investing in the preservation of their physical health; both in integrating a system of care and in motivation to perform preventive oral hygiene (Almomani et al., 2006; Nielsen et al., 2011). Poor oral health alters certain functions essential to a good quality of life, such as chewing, speech and smile aesthetics, which have a direct impact on self-esteem Hofer et al., 2016; Persson et al., 2010). The dental index, like the DMFT (decayed, missing and filled teeth) index which is the sum of missing, decayed and filled teeth, indicates a number of decayed teeth twice as high in people with schizophrenia (Arnaiz et al., 2011). The same is true

for periodontal indexes (Morales-Chavez et al., 2014; Kisely et al., 2011). Poor periodontal health in patients with schizophrenia can be attributed to the mental condition in these patients which contributes to bad oral hygiene maintenance and medications that lessen the flow of saliva. Indeed periodontal disease is a complex disorder of all periodontal tissues (gingiva, alveolar bone, periodontium and dental cement), and is associated with certain diseases and systemic risk factors, such as smoking, diabetes and obesity (Arigbede et al., 2012).

## **1.2. Coping Strategies in PWS**

Coping strategies are conscious efforts used by individuals to solve problems or needs in daily life (Carver et al., 1989). According to the transactional stress model, an individual's reaction to stressors is determined, in part, by his/her appraisal of the stressor (Lazarus, 1996). Stress is somewhat subjective both in the measurement of severity and experience, and the way in which individuals perceive and interpret stressors may vary greatly. The impact of a stressor is also determined by one's ability to cope with the situation, which in turn is related to the availability of various coping resources (Lazarus, 1996).

Studies of coping strategies in schizophrenia have revealed that coping style might be related to various psychological and cognitive factors (Lysaker et al., 2004). For example, among individuals with schizophrenia, high self-efficacy (operationally defined as high self-esteem, self-report of positive coping with stressful events and perceived social support) is significantly positively correlated with approach coping. Problem-based coping (changing the problem that causes stress through a combination of efforts to cope with the situation) and emotion-focused coping (regulating the emotional responses to the problem that generates the stress) are two types of coping strategies (Grisso & Appelbaum, 1995). Of these two strategies, PWS use more passive emotion focused strategies, such as avoiding, ignoring and not thinking about the problem (Aghevli et al., 2003). PWS demonstrate significant difficulty coping with stressful situations



compared to people without a mental illness (Carver et al., 2010). These persons often employ a more limited range of coping strategies, which are characterized by a preference for avoidance and passive coping rather than help seeking or active problem-solving approaches (Allott et al., 2015). They are also at risk of becoming isolated and victimized, reducing the effectiveness of learning new coping efforts (Kao et al., 2017; Moore et al., 2015; Wey et al., 2016; Wartelsteiner et al., 2016).

### **1.3. Coping Strategies and Dental Health Behaviors in PWS**

Cognitive dysfunction is a core feature of schizophrenia. Deficits are moderate to severe across several domains, including attention, working memory, verbal learning and memory, and executive functions. People with schizophrenia develop a multitude of coping strategies to cope with the disease. These various strategies have a crucial role to play in making conscious efforts to solve different problems (Carver et al., 1989). We note that the effectiveness of the coping effort depends on the symptoms of mental illness, stress, situation and previous experience. When the patient is confronted with a situation (e.g., dental pain), he can adapt schematically in 2 ways, either active or passive. In the first case, his adaptation is centered on the problem. For example, he can ask for help to be accompanied to the dentist and thus take preventive action. This adaptation strategy is therefore qualified as positive. Conversely, passive adaptation, centered on emotions, is described as negative. In this case, the patient can adapt irrational behaviors related to dental pain by seeking to relieve himself by taking alcohol or taking psychoactive substances. In this schema he will modify the meaning of the situation by minimizing its gravity or by denying his reality (denial, magical thinking, etc.). He then takes no action and his oral health deteriorates. Dental health behaviors for PWS could also be influenced by many personal factors (e.g., psychological symptomatology, neuropsychological functioning, self-esteem, self-stigma, self-determination, sense of coherence, and resilience), and environmental factors (e.g., support and stress situation).

Coping strategies and dental health behaviors in PWS are summarized in Figure 1 below.

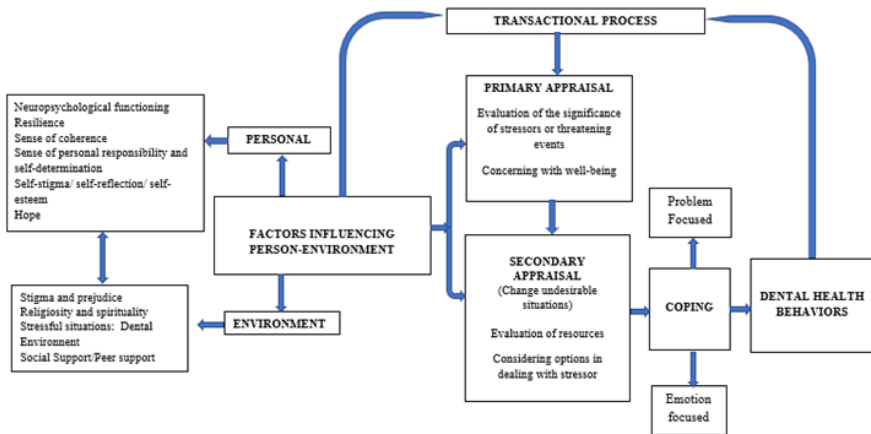


Figure 1. Coping strategies and dental health behaviors in PWS.

Studies demonstrated that cognitive behavioral intervention would produce significantly greater change in the person's own perceptions of ability to improve oral hygiene (Wolfe et al., 1996; Jacobs-Schoen, 1986; Stewart et al., 1991). Wolfe et al., (1996), developed a questionnaire, the Dental Coping Beliefs Scale (DCBS) which was administered to 100 subjects without mental disabilities. In developing this scale, three models of cognitive psychology were used for generating and selecting items for the questionnaire, namely, locus of control, self-efficacy and the cognitive model of behavioral change. The purpose of the DCBS was to quantify cognitions and to quantify cognitive changes. Wolfe and colleagues found that oral hygiene interventions induced a shift from an external locus of control to an internal locus of control. In other words, participants developed the belief that they could impact their own dental hygiene.

A recent study by our own team (Denis et al., 2019) confirms that people with schizophrenia have poor dental hygiene in that they do not regularly attend the dentist and do not brush their teeth enough. We also note the appearance of side effects with first generation antipsychotic use, such as irreversible dyskinesias, which may lead to difficulty with brushing teeth

(Arnaiz et al., 2011). In addition, poor oral health impairs certain functions essential to a good quality of life, such as chewing, speech, and smile aesthetics that have a direct impact on self-esteem (Kwong et al., 2017). Finally, dentists are poorly trained to take care of a person with a mental disability. Mental illness “scares”! This is one of the reasons why these people are often stigmatized.

To our knowledge, coping strategies used by PWS to address poor OHRqoL, have never been explored. In this context, we developed a simple questionnaire for PWS that focuses on oral health coping and which should contribute to a better understanding of oral health needs. For caregivers, this information could inform care strategies to encourage positive behavior in oral health and improve OHRqoL in PWS.

To this end, a qualitative study was conducted by our team, implementing a newly developed self-questionnaire (Schizophrenia Coping Oral Health Profile: SCOOHP) to identify the different coping strategies used by people with schizophrenia in OHRqoL.

## **2. METHODS**

### **2.1. Study Design**

Qualitative and feasibility studies were conducted to explore the experience of the participants and their feelings regarding the coping strategies in Oral-Health-related Quality of Life (OHRqoL).

#### ***2.1.1. First Step: Generation of Items for Including in Coping in Oral Health (SCOOHP)***

This step included 26 semi-structured individual interviews (Hesse-Biber & Leavy, 2010) (20 with PWS and 6 with health professionals (HPs)), and 2 focus groups (Krueger & Casey, 2000) (PWS and HPs), to explore the experiences of the participants and how they felt about coping strategies in OHRqoL. Participants replied based on their experiences (for the PWS) or based on their direct observations and reported experiences (for the HPs).

The semi-structured interviews took place in two stages. The first stage consisted of addressing the main themes of the interview guide with the patient by insisting on spontaneous oral reactions in order to explore the experiences of the participants and the meaning that they attributed to OHRqOL. The second stage consisted of completing open-ended questions with follow-up questions.

The interviewer might reword, reorder, or clarify the questions to further investigate topics introduced by the respondent. It was hypothesized that spontaneous replies would help with understanding the most important priorities, the experiences, and meanings of the disease, as well as to explore personal and sensitive themes or to identify potential modifiable factors for improving health care (Hesse-Biber & Leavy, 2010).

Focus Group (FGs) of PWS and HP were also carried out. These FGs were semi-structured discussions with groups of 4–12 people that aimed to explore a specific set of issues. The group interaction encouraged respondents to provide insights that would not have surfaced in individual interviews and to enrich the information gathered during the individual interviews.

Semi-structured interviews and focus groups were drawn up by a psychologist who was experienced in managing individuals with mental health issues. The psychologist had assistance from an interview guide covering several specific areas of OHRqOL for PWS. These guides were based on the literature, our recent studies (Denis et al., 2017; Denis et al., 2016), and consensus meetings with experts from the work group (WG) (one dental researcher, one psychosociology researcher, one methodologist, one nursing researcher, and one PWS).

The aim was to include all issues relating to OHRqOL and to obtain a “point of saturation” (Braun & Clarke, 2006). Only items related to the concept of coping in OHRqOL were validated for SCOHP.

### ***2.1.2. Second Step: Feasibility Study***

A feasibility study was conducted with a further 30 PWS, recruited at the Chartreuse hospital. This study involved a statistical analysis to test the acceptability and internal consistency (Cronbach’s  $\alpha$ ) (Denis et al., 2017) of

the coping items. The purpose of the feasibility study was to determine whether the patients found the coping items of the scale ‘Schizophrenia Coping Oral Health Profile (SCOOHP)’ understandable, awkward, disturbing or surprising. We also sought to establish if certain questions could be added or if certain individuals had problems answering this questionnaire.

## **2.2. Participants**

The 50 PWS and 6 HPs were recruited from the administrative database of the Chartreuse Hospital (Dijon, France) by telephone for outpatients or face-to-face for inpatients. PWS were eligible to participate if they were at least 18 years old, they had a diagnosis of schizophrenia (according to the International Classification of Diseases 10th Revision: ICD-10) (OMS, 2015), they provided informed consent to participate in the study, and French was their native language.

The exclusion criteria were a diagnosis other than schizophrenia, individuals who were unstable from a psychiatric perspective, serious physical illness, and intellectual disability.

## **3. RESULTS**

### **3.1. First Step**

The individual semi-directive interviews and the focus group (FG) interviews yielded 3245 pieces of oral information gathered (oral reports). An initial analysis of the thematic content provided 837 oral reports and 166 subthemes or dimensions. The transcript yielded no new codes, indicating data saturation.

We retained 277 oral reports according to the criteria: “information related to OHRQoL for PWS 65% (180 oral reports) were recounted by PWS and 10% (28 oral reports) were recounted by HPs during the semi-structured interview process. Only 9% (25 oral reports) were brought up by FG patients and 5% (14 oral reports) by FG professionals. We observed that 11% (30 oral reports) were common to patients and health professionals.

After exclusion of non informative items we retained 74 preselected oral reports relating to OHRQoL in PWS, 32 potential for coping strategies, and 19 potential reports for satisfaction with oral health care. Of these 32 potential oral reports for coping strategies, 9 were not retained (they were not informative enough in regard to coping strategies). At the end of this step, the first draft of the SCOOPHP scale included 23 preselected coping strategies.

### **3.2. Second Step**

A feasibility study was developed for the 23 preselected oral reports (items for questionnaire). The following table summarizes the SCOOPHP questionnaire (Table 1).

These items were classified as either positive or negative strategies relating to OHRQoL for the development of the SCOOPHP scale.

Positive coping strategies were associated with:

- well-being in everyday life, such as: “I engage with simple pleasures” (walk, drink coffee, listen to music, watch TV...) (item 1) or “when I move, I feel good” (item 5).
- good habits, such as: “I have a balanced diet” (item 8) or “Alcohol, tobacco, drugs have negative effects on oral health” (item 21)”.
- good oral health practices, such as: “I brush my teeth and/or my denture” (item 12) or “I brush my tongue” (item 14). Regarding the ability to manage regular dental visits, such as: “I manage to visit my dentist” (item 22).

**Table 1. SCOHP: Coping items**

1. I engage with simple pleasures (walk, drink coffee, listen to music, watch TV ...).
2. I leave my home
3. I eat for pleasure
4. I have a hobby (music, singing, drawing, movie, and ballads ...)
5. When I move, I feel good
6. I feel trapped by my relationship with sugar.
7. I have my own medicines to manage my health
8. I have a balanced diet
9. I snack between meals
10. When I am stressed or don't feel good, I eat less, or I eat more
11. I think about washing myself (shower, bath, cleaning)
12. I brush my teeth and/or my denture
13. I neglect my oral health
14. I brush my tongue
15. I take care of my mouth to have good breath
16. I take care of my mouth to have good dentition
17. I eat healthy food
18. I think about drinking water (normal or sparkling) when my mouth is dry
19. I can coordinate the movement of my hands in order to brush my teeth
20. I forget to brush my teeth
21. Alcohol, tobacco, drugs have negative effects on oral health
22. I manage to visit my dentist
23. I'm afraid to go to the dentist

Conversely, negative strategies linked to obstacles encountered on the care path, refer to:

- bad eating habits, such as: “I feel trapped by my relationship with sugar” (item 6).
- poor oral hygiene such as “I forget to brush my teeth” (item 20).

- the consumption of substances such as tobacco, alcohol and psychostimulants, such as: “I have my own medicines to manage my health” (item 7).
- obstacles related to access to dental care, such as: “I’m afraid to go to the dentist” (item 23).

The feasibility study also allowed us to evaluate the acceptability criteria, such as the time taken for completion, the amount of missing data, and acceptance and participation of patients were equally assessed. Nobody suggested adding new questions to the SCOOHP scale or found that the questions were hard to understand. The SCOOHP was a self-administered questionnaire with five possible answers for each item. These were matched with scores from 1 to 5, where “1” meant “strongly disagree” and “5” meant “strongly agree.” Scores from the positively worded questions were reversed to calculate the overall score so that the direction of all responses was the same (Siu-Paredes et al., 2018). PWS were all enthusiastic about using emoticons as a visual representative of their answer choices (Figure 2).

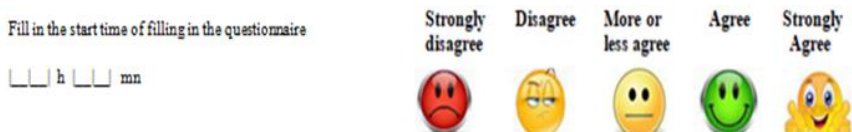


Figure 2. Modalities of answers of the SCOOHP.

## 4. DISCUSSION

The objective of this chapter was to explore coping strategies used by PWS in oral health. To capture the essential items of the coping concept in OHRqoL, our group explored comments made by patients and HPs in psychological and adaptive processes in OHRqoL (Rat et al., 2007). The ability of PWS to discuss their condition remains an issue of debate in the psychiatric community (Trauer & Mackinnon, 2001), which explains why most of the scales exploring perception of quality of life for PWS were



generated either from the literature or expert opinions (Trauer & Mackinnon, 2001).

We observed that the coping strategies were associated with both subjective (like self-esteem) and objective (negative symptoms) domains of recovery (Hofer et al., 2016). Poor diet and lifestyle behaviors (diet rich in sugar, use of psychoactive substances, and inadequate oral hygiene) all contribute to poor health and diminished sociality, thus impacting self-esteem and mental health (Arnaiz et al., 2011).

Application of cognitive-behavioral techniques have often been effective for changing health-related behaviors and improving oral hygiene. However, to have a complete understanding, it is necessary to have an instrument to quantify coping and cognitive changes in dental beliefs (Wolfe et al., 1996; Jacobs-Schoen, 1986; Stewart et al., 1991).

PWS widely expressed their specific oral health problems: “I have trouble biting firm meat because my teeth move when I chew”/“I know I must brush my teeth every day, but when I do not feel well, I cannot do it”/“I am afraid to visit the dentist.” HPs have a good knowledge of the difficulties faced by PWS in OHRQoL and are able to provide solutions: “We pay attention to whether they take showers every day when they are in hospital, but we do not pay attention to whether they brush their teeth!”.

The selection of items of the SCOOHP questionnaire was in accordance with Gronholm et al., (2016). We noted different types of coping when PWS have been under significant stress. PWS can avoid and deny the stressful situation, in which case, coping is centered on emotion in the SCOOHP, for example: “I feel trapped by my relationship with sugar” (item 6), “I’m afraid to go to the dentist” (item 23). PWS can also choose to actively address the stressful situation, in which case coping is centered on the problem, for example: “I have a balanced diet” (item 8) or “I manage to visit my dentist” (item 22).

As such, both positive and negative coping strategies were highlighted in our study. Negative coping was the strategy used by PWS to adjust to the disease but not to improve OHRQoL. A negative outlook is related to depression and is associated with poor oral health [47,48, 49].

In contrast, positive coping was the strategy used by patients to improve their OHRqoL on a daily basis. The ability to make life plans emerged in our research as a positive outlook.

Application of cognitive-behavioral techniques have often been effective for changing health-related behaviors and improving oral hygiene. Wolfe et al., (1996) developed the Dental Coping Beliefs Scale (DCBS). In developing this scale, three models of cognitive psychology were used for generating and selecting 44 items for the questionnaire, namely, locus of control, self-efficacy and the cognitive model of behavioral change. Examples of items on the DCBS include “I believe I can remove most of the plaque from my teeth on a daily basis,” “Only the dentist can prevent gum disease,” “I believe dentures are less trouble than taking care of my natural teeth,” and “I believe I can help prevent gum disease.” This study evaluated faulty or irrational beliefs about dental disease, higher values on the questionnaire indicate beliefs consistent with the role of the individual as an active participant in ensuring oral health and increased longevity of natural teeth.

The intensification of risk factors (stressors) or attenuation of protective factors (i.e., psychological potential) in the course of schizophrenia are reported to be a significant force behind healthy adjustment to life stresses (Nuechterlein & Dawson, 1984). In addition to this, the level of mental toughness of an individual, involving the ability to recover (adapt) from difficult experiences is important (Denis et al., 2018; American Psychological Association, 2018; Luthar, 2006). What we found in this study, is that the same factors that apply to health in general, also apply to oral health in particular.

However, to have a complete understanding of how oral health is impacted in PWS, it is necessary to have an instrument to qualify coping strategies and cognitive changes in dental beliefs (Wolfe et al., 1996; Jacobs-Schoen, 1986; Stewart et al., 1991). We believe we have developed such an instrument.

## **5. STRENGTHS AND LIMITATIONS**

A strong aspect of this study lies in its systematic use of knowledge provided by PWS through the individual semi-structured interviews, FG interviews and the WG. All of the steps of this study reduced the risk that measurement or observation biases could affect the quality of the questionnaire that was developed. The flexible and responsive interviewing style enabled participants to discuss aspects of their experience that were relevant to them, and minimized the risk of biasing the participants' responses.

A difficulty observed during these interviews was in regard to how to discriminate coherence of the discourse and the potential unreliability of information elicited from patients, even though the PWS included were stable from a psychiatric perspective. Psychiatric diagnoses may be especially vulnerable to instability over time (Baron-Epel et al., 2001). This is why a psychologist with experience in managing individuals suffering from mental health carried out the interviews in order to discriminate certain delirious remarks made by the patients.

## **CONCLUSION**

To our knowledge, this is the first study to develop a specific tool for evaluating coping strategies in oral health related quality of life in PWS (Siu-Paredes et al., 2018). The SCOHP was established by analyzing the content of semi structured individual and group interviews with PWS and HPs and was well-accepted and understood. However, this work needs to be confirmed with a larger number of subjects. For this, a study is currently being conducted in different centers in France (Reims, Tours, Dijon, Rennes) in order to statistically validate the final version of SCOHP questionnaire before making it available to care teams in early 2020.

ipsum dolor sit amet, consectetur adipiscing elit. Maecenas porttitor congue massa. Fusce posuere, magna sed pulvinar ultricies, purus lectus malesuada libero, sit amet commodo magna eros quis urna.

Nunc viverra imperdiet enim. Fusce est. Vivamus a tellus.

Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Proin pharetra nonummy pede. Mauris et orci.

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*Chapter 8*

**THERAPEUTIC EDUCATIONAL PROGRAM  
IN ORAL HEALTH FOR ORAL HEALTH  
EMPOWERMENT AND RECOVERY  
IN PATIENTS WITH SCHIZOPHRENIA**

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## ABSTRACT

*Background:* People with severe mental illness, such as persons with schizophrenia, have a life expectancy that is 20 years lower than that of the general population and an overrepresentation of cardiovascular diseases. Additionally, dental caries and periodontal measurement indexes are often twice as high as the levels found in the general population. The occurrence, importance, and gravity of somatic disorders in mental patients have long been underestimated. The gap in life expectancy between the general population and people with severe long-term mental illness is increasing at a continuous rate because the life expectancy of the general population is increasing. Poor oral health can also affect the quality of life, and oral health is inseparable from general health. Recently, a type of secular knowledge has tended to acquire rights; we increasingly recognize that individuals possess concrete, pragmatic knowledge that will allow them to adapt so-called scientific knowledge to the requirements of everyday life. In this model, patients appear to be at least as well placed as doctors to know their needs. Consideration of the experience of having the disease and the experiential knowledge acquired by the patient during his illness are at the center of approaches favoring the *empowerment* concept. At the collective and organizational levels, *empowerment* involves designing the health care system as a learning organization that promotes change. This process involves changes in attitudes, policies, training, and methods for providing care, including mental health. *Empowerment* becomes a fundamental concept in health promotion that aims to increase the power to act and the ability to steer one's own life and extends beyond the role of assistance with medical and social practices. According to the World Health Organization, the aim of therapeutic education is to help patients take care of themselves and to improve empowerment and recovery.

*Aims:* In this chapter, we present an educational approach that takes into account the patient's personal experience with oral health to build a therapeutic educational program in oral health using a multidisciplinary approach.

*Methods/Design:* In a qualitative study, we explored the representation of oral health for persons with schizophrenia.

*Discussion:* This chapter, for the first time, provides a complete description of the construction, use and evaluation of the effectiveness of a therapeutic educational program for oral health specifically designed for persons with schizophrenia with their active participation and suggests a method to assess this program with a high level of proof.

Finally, this approach to building therapeutic educational programs can be used to promote oral health in a global health approach and to develop appropriate strategies to encourage and facilitate financial support for healthcare, the multidisciplinary treatment of dental disorders,

prospective support for patients, and the development of training in oral or mental health for caregivers.

**Keywords:** dental health, oral health, schizophrenia, periodontal, dental hygiene, dental education

## **1. INTRODUCTION**

### **1.1. A Gap of Care between the General Population and People with Severe Mental Illness**

People with severe mental illness (SMI), such as persons with schizophrenia (PWSs), have a life expectancy that is 20 years lower than that of the general population and an overrepresentation of cardiovascular diseases (De Hert et al., 2011). Studies show that 19 to 57% of people with SMIs have at least one associated somatic pathology, including cardiovascular, gastrointestinal, respiratory, neoplastic, infectious, endocrine, and oral disorders. Approximately half of these comorbidities are undiagnosed (Hennekens et al., 2005; Capasso et al., 2008; Joukamaa et al., 2006; Chafetz et al., 2005). Dental caries and periodontal measurement indexes are often twice as high as the levels found in the general population (Wey et al., 2015; Arnaiz et al., 2011; McCreadie et al., 2004; Chu et al., 2012). The occurrence, importance, and gravity of somatic disorders in mental patients have long been underestimated. Furthermore, the gap in life expectancy between the general population and people with severe long-term mental illnesses is increasing at a continuous rate, because the life expectancy of the general population is increasing (Oakley et al., 2018). The life expectancy of PWS is not increasing at the same pace.

## **1.2. The Relationship between Oral and General Health for Persons with Schizophrenia**

Poor oral health can affect quality of life, and oral health is inseparable from general health. The relationship between oral and general health is complex, particularly for persons with SMIs, such as schizophrenia. Oral diseases affect the patient's quality of life through social and psychological impacts, such as deterioration of the smile's aesthetic, which leads to lower self-esteem and self-confidence (Wey et al., 2015; Chu et al., 2012). Furthermore, antipsychotics generally induce hyposalivation (xerostomia), which favors the progression of oral diseases, such as dental caries (Bardow et al., 2001). Conversely, clozapine and olanzapine can cause hypersalivation due to peripheral acetylcholinesterase inhibition, thereby causing discomfort in daily life (Matos Santana et al., 2017). First-generation antipsychotics may induce neurological side effects (e.g., dystonia and dyskinesia), especially shaking, which prevent effective tooth-brushing, increase the risk of oral diseases, and even impair the chewing and swallowing capacities (Nielson et al., 2011). Second-generation antipsychotics tend to induce metabolic side effects, such as obesity or diabetes, which are also chronic conditions affected by oral diseases (Vancampfort et al., 2015; Kaye et al., 2016). Indeed, oral diseases are chronic noncommunicable diseases that share common social, environmental and lifestyle determinants with other chronic medical conditions (Williams et al., 2008). Additionally, PWSs are patients who tend to neglect self-care (Pelletier et al., 2015) due to the negative symptoms of schizophrenia, such as a lack of concern for personal health and a lack of motivation. Negative symptoms impair the desire of a PWS to maintain good oral hygiene. In this case, they neglect their oral health or have a poor perception of their dental treatment needs. Therefore, routine dental care becomes a challenging task for the patient and their caregivers (Arnaiz, et al., 2011).

### 1.3. Empowerment and Oral Health

Recently, a certain type of secular knowledge has tended to acquire rights; we increasingly recognize that individuals possess concrete, pragmatic knowledge that will allow them to adapt so-called scientific knowledge to the requirements of everyday life. In this model, patients appear to be at least as well placed as doctors to know their needs. Consideration of the experience of having the disease and the experiential knowledge acquired by the patient during his illness is at the center of approaches favoring the *empowerment* concept (Augoyard & Renaud, 1998). At the collective and organizational levels, *empowerment* includes designing the health care system as a learning organization that promotes change. This process involves a change in attitudes, policies, training, and methods for providing care, including mental health. Therefore, *empowerment* becomes a fundamental concept in health promotion (OMS, 2006; Fisher, 1994) that aims to increase the power to act and the ability to steer one's own life that extends beyond the role in assistance with medical and social practices. According to the World Health Organization (WHO), the aim of therapeutic education is to help patients take care of themselves and to improve empowerment and recovery (Pelletier et al., 2014). In the case of chronic illnesses, the information about such conditions need not be limited to the nature or etiology of the underlying pathology, but rather about how to live 'in recovery' as satisfactorily and as independently a life as possible in spite of, and beyond the persistence or the severity of these conditions, and while continuing to strive to achieve full potential. Indeed, the recovery paradigm in mental health refers to living a satisfying, hopeful, and contributing life, even when a person may still be experiencing ongoing symptoms. Recovery journeys build on individual, family, cultural, and community strengths and can be supported by many types of services, supports, and treatments. Recovery principles, including hope, dignity, self-determination, and responsibility, can be adapted to the full range of mental health problems or illnesses, and to the realities of different life stages. Nowadays much effort is going into the transformation of mental health policies and systems to achieve recovery-oriented outcomes (Slade et al.,

2008; Slade et al., 2012). The experience of living in recovery without necessarily being cured from a mental health problem or illness is particularly conducive to sharing among peers who are, or who have been struggling with similar issues. They can share coping strategies with each other.

We hypothesize that a multidisciplinary therapeutic education program involving dentists, psychiatrists, nurses, doctors, psychologists, PWSs, caregivers and specialists in therapeutic education will promote clinical improvements in oral health.

In this chapter, we present a novel approach that considers the patients' personal experiences with oral health to build a therapeutic educational program in oral health (TEP-OH) using a cross-sectoral approach that improves empowerment and recovery in oral health.

## **2. METHODS**

### **2.1. Study Design**

This study is a prospective, multicentric study that has been conducted in mental healthcare facilities in France. This study combines a mixed methodology with a qualitative and quantitative component in three steps.

#### ***2.1.1. First Step***

In a qualitative study that started from field realities with their clinical variety and their effects on the psychosocial determinants of oral health risk factors, we identified a set of oral health risk factors to include in the TEP-OH.

We favored the inductive and abductive approach through focus groups (FGs) (Rabiee, 2004). This method has primacy over other qualitative methods in the context of this study because FGs allow in-depth inquiry of the phenomenon, ensure the confidentiality of the participants and enable prespecified topics to be explored while also permitting exploration of other ideas and thoughts that may spontaneously arise during the collective



conversation. These FGs should be conducted separately for patients, their caregivers, and mental health care professionals.

### **2.1.2. Second Step**

We tested the feasibility of the TEP-OH. We used a focus FG meeting to explore the evolution of oral health markers before and after the TEP-OH. First, we explained the TEP-OH to the PWSs and their caregivers. Second, we explored the experiences of the participants and the meaning of oral health for approximately 90 min using the following questions: (i) What do you think about your oral health? (ii) Why do you not take care of your oral health? (iii) Are you afraid of the dentist? (iv) Do you think there is a link between oral health and dental health? These open questions served to guide the interview and were selected from a qualitative study conducted to build the TEP-OH content with an expert group composed of health professionals, PWSs, and their caregivers (Locker & Leake, 1993). The post-it meeting technique was used to collect information, which was classified into three categories on a paper board as follows: positive, negative, and neutral experiences in oral health. According to researchers, positive assertions are assertions made by the PWS indicating ways to improve oral health. Negative assertions are assertions made by the PWS indicating a lack of proper oral hygiene. Neutral assertions involve other topics that emerge during the FG meeting. Group interactions encouraged respondents to provide insights that would not have surfaced during individual interviews. The participants were free to talk to other group members. The FG meeting covered personal data and insights that would have been less accessible without interactions in a group setting.

The audio recordings of all FGs were analyzed by a working group of researchers composed of a specialist in therapeutic education, a dentist, and a nurse specializing in mental health.

During this feasibility study, we tested the tools of the TEP-OH, especially the log book intended to help the patients in their daily lives with taking care of their own oral health and the movie used to demystify dental consultations.

### 2.1.3. Third Step

We assessed the effectiveness of the TEP-OH with a cluster randomized controlled trial. The 12 hospitals participating in the study were randomly allocated to four clusters (a cluster was composed of three hospitals) based on the availability of the benefits from the TEP-OH, and 230 PWS were recruited and randomly allocated with a 1:1 ratio to one of two conditions: a control group without an intervention versus the group benefitting from the TEP-OH. *Our primary endpoint* is the impact on periodontal disease. We chose a periodontal index for our primary outcome. Indeed, periodontal diseases are related to predictors of oral health. Secondary endpoints were: medical and dental conditions, behavior and socio-economic status (Locker & Leake, 1993; Taylor & Borgnakke, 2008). The literature highlights that up to 40% of PWS disorders have a mean CPI  $\geq 3$  (Kenkre & Spadigam, 2000; Velasco et al., 1997) compared with a mean CPI less than 10% in the general population [30,31]. Anticipating that the TEP-OH will lead to a mean 20% reduction in the patient CPI index and based on cluster variability (CV = 0.37) and the intraclass correlation coefficient (CCI = 0.01), we needed to recruit a total of 202 patients to highlight a statistically significant difference between the two groups with a type I error of 5% and type II error of 20%.

## 2.2. Participants

A potential participant must have been diagnosed with schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders-Fifth edition (DSM-5) (American Psychiatric Association, 2013) and be receiving in- or outpatient care in one of the hospitals taking part in the study. Potential participants over 18 years of age and could be of either sex. Schizophrenia is a severe mental disorder that is characterized by a set of different symptoms with varying intensities (American Psychiatric Association, 2013). Persons not stabilized from a psychiatric viewpoint were excluded. Persons were excluded if they did not perceive the significance of the study or were not motivated to take care of their oral health. We excluded people

with severe somatic disorders based on the aims of the study to avoid generating management problems for health care. Finally, we excluded edentulous persons, because the absence of teeth was a limitation of our TEP-OH for our end-point (periodontal disease) and temporarily excluded persons who did not update their social benefits to cover the cost of medical and dental care. In France, medical and dental care costs are covered by national health insurance and complementary health insurance or by universal health insurance (CMU) depending on the income level. For people with low incomes (below €7771 per year), the CMU is free (Cabaret, 2010). Indeed, because the aim of the program is to motivate participants to improve their oral health, the program will be counterproductive if a participant does not have the financial resources to access the health care system. PWS have less access to dental care because of its cost. This problem must be solved prior to inclusion in the study.

### **2.3. Recruitment Procedures**

In 1960, France opted for mental health care based on the definition of local catchment areas. The country was divided into sectors with approximately 70,000 inhabitants (Krueger & Casey, 2000). Each sector is run by a reference hospital and a multidisciplinary team that is intended to provide preventive, curative and rehabilitative care for all those within the catchment area who need it. Care is provided as close to home as possible. Patients only have ongoing contact with the psychiatric sector's outpatient unit for the community in which they live or are hospitalized depending on the severity of their mental disorders (Kovess et al., 1995). The hospitals that took part in the study covered 42 psychiatric sectors, including potentially 2,940,000 inhabitants and approximately 29,400 PWS available for recruitment in the study. The local catchment areas of the psychiatric hospitals were sufficiently distant from each other. The two closest hospitals were 60 km apart, and the farthest were 600 km apart.

To maximize recruitment, coinvestigators provided information on the study to the different hospitals. They informed potential participants about

the study via the internal communication system for caregivers of the institution (e-mail or newsletter) and distributed flyers informing PWSs about the study. Those who expressed interest were given details about the study and screened for their eligibility by the study team of coinvestigators. All participants (caregivers and PWSs) were aware that the study was related to an assessment of the effectiveness of a TEP-OH and the exact nature of the research project (i.e., the existence of the intervention and control groups and the comparison of outcomes between them). Upon debriefing at the end of the study, the PWSs who were in the no-TEP-OH group could benefit from the TEP-OH.

Participants could withdraw from the trial either at their own request or at the discretion of the investigator (acute psychiatric disorders). The participants were made aware that withdrawal would not affect their future care. All participants (PWSs and caregivers) were made aware (via the information sheet and consent forms) that the data collected to date could not be erased should they withdraw and might still be used in the final analysis.

### **3. RESULTS**

#### **3.1. First Step**

This stage revealed a set of oral health risk factors for inclusion in the TEP-OH, including the number and educational techniques to be used as well as the evaluation method for this program. The preliminary phase of this study consisted of the creation of the program content. An expert group comprising health professionals, stabilized PWSs, and PWS caregivers was created. A focus group (FG) led by a specialist in TE “Instance Régionale d’éducation et de promotion de la santé” (IREPS) explored the needs and expectations for oral health among PWSs (Krueger & Casey, 2000). The participants were able to defend their priorities, preferences, values or experiences. Generally, the FG method is used to collect opinions, beliefs and attitudes about a topic or issue and to encourage discussion of particular

problems (Britten, 1995; Steine et al., 2001). After three FGs targeted on oral health, the problems faced by PWSs were identified and summarized in the form of a questionnaire. These semi-structured questionnaires were presented with the same methodology to two distinct groups (composed of different people from the expert group): a group composed of only health professionals and a group of PWSs and patient caregivers. After the information collection step, the expert groups met again to validate the themes chosen for construction of the TEP-OH program and the educational tools necessary for its implementation.

The essential themes resulting from the content analysis of the exploratory corpus sought to:

### ***Promote the Action of Taking Care of One's Health***

One of the elements put forward by patients was difficulty in brushing their teeth every day, especially when the negative symptoms of the disease invaded them. "I know I have to brush my teeth, but when I'm not feeling good I do not have the courage to do it ...".

On the other hand, telling these individuals what they had to do was counterproductive: "I'm not a kid, I know how to brush my teeth...".

Patients were aware that having a beautiful smile was important and would like to achieve this goal: "To have the same white teeth ..." as those shown in advertisements, "She has a beautiful smile, she! ...".

The loss of self-esteem was clearly highlighted by patients: "I do not dare to smile ..." and was similar to the responses of professionals, "I lost my dental crown, I was so uncomfortable that I did not go to work ...".

The professionals evoked a lack of material means for the oral hygiene of PWSs, "Some do not even have a toothbrush ...", and a lack of attention to dental hygiene, "It's true we pay attention to when he takes a shower, but the teeth ...".

### ***Improve Accessibility to the Health System***

Fear of the dentist was frequently mentioned by the patients: "noises, smells give me anxiety ...". Additionally, fear was also mentioned by the professionals: "I always have apprehension about going to the dentist."

Similarly, the participants reported difficult relationships with dentists: “I was scared, and he did not take the time to listen to me ... I did not go back ...” and “As I had missed an appointment, he did not want to give me another ...”

Professionals agree with the possibility of supporting the patients and accompanying them to appointments at the dentist. “Last time, I accompanied Mr. X to the dentist and it went very well, it was at least 10 years since he had seen a dentist! However, it takes a long time to get an appointment. In the meantime, the patient will not want to go ... “.

The fear of mental illness was mentioned by the caregivers: “I see that the dentist is not comfortable with our patients ...”.

The cost of dental care was often put forward by the patients, “How much does a dental restoration cost?”, and by the professionals, “I would need a dental implant but it is too expensive...”.

### ***Promote a Global Health Approach***

Patient knowledge of oral health determinants is important. “Tobacco yellows teeth ...”, “I know that soft drinks and sweets make caries ...”, and “I have a metallic taste in my mouth with my treatments and food has no taste ...”.

The knowledge of the professionals was also important. “It's true, we do not take enough account of the side effects of antipsychotics (a somatic doctor)”.

Health professionals mentioned transverse and multidisciplinary possibilities for oral health management: “The dentist could help us with smoking cessation (a doctor) ...” and “We should talk about diet with the dietician... (a nurse)”.

Finally, the TEP-OH consisted of three workshops, each of which included an introductory session and a debriefing session that lasted 90 min and were conducted 2 weeks apart. The different themes of the workshops included mobilization of motivational approaches by improving self-esteem and well-being, which was called “Yes we can”. The second workshop was devoted to demystifying dental surgery and was called “Even more afraid”. The third theme was improvement of oral health by a transverse approach to

quality of life (cessation of smoking, controlling diabetes, management of a good diet, etc.) and was called “Take care of myself” (Peteuil et al., 2018).

### **3.2. Second Step (Steine & Laurem, 2001)**

PWS (7) and their caregivers were recruited following face-to-face interviews in a psychiatric outpatient center and included in the study. We confirmed that participation was voluntary, the participants could not be identified from the material presented, and no plausible harm to participating individuals could result from the study. Four females and three males participated in this study, with a mean age of  $29.4 \pm 5$  years. The PWSs produced 28 ideas regarding oral health perception before the TEP-OH and 37 after the TEP-OH. One caregiver from the psychiatric outpatient center of the study was present during the course of the study to ensure proper organization of the sessions (paper board, meeting room, etc.). The caregiver also contributed to the creation of a friendly atmosphere, which allowed good progress in the FG meetings. The caregiver suggested the organization of two sessions in the future to encourage more PWSs to use the log book. Before the TEP-OH, the most frequently cited positive elements were related to the methods and tools used for tooth brushing and the risks of dental diseases (pain, infections, etc.). We did not identify any negative assertions. All participants were motivated to improve their oral health. At this step, the determinants of oral health were not spontaneously addressed. After the TEP-OH, the elements related to the tooth brushing methodology were less cited (13 to 11) than at the inaugural session. Conversely, the determinants of oral health (tobacco and a poor diet) emerged. These results emphasize an evolution in oral health representation, which translates as an enlargement of general knowledge concerning the subject as indicated by the content and number of words produced. Other topics emerged (neutral), such as the cost of dental treatment and the different payment methods, which was an emergent problem for PWSs. The log book was of little use in noting the patients' efforts at improving their oral health. Generally, the patients

declared “I forgot to use it”. In contrast, the movie was a good resource to help the patients demystify the dental consultation process.

### **3.3. Third Step**

A multicenter, cluster, randomized controlled trial designed to assess the effectiveness of the TEP-OH for PWSs is in progress in France and soon in Montreal (Canada).

## **4. DISCUSSION**

This chapter provides for the first time a complete description of the construction, use and evaluation of the effectiveness of a TEP-OH specifically designed for PWSs with their active participation. The current study is innovative because it proposes investigating the impact of a strong partnership between PWSs and their caregivers in France to improve their oral health and promotes OHRQoL using a holistic health approach. We also developed an appropriate multidisciplinary treatment approach for dental disorders, provided prospective support for the patients, and established training in oral or mental health for the caregivers. Active patient participation is a key component of the study. Our results confirmed the benefit of conducting individual and group interviews with both patients and health professionals in regard to the richness of the obtained information. However, the major difficulties with the inclusion of PWSs in a long-term protocol study are that many of these individuals may be unable to cooperate due to their psychiatric illness or may be lost to follow-up.

### **4.1. Patient’s Perspective**

The aim of the study was to build a TEP-OH for and with PWSs. In this case, we explored the impact of oral health on the quality of daily life of



PWSs. Beyond the expressed needs, this research also aimed to observe the discordance between the perception of quality of life related to oral health (or satisfaction) and the thoughts expressed by health professionals. Dominance of participants not suffering from the disease is a risk when using FGs (Paille & Mucchielli, 2012). This aspect was framed by precise rules of operation for the groups. The answers and experiences of each individual were addressed without prejudice. Even a single minority idea was taken into account. The advantage of the FGs in this case was the positive aspects of interaction and group dynamics. The exchanges among participants fostered the emergence of knowledge and provided different perspectives, opinions and experiences. The PWSs were able to convey strong messages about their experiences with mental illness and their quality of life related to oral health and care. This approach provided an opportunity for caregivers to study some aspects of their practices. Thus, different perspectives on oral health have been clarified. This work was important, because Jachuck et al. (Jachuk et al., 1982) stressed that disagreement between doctors and patients was greater than 50%. Whereas doctors pay attention primarily to clinical signs and symptoms, patients are interested in how they feel and their ability to meet their needs and desires. In practice, clinicians, rather than the patients themselves, make decisions about the type of social skill training that the patients will receive. This reality indicates that a gap exists between what clinicians think is timely for patients and what the patients themselves think that they need (Attkisson et al., 1992). This study is specifically aimed at reducing this misunderstanding. However, the ability of patients to discuss their condition is still very much an issue of debate in the psychiatric community.

#### **4.2. Implementation of the TEP-OHP**

The feasibility study showed the possibility of enriching the TEP-OH by explaining the calculation of social security reimbursements (and other financial options) or the possibility of manipulating medical equipment to reduce fear (e.g., a syringe for anesthesia). Although the three steps of the

TEP-OH were planned, the order of the sessions could be adjusted according to the most essential representations of oral health that emerged during the introductory session. This flexibility in the session choices could favor interactivity between the workshops and their appropriation by the participants. In this spirit, we think that relying on the group to maintain the motivation of the participants to take care of themselves (i.e., limitation on nibbling, decreasing or stop smoking, or brushing teeth after a meal) is interesting. Thus, oral health determinants can be addressed in the first workshop (food, tobacco and brushing were spontaneously addressed during the introductory session), and participants and their caregivers and/or the caregivers could be encouraged to commit to helping others choose to implement oral health-promoting behavior (e.g., offering a favorable place for dental brushing within the institution or taking into account and taking care of the side effects of treatments on oral health by the caregivers).

### **4.3. Perspectives**

From the perspective of a partnership with their caregivers, the patient must be able to use his experiential knowledge to take part in decisions concerning himself and exercise a certain level of leadership, similar to the ability of professionals to bring their clinical expertise (Lindenmayer et al., 2009). However, the ability of a patient to interact with professionals depends in part on his/her level of experience with his/her illnesses (mental and oral). This is why, in recent years, recovery mentorship and peer support have formally emerged in the field of mental health. Peer support is a supportive (not curing) relationship and the recovery mentor provides emotional and social support to others who share a common experience. The commonality is to the struggle and emotional pain that can accompany the feeling of loss and/or hopelessness due to a mental health problem, rather than in relation to a specific symptom or illness. Recovery mentors focus on health and recovery rather than illness and disability.

Additionally, clinical signs of mental illness are more or less marked by the presence or absence of negative symptoms, such as abolition and

apragmatism, which are associated with poor oral health (Kilbourne et al., 2007). This ability also depends on the experience with clinical signs of oral health (e.g., dental pain, functional disorders, and side effects of antipsychotic treatments) and the level of development of his relational skills (ability to communicate his knowledge to the team) (Pelletier, 2014).

To the best of our knowledge, the involvement of PWSs with an expert status is novel in France within the framework of a recovery-oriented research process aimed at the construction of an educational program for the improvement of oral health. This research is part of the recommendations of the “*British Medical Journal*”, which invites promotion of patient partnerships (Richards et al., 2013) to improve the quality, safety, and sustainability of health systems. Peer support and recovery mentorship are indeed a form of patient/patient partnership. This work also joins that of Pelletier et al. (2015), which showed that patient partnership could lead to new avenues for the provision of care and services during management of the physical health of patients suffering from severe psychiatric disorders.

We found that this study upset the postures of caregivers of in-patient institutions (infantilization trends). Therefore, caregivers should also be part of this TEP-OH process with an approach that involves their beliefs and with representations that are not limited to accompanying the patients.

If this TEP-OH shows effectiveness, it can be used in future practice to promote oral health in a global health approach and to develop appropriate strategies to encourage and facilitate financial support for healthcare, multidisciplinary treatment of dental disorders, prospective support for patients, and development of training in oral or mental health for caregivers. This approach may promote the possibility of teaching by the patients themselves.

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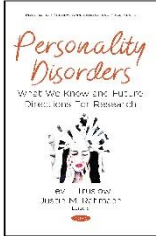
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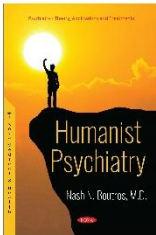
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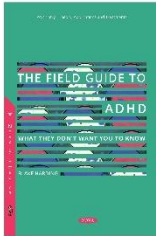
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