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Cognition and inflammation as transdiagnostic dimensions in psychiatry

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Cognition and inflammation as transdiagnostic dimensions in psychiatry

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Résumé

La cognition a longtemps été considérée une dimension essentielle de la dépression. De plus en plus, cette dimension est conçue comme transdiagnostique, tranchant à travers les catégories syndromiques de la conceptualisation classique des troubles psychiatriques. L'importance de cette dimension, non seulement pour l'expérience subjective, mais aussi pour le fonctionnement des patients est devenue une cible d'intérêt.

L'étude des déficits cognitifs dans la schizophrénie a précédé celle concernant ce type d'atteinte dans d'autres catégories diagnostiques en raison de leur proéminence dans cette pathologie. Néanmoins, des atteintes cognitives ont été identifiées dans toutes les phases du trouble bipolaire. Récemment, stimulé par l'émergence de traitements qui aspirent à démontrer un effet spécifique sur la cognition, l'intérêt dans les atteintes cognitives de la dépression a mobilisé l'attention des académiciens et cliniciens. Au-delà de ces pathologies, les atteintes cognitives se retrouvent dans divers troubles psychiatriques, sans oublier celles définies par ces atteintes, tels les troubles neurocognitifs majeures et mineurs et la déficience intéllectuelle. De plus, l'atteinte cognitive est une dimension symptomatique proéminente dans le Trouble Déficitaire de l'Attention avec ou sans Hyperactivité. Il est devenu clair que l'évaluation adéquate de la dimension cognitive des troubles psychiatriques est critique à la bonne pratique clinique.

Les causes des atteintes cognitives en psychiatrie n'ont pas été complètement déterminées. Bien qu'il soit possible que ces causes soient spécifiques à chaque pathologie, il est également concevable que des facteurs transdiagnostiques puissent contribuer aux déficits cognitifs de la psychiatrie. Parmi ces facteurs, l'inflammation pourrait être identifiée comme un déterminant de la cognition à travers les pathologies. Elle se retrouve tant dans la schizophrénie, et dans le trouble bipolaire que dans la dépression. Le traitement somatique de ces conditions est essentiellement pharmacologique, les antipsychotiques étant les agents principaux pour le traitement

de la schizophrénie et les antidépresseurs pour le traitement de la dépression. Les deux classes d'agents ont été associées à des effets anti-inflammatoires.

Certaines données suggèrent que l'inflammation est associée aux déficits cognitifs et il est plausible de considérer que ce lien est aussi présent comme dimension transdiagnostique dans le cas des troubles psychiatriques.

Cette thèse présente une revue extensive de la littérature démontrant que les troubles psychiatriques sont caractérisés par des déficits cognitifs qui contribuent à l'impact de ces conditions sur le fonctionnement. Cette revue réaffirme l'importance de l'évaluation clinique de la cognition. En réponse aux besoins de développer des outils cliniques pour évaluer la cognition, une traduction française du Screen for Cognitive Impairment in Psychiatry a été validée (article 1). Une fois développé, cet outil a été testé dans deux populations cliniques caractérisées par la dépression majeure et le déficit d'attention chez l'adulte, respectivement. Le lien entre le déficit cognitif et le fonctionnement se retrouve aussi dans les deux catégories diagnostiques. Le constat important de la discordance relative, plus établi en schizophrénie, entre l'auto-évaluation et l'évaluation objective de la cognition. Un survol de la littérature révèle l'ubiquité d'un état pro-inflammatoire dans les pathologies psychiatriques, et une revue de la littérature confirme un lien entre les déficits cognitifs et les marqueurs inflammatoires. Une méta-analyse confirme un effet anti-inflammatoire des antipsychotiques (article 5). Ces travaux ont contribué à la démonstration qu'il est possible de mesurer la cognition avec un outil rapide et bref dans le contexte clinique et à l'avancement des connaissances sur l'inflammation en schizophrénie. Des travaux supplémentaires sont nécessaires pour clarifier la contribution de l'inflammation au déficit cognitif des troubles psychiatriques.

Mots-clés : Cognition, Psychiatrie, Schizophrenie, Dépression, Trouble du Déficit de l'Attention avec ou sans Hyperactivité (TDAH), Inflammation, Transdiagnostique, Antidépresseur, Antipsychotique

Abstract

Cognition has long been considered a core symptomatic dimension of depression. Increasingly this dimension is seen as transdiagnostic, cutting across syndromic conceptualisations of psychiatric illness. The importance of this dimension, not only on subjective patient experience, but also on patient functioning has become a focus of interest.

Cognitive deficits are prominent in schizophrenia and research in this disorder has preceded that in other psychiatric disorders. Impairments have also been identified in all phases of bipolar disorder, as well as during the remitted state. Recently, interest in the cognitive impairments associated with depression have mobilised academic, and clinical attention as a result of treatments claiming to have a specific effect on this dimension. Clearly, cognitive impairment is a prominent symptomatic domain in attention deficit disorder. It has become a clinical imperative to appropriately assess the cognitive dimension of psychiatric disorders.

The causes of the cognitive deficits seen in psychiatric illness have not been completely elucidated. Although it is possible the causes vary and are unique in each condition, it is also conceivable that other transdiagnostic factors such as inflammation may contribute to the cognitive deficits of psychiatric disorders. Inflammatory processes have been identified in several psychiatric disorders; for example, a pro-inflammatory state is seen in schizophrenia, bipolar disorder and depression. The treatment of psychiatric disorders has also been associated with changes in inflammatory markers. The somatic treatment of these disorders is predominantly pharmacological with antipsychotics in the case of schizophrenia and with antidepressants, as well as with antipsychotics in the case of depression. Both antipsychotics and antidepressants are associated with an anti-inflammatory effect.

There is evidence to suggest that inflammation is associated with cognitive deficits and it is intriguing to consider that this may be the case in psychiatric disorders, particularly depression and that these transdiagnostic dimensions may be related.

This thesis presents an extensive review of the literature which demonstrates that psychiatric conditions are characterised by cognitive deficits which contribute to the impact of these conditions on functioning. This review confirms the importance of the clinical evaluation of cognition. As a response to the need to develop clinical tools to evaluate cognition, a French version of the Screen for Cognitive Impairment in Psychiatry was validated (Article 1). Once developed, this tool was tested in two clinical populations, characterised by major depression and adult attention deficit disorder respectively. The link between cognitive deficit and functioning is demonstrated in these two clinical populations. The important observation, established in schizophrenia, of a relative discordance between self and objective evaluation of cognition is also found in these diagnostic categories. An overview of the literature reveals the ubiquitous presence of a pro-inflammatory state in psychiatric conditions and confirms the link between cognitive deficits and inflammatory markers. A meta-analysis confirms the anti-inflammatory effect of anti-psychotics (Article 5). This work contributes to the demonstration that it is possible to measure cognition with a brief and rapid tool, as well as to the advancement of knowledge regarding inflammation in schizophrenia. Future research will need to focus on clarifying the contribution of inflammation to the cognitive deficits characteristic of psychiatric disorders.

Keywords : Cognition, Psychiatry, Schizophrenia, Depression, Attention Deficit Disorder with or without Hyperactivity (ADHD), Inflammation, Trandiagnostic, Antidepressant, Antipsychotic

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Liste des abréviations

ADD: Attention deficit disorder

ADHD : Attention deficit hyperactivity disorder

ASA: Aspirin

ASRS: Adult ADHD self-report scale

BAC-A: Brief assessment of cognition in affective disorders

BACS: Brief assessment of cognition in schizophrenia

BADD:: Brown ADD Scales

BCA: Brief cognitive assessment

B-CATS : The Brief Cognitive Assessment Tool for Schizophrenia

BC-CCI: British Columbia cognitive complaints inventory

BDI:Beck Depression inventory

BBB: Blood brain barrier

BD : Bipolar disorder

BDI: Bipolar disorder type I

BDII: Bipolar disorder type II

BDNF: Brain derived neurotrophic factor

BMI: Body mass index

BNA: Brief neurocognitive assessment

BPD : Borderline personality disorder

BPRS: Brief Psychiatric Rating Scale

CAI: Cognitive assessment interview

CAARS: Conners Adult ADHD Rating Scale

CANTAB: Cambridge Neuropsychological Test Automated Battery

CC: Cehmokine

CCL: Chemokine ligand

CGI: Clinical global impression

CGI-CogS: Clinical global impression of cognition in schizophrenia

CPT: Continuous performance test

COX-2 : Cyclooxygenase-2

CPFQ: Cognitive and physical functioning questionnaire

CPT: Continuous performance task

CRP: C- reactive protein

CTL: Control

CVLT: California verbal learning test

DALY : Disability adjusted life year

DF: Design fluency

DH: Dopamine hydroxylase

D-KEFS: The Delis–Kaplan Executive Function System

DSST: Digit symbol substitution test

EDEC: Échelle d'auto-évaluation cognitive

EF : Executive function

FCAT: Financial Competency Assessment Tool

FEDN: First episode drug naive

FTT: Finger-Tapping Test

GAF: Global assessment of functioning

GM-CSF : granulocyte macrophage- colony stimulating factor

HAMD: Hamilton depression rating scale

3-HAA: 3-hydroxyanthrallic acid

3-HK: 3-hydroxykynurenine

HAMD: Hamilton depression rating scale

HC: Healthy control

3-HK: 3-hydroxykynurenine

5-HT:5-hydroxytryptophan

HIV: Human immunodeficiency virus

IDO: indoleamine 2,3 dioxygenase

IFN-γ: Interferon- γ

IGF: Insulin growth factor

IL-1: Interleukin 1

IL-1RA-I : Interleukin 1 receptor antagonist

IL-1RII : Interleukin-1 receptor type II

IL-6 :Interleukin 6

IL-8 : Interleukin 8

IRB: Institutional review board

KynA: Kynurenic acid

MATRICS : The Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCCB : MATRICS Consensus Cognitive Battery

MCP:Monocyte chemoattractant protein

MD, MDD : Major depressive disorder

MMSE: Mini Mental State Examination

MoCA: Montreal cognitive assessment

mRNA: Messenger Ribonucleic Acid

MTXR: Matrix Reasoning NAC: N-acetyl cysteine

NAC: nAcetyl cysteine

NKC: Natural killer cells

NFKB-Nuclear factor-κB

NLR: Neutrophil lymphocyte ratio

OPG: Osteoprotegerin

PANSS: Positive and negative syndrome scale

PASAT: Paced Auditory Serial Addition Test

PDQ: Perceived deficit questionnaire

PH: phenylalanine hydroxylase

PPS: Psychomotor and processing speed

PS: Psychomotor speed

QA/Quin: Quinolinic acid

RBANS: Repeatable battery for the assessment of neuropsychological status

RNA: Ribonucleic acid

ROCD: Rey Osterrieth Complex Design

SA: Schizoaffective disorder

SAQ: Self-administered questionnaire

sCD40L: CD40 Ligand

SCF: Stem cell factor

SCIP : Screen for Cognitive Impairment in Psychiatry

SCIP-F: SCIP-French

SCIP-S: SCIP-Spanish

SCoRS: Schizophrenia cognition rating scale

SCZ: Schizophrenia

SDS: Sheehan disability scale

sIL-2R: Soluble interleukin 2 receptor

SNRI: serotonin norepinephrine reuptake inhibitor

SSRI: Selective serotonin inhibitors

SSTICS: Subjective scale to investigate cognition in schizophrenia

ST: Stroop Test

TD: Tardive dyskinesia

TGF: Transforming growth factor

TH: Tyrosine hydroxylase

sTNF-R1: soluble tumour necrosis factor receptor 1

sTNF-R2: soluble tumour necrosis factor receptor 2

TLR: Toll-like receptors

TLT: Tower of London task

TMT: Trail making test, TMTA-Trail making test A, TMTB- trail making test

TNF−∝ : tumour necrosis factor-∝

TPH:tryptophan hydroxylase

TRD: Treatment resistant depression

TYR: tyrosine

UPSA-B : University of California at San Diego Performance-based Skills Assessment-Brief

US/USA : United States of America

USD: United States Dollars

VF: Verbal fluency

VLT: Verbal learning test

VLTd: Verbal learning test delayed

VLTi: Verbal learning test immediate

VMT: Visuomotor tracking

V&SM: visual and spatial memory

VR: Visual reproduction

WAIS: Wechsler Adult Intelligence Scale

WCST: Wisconsin card sorting test

WHO: World Health Organisation

WHO-QLBFWorld Health Organisation Quality of Life-Brief Form

vWF: Von Willebrand factor

WM: Working memory

WMT: Working memory test

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Introduction

Psychiatric disorders affect approximately a third of the population ((Kessler et al., 2005b). These conditions tend to have a chronic course which contributes to an accrual of prevalence and burden of disease (Patel et al., 2015). A recent review of the literature concluded that, compared to the general population, mental disorders carry a relative risk of mortality of 2.22 (Walker et al., 2015). Mental disorders were associated with a median of 10 years of potential life lost (Walker et al., 2015).

Although the excess mortality associated with mental illnesses such as MDD, bipolar disorder and schizophrenia (Charlson et al., 2015) is undeniable, the burden of these disorders derives mainly from their impact on suffering, functioning and quality of life. While the health loss from cancer, cardiovascular, and circulatory diseases is declining, that attributable to mental illness, as well as visual and hearing loss, diabetes, musculoskeletal and neurological disorders is increasing (GBD 2015). In 2010 mental, neurological and substance use disorders accounted for 10.4% of disability-adjusted life years (DALYs) (Whiteford et al., 2015). Arguing that previous studies underestimate the impact of mental illness, Vigo and colleagues (Vigo et al., 2016) estimate that mental illness accounts for 32.4% of DALYs, placing the burden associated with these conditions on par with that incurred by cardiovascular and circulatory diseases.

The lifetime prevalence of schizophrenia in the general population has recently been estimated at about 0.48% (Simeone et al., 2015). Schizophrenia figures among the 25 leading causes of disability worldwide and the economic burden associated with it ranged from 0.02 to 1.65% of gross domestic product (Chong et al., 2016).

Classic bipolar disorder, type I, has a lifetime prevalence of 1.06%, and type II has a lifetime prevalence of 1.57% (Clemente et al., 2015). Bipolar spectrum disorder may affect 4.4% of the population. It is associated with a disproportionate economic burden compared to other mental illnesses and is the 12th leading cause of disability worldwide (Miller et al., 2014).

A study of 18 countries found the average lifetime prevalence of MDD to vary from 1.5 to 19% (Kessler and Bromet, 2013). The economic burden of individuals with major depressive disorders was estimated at 210.5 billion USD, 50% of the costs of MDD are linked to the workplace (Greenberg et al., 2015).

Patients in general practice indicate that acute and chronic mental disorders have the greatest impact on impairment, followed by musculoskeletal disorders (Linden et al., 2015). The impact of mental illness is varied. Frequent users to emergency are frequently sufferers of mental illness. Canadian studies report that 24-60% of frequent emergency room users presented for a mental health problem (van Tiel et al., 2015).

For example, an analysis of the National comorbidity data showed that mental disorders account for 5.8 to 11% of high school and 3.2-11.4% of college non-completion (Mojtabai et al., 2015a) . Mental illness is associated with a lower rate of employment on follow-up (Davidson et al., 2016; Mojtabai et al., 2015b) with a resulting estimate of 1.7-3.2 million adults in the US (Mojtabai et al., 2015b) being unemployed. Employment in schizophrenia ranges from 4-50.4% (Bouwmans et al., 2015). Similarly 40-60% of individuals with bipolar disorder are employed (Elinson et al., 2007; Marwaha et al., 2013), although a decline in occupational status may be observed. Long-term unemployment is associated with major depression (Hamalainen et al., 2005). Depressive symptoms are associated with a 1.9 rate of unemployment (Whooley et al., 2002) and conversely depression carries a 1.58 risk of unemployment (Jefferis et al., 2011).

The decline in functioning can be attributed to many causes ; however, the deficits in cognitive function found in most mental illnesses have been associated with difficulties in function. This thesis will elaborate on the incidence and implication of cognitive deficits as a transdiagnostic dimension in psychiatric disorders. In addition, the role of inflammation and cognition as parallel transdiagnostic psychiatric dimensions, with the former as a possible contributor to the latter, will be explored.

Chapter 1 : Cognition in psychiatric disorders

Chapter 1.1 : Introduction

Cognition refers to mental functions that involve the processing of perceptual input, attention, memory, regulation of behaviour and emotion, and problem solving. Cognitive deficits have been identified in most psychiatric disorders (Etkin et al., 2013). Core executive functions (EFs) are inhibition, (response inhibition, self-control, resisting temptations and resisting acting impulsively) and interference control (selective attention and cognitive inhibition)], working memory, and cognitive flexibility (including creative thinking, seeing anything from different perspectives, and adapting to changed circumstances)(Diamond, 2013). Based on data from improved imaging technology, many cognitive functions once assumed to be located in specific areas of the brain are now thought to result from deficits in three key networks (the central executive network, the salience network, and the default mode network) and their interactions with each other and other brain areas (Culpepper, 2015b). The neuroanatomical interconnectivity mirrors the complexity of cognition in general and as a clinical dimension of psychiatric pathologies.

The role of cognition and cognitive deficits in schizophrenia and psychotic disorders has received the lion's share of research attention. More recently the cognitive deficits of mood disorders have become a focus of attention. Yet other disorders are also characterised by significant cognitive dysfunction. Attention deficit disorder is defined in part by cognitive deficit and deficits have been described in anxiety disorders, and personality disorders. Assessment of cognition in Swedish conscripts showed cognitive deficits to be associated not only with psychosis but also with depression, personality disorders, alcoholism and drug dependence (David et al., 2008).

Cognitive dysfunction is of more than academic interest. The potential functional impact of cognitive deficits is increasingly appreciated but remains insufficiently

explored for most if not all disorders (Royall et al., 2007). Although the link between specific cognitive deficits and function is modest, general cognitive measures are strongly correlated to function (Royall et al., 2007). Consequently this dimension is an important consideration in the development of treatment plans and personalized rehabilitation programs.

Chapter 1.2 : Cognition in schizophrenia

Cognitive impairment is a core feature of schizophrenia (Aquila and Citrome, 2015; Mesholam-Gately et al., 2009; Nuechterlein et al., 2014) that persists over the course of the illness (Keefe, 2014; Lysaker et al., 2015). In addition, the cognitive deficits characteristic of the illness present a barrier to the recovery of those affected (Aquila and Citrome, 2015).

Cognitive deficits have been identified before the onset of the illness (Harvey, 2014); however their longitudinal course remains unclear (Bozikas and Andreou, 2011; Keefe, 2014; Nuechterlein et al., 2014). A recent review identifies two distinct periods of deterioration; the first before the onset of the illness, and the second at 65 years of age (Harvey, 2014). The presence of both deficits and developmental lags before the onset of the full schizophrenic syndrome is well established (Keefe, 2014).

Impairment in the cognitive functioning of schizophrenia has been identified in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Green MF 2006). In their review, Heinrichs and Zakzanis found moderate to large effect sizes in a broad range of domains : decrements in selective verbal memory, nonverbal memory, bilateral and unilateral motor performance, visual and auditory attention, general intelligence, spatial ability, executive function, language, and interhemispheric tactile-transfer test performance, as well as global cognition (Heinrichs and Zakzanis, 1998). A more recent review confirmed deficits in memory and learning, working memory, executive functions, attention, processing speed, and a generalised global deficit (Reichenberg, 2010). Both verbal and nonverbal memory performance was impaired relative to age-matched controls (Reichenberg, 2010; Tracy et al., 2001). The processes most severely impaired involved learning and recall, with important difficulties in memory storage and recognition memory. Encoding was deficient on most measures, while difficulties in retrieval seemed task specific. It is possible that the higher order impairments seen in schizophrenia may be a consequence of

underlying deficits in basic skills (Savla et al., 2011). An analysis of the cumulative results of cognitive testing in schizophrenia using the Cambridge Neuropsychological Test Automated Battery (CANTAB) determined that the most consistent deficit is attentional set-shifting (Levaux et al., 2007).

The cognitive deficits of schizophrenia are relatively stable with the exception of verbal memory deficits which seem to deteriorate over time (Bozikas and Andreou, 2011). A recent review focusing on first episode subjects found similar results (Mesholam-Gately et al., 2009). These deficits are generally more severe than those in people affected by schizoaffective disorder or affective psychosis (Bora et al., 2009). A study conducted by Reichenberg and colleagues confirmed this finding, but also found normal neuropsychological performance in a significant number (16-45%) of individuals with schizophrenia (Reichenberg et al., 2009) depending on the parameter evaluated. Individuals with poorer clinical outcomes showed the largest deficits (Lepage et al., 2014). Loughland and colleagues found that patients recruited in a health service were impaired across a greater number of domains than those recruited from a schizophrenia register (Loughland et al., 2007). Self-perceived cognitive deficits predicted increased Brief Psychiatric Rating Scale global scores at follow-up . Furthermore, memory dysfunction was the strongest predictor of clinical deterioration.

Studies of functioning in schizophrenia reveal deficits in all aspects (Lepage et al., 2014). These impairments are correlated with cognition (Green, 2006). For example, deficits in EF are related to the performance of activities of daily living such as planning a menu, shopping tasks, and cooking tasks (Semkovska et al., 2004). Decrements on the digit span test and the Controlled Oral Word Association Test are correlated with reduction of scores on the social domain of the World Health Organisation Quality of Life-Brief Form (Alptekin et al., 2005).

In a study using the Financial Competency Assessment Tool (FCAT) patients with schizophrenia showed important difficulties which were correlated with neuropsychological performance (Niekawa et al., 2007). In another investigation, functional capacity was significantly associated with observed ecological

functioning but not with self-reported functioning (Ho et al., 2013). However, not all observations are consistent. A longitudinal study of symptom status, cognitive functioning, and community outcome found these to be stable in treated individuals with schizophrenia. This study did not find cognition to contribute disproportionately to functional outcomes relative to symptoms (Miles et al., 2014). Although cognition is clearly a significant determinant of functioning in schizophrenia, other factors play a prominent role (Lin et al., 2013) which may confound statistical significance. For example, the severity of baseline cognitive deficits as well as the phase of illness, may affect the impact of cognition on function in this population (Rajji et al., 2014). Although the number of hospitalisations seems associated with cognitive and functional deficits, it is likely that both are attributable to common underlying factors rather than exerting a specific effect (Harvey et al., 2013). For example, in one study symptoms assessed by the positive and negative syndrome scale (PANSS) explained 16% of variance in a quality of life scale score, while cognition explained only an additional 4% of the variance (Perlick et al., 2008). Another study identified clinical symptoms as a mediator between cognitive function (including all 7 domains of MATRICS) and functional outcome in schizophrenia (Lin et al., 2013). Despite the clear importance of other clinical dimensions, the cumulative evidence confirms that the cognitive impairment of schizophrenia has a significant impact on both clinical course and functional outcome (Moritz et al., 2000).

Despite early hopes that a new generation of antipsychotics would result in improved cognitive function compared to earlier treatments, there has been little evidence of differences in the effect on cognition of different drugs, or different generations of drugs (Ahmed and Bhat, 2014; Keefe, 2014; Keefe et al., 2014). Cognitive remediation is a popular non-pharmacological approach aimed at improving the cognitive deficits of schizophrenia. Cognitive remediation is associated with increased activation in various brain regions during cognitive tasks (Isaac and Januel, 2016; Thorsen et al., 2014). Despite some limitations (Bryce et al., 2016), meta-analyses and reviews concur that small to modest improvements in cognition are

associated with cognitive remediation (Barlati et al., 2013; Lin et al., 2014) particularly when applied early in the course of illness (Lewandowski, 2016).

Chapter 1.3 : Cognition in bipolar disorder

As in schizophrenia, there is increased recognition that cognitive impairment is a central feature of bipolar disorder (Green, 2006). Harvey and colleagues suggest that the lessons learned through the study of cognition in schizophrenia may guide research and clinical approaches in bipolar disorder (Harvey et al., 2010) both as regards its evaluation, its functional impact and the effects of treatment on this important dimension.

Individuals with bipolar disorder are not cognitively impaired during the premorbid phase; however, impairment is evident as early as the first episode and thereafter (Martino et al., 2015). Deficits are seen in all phases including in the euthymic phase (Balanza-Martinez et al., 2010; Latalova et al., 2011; Martino et al., 2015). In general, bipolar patients are less cognitively impaired than those with schizophrenia (Pradhan et al., 2008). Further, the proportion of individuals without cognitive impairment is higher in bipolar illness than in schizophrenia : 42-64% as opposed to 16-24% respectively (Reichenberg et al., 2009).

The cognitive impairments of BD are most evident in attention, verbal memory, and executive function (Balanza-Martinez et al., 2010; Latalova et al., 2011; Martino et al., 2015). Current findings of studies investigating executive functions, psychomotor speed and memory functions underline the heterogeneous performance found in bipolar patients (Jamrozinski, 2010). A higher variability of performance is seen in individuals with BD compared to controls (Budde and Schulze, 2014). However, bipolar patients do not seem to suffer a greater decline in cognitive function with age relative to controls (Budde and Schulze, 2014; Cardoso et al., 2015).

Numerous factors can affect the manifestation of cognitive deficits in bipolar disorder. They include age of onset, response to treatment, familial risk factors, and clinical features (Jamrozinski, 2010; Latalova et al., 2011). Other factors affecting cognition in bipolar disorder such as the phase of illness, and seasonality (Latalova et al., 2011), as well as the number of mood episodes, illness duration and

hospitalisations (Cardoso et al., 2015). The negative impact of pharmacological treatments on cognition may also contribute to the cognitive deficits seen in bipolar disorder (Balanza-Martinez et al., 2010; Jamrozinski, 2010; Latalova et al., 2011).

Cognitive impairment and functional impairment seem linked in bipolar disorder as they are in schizophrenia (Balanza-Martinez et al., 2010; Yatham et al., 2010). Deficits in function often remain beyond remission of the acute phase of BD (Wingo et al., 2009). Notwithstanding the prominent role of affective symptoms in determining functional recovery (Andreou and Bozikas, 2013), persistent cognitive symptoms are undoubtedly among the factors which contribute to poor psychosocial functioning (Andreou and Bozikas, 2013; Baune et al., 2013; Green, 2006). As yet, no consistent relationship between specific domains of cognition and psychosocial function is evident (Baune et al., 2013). In one study, Mur and colleagues found psychosocial functioning to be correlated to processing speed, as well as to clinical severity of symptoms and residual depressive symptoms (Mur et al., 2009). Furthermore, employment status was correlated with visual memory and chronicity of illness (Mur et al., 2009). In a small study, attention and EF were significant determinants of measures of psychosocial functioning(Martino et al., 2009). In another investigation of euthymic bipolar patients, Altshuller and colleagues found that functional disability was restricted to a subgroup of patients with cognitive impairment (Altshuler et al., 2008) while Wingo and colleagues found that cognitive impairment in BD is invariably associated with functional impairment in non-euthymic patients, and generally so in euthymic patients (Wingo et al., 2009). Treatments that target cognitive deficits may therefore have potential for improving long-term vocational functioning in bipolar illness (Bearden et al., 2011). Thus, in bipolar illness, as in schizophrenia, impairment in cognition is clinically pertinent given its importance in determining psychosocial functioning. Unfortunately, there are no current pharmacotherapies that substantially improve cognition in bipolar disorder (Goldberg and Chengappa, 2009), beyond that which would be anticipated through the remission of the manic or depressive symptomatology.

Chapter 1.4 : Cognition in depression

Although cognitive dysfunction is one of the criteria used to diagnose major depressive disorder, cognitive function has not been as extensively studied in depression as it has in schizophrenia or even bipolar disorder. This domain has garnered increased attention recently (Culpepper, 2015b; Papakostas, 2014) as its contribution to psychosocial functioning has been recognised.

Cognitive dysfunction in MDD falls into two main categories : cognitive biases and cognitive deficits (Murrough et al., 2011). In depression, cognitive bias, also called 'hot cognition', involves a distortion of information processing and increased salience of negative stimuli. Cognitive deficits, also called 'cold cognition', comprise impairments in both basic and complex cognitive processes such as attention, short-term memory and executive functioning (Murrough et al., 2011). Although both types of deficit may be interrelated, this brief review will focus on cognitive deficits. Both patient reports and objective measures highlight the prevalence of cognitive deficits in depression (Culpepper, 2015b; Papakostas, 2014; Papakostas and Culpepper, 2015; Porter et al., 2007). Nevertheless, the data is inconsistent (McClintock et al., 2010). Reichenberg and colleagues found that 42 to 77% of patients with depression do not manifest neuropsychological deficits (Reichenberg et al., 2009). Findings of cognitive impairment are more consistent in the elderly affected by MDD (Porter et al., 2007). The variability of cognitive performance observed in MDD may be a result of several factors such as the diversity of instruments used for assessing cognition (Bortolato et al., 2014), the variable levels of depression severity in the studies (Murrough et al., 2011) as well as small sample sizes, and confounding clinical factors such as illness characteristics (Porter et al., 2007) and effects of treatment.

Several reviews have examined the prevalence of cognitive impairment in MDD. Hasselbach and colleagues found that, in nine of eleven studies, patients with MDD performed less well than controls on at least one neuropsychological test

(Hasselbalch et al., 2011). A recent review of EF in major depression identified 28 pertinent articles (Alves et al., 2014). Most of these demonstrated decrements in EF but did not control for confounding factors. Baune and colleagues conducted a similar review restricted to MDD in adolescence and early adulthood (Baune and Renger, 2014) and also identified significant deficits in executive function (EF), working memory (WM), psychomotor and processing speed (PPS), verbal fluency (VF) and verbal and spatial memory (V&SM). While WM was impaired in 3 out of 4 studies, EF was only impaired in 3 of 7 studies (Baune and Renger, 2014). Papakostas confirmed the prevalence of cognitive dysfunction as well as its association with earlier onset of illness and longer duration of episodes (Papakostas, 2014). Executive dysfunction may also vary with the severity of depression (DeBattista, 2005). In addition, a subset of geriatric depression is also characterised by prominent deficits in EF (DeBattista, 2005). In fact, in Bora's reviews deficits were modest after the exclusion of late-onset cases of MDD (Bora et al., 2013). Nevertheless, young adult individuals with MDD performed less well in comparison to controls on tests of EF, although verbal memory was unimpaired (Smith et al., 2006). In an evaluation of the contribution of effort to cognitive performance in MDD, Den Hartog and colleagues found that, contrary to expectation, individuals with MDD were not impaired on effortful tasks but manifested reduced speed of information processing in automatic subtasks (Den Hartog et al., 2003).

After recovery from depression patients continue to display significant deficits even after controlling for the persistence of subclinical depressive symptoms; these deficits are correlated with the number of previous episodes of depression (Bhardwaj et al., 2010). Mild to moderate MDD in young outpatients is characterised by intact cognitive function; nevertheless symptom severity and age of onset of illness were correlated with poorer performance on some tests (Grant et al., 2001). In yet another investigation of young patients with MDD, cognitive function was globally intact despite 'latencies' on the Tower of London task, and on attentional set shifting task (Purcell et al., 1997). Patients who manifest impairment were more likely to have required inpatient hospitalisation (Purcell et al., 1997).

While in some patients cognitive symptoms improve as depression improves, a substantial portion of patients continue to show impairment even while euthymic (Bora et al., 2013; Papakostas and Culpepper, 2015). The subjective complaints of individuals suffering from MDD concord with the persistence of cognitive deficits in the remitted state (Bortolato et al., 2014; Fava, 2003). Decrements in EF and attention have been identified during remission from MDD (Bortolato et al., 2014). It is likely that these impairments may contribute to poor psychosocial functioning (Bortolato et al., 2014; Papakostas, 2014). Evidence indicates that cognitive dysfunction in MDD is a critical mediator of workplace disability (McIntyre and Lee, 2016). The presence of executive dysfunction in depression is associated with vocational disability and possibly poorer treatment response (DeBattista, 2005). Deficits in cognition, explain functional outcome 6 months following hospitalisation for a major depressive episode (Jaeger et al., 2006). In a Korean sample of individuals with moderate to severe MDD, greater functional disability and impairment in daily activities were associated with both greater severity of depression and greater perceived cognitive dysfunction. Even after controlling for severity of depression, patients with more severe perceived cognitive dysfunction reported deficits in work productivity (Kim et al., 2016).

While few studies have examined the treatment of executive dysfunction in depression, preliminary results suggest that both pharmacologic interventions and psychosocial interventions such as problem solving therapy may be effective (DeBattista, 2005; Lam et al., 2014; Mandelli et al., 2006). Agents used for the treatment of MDD may have differential therapeutic effects on the cognitive symptoms of depression (Fava, 2003; Orzechowska et al., 2015) and future research should clarify the differences and explore new alternatives.

In view of the importance of cognition to clinical symptoms, prognosis, and psychosocial functioning, it is recommended that clinicians assess and monitor cognitive symptoms in patients with MDD (Bortolato et al., 2014; Culpepper, 2015a; McIntyre and Lee, 2016). It is likely that both subjective (self-reported) and objective measures of cognition measure differing and complementary aspects of cognition

and that the evaluation of both is necessary to the clinical management of major depression (McIntyre and Lee, 2016).

A survey conducted by El Hammi and colleagues found that most psychiatrists evaluated cognition through clinical interviews (83% in France and approximately 60% in the USA, Germany, Australia and Hong Kong); others used an assessment tool or a combination of a tool and interview. In many cases, the tool chosen was not appropriate for the evaluation of cognition (El Hammi et al., 2014). Consequently, the identification of both a standardised battery of cognitive tests and a common instrument that can be used by clinicians in routine clinical practice is clearly important for the optimal evaluation and management of patients.

Chapter 1.6 : Cognition in other psychiatric disorders

Deficits in cognition have been observed in numerous psychiatric disorders other than schizophrenia, bipolar disorder, and MDD. The following is a brief and non-exhaustive review of cognitive impairment in other psychiatric disorders.

Attention-deficit hyperactivity disorder (ADHD) is a behaviourally defined diagnosis (Koziol and Stevens, 2012; Seidman, 2006) whose symptoms are similar to neuropsychological disorders of executive dysfunction (Seidman, 2006). As a group, individuals with ADHD manifest EF deficits (Seidman, 2006). Working memory (WM) (Alderson et al., 2013) and abnormal Stroop interference are consistently impaired in individuals with ADHD (Lansbergen et al., 2007). They show deficits in attention, auditory-verbal list learning, and in information processing speed (Woods et al., 2002). Furthermore, individuals with ADHD make more perseverative and non-perseverative errors (Rapport et al., 2001).

Nevertheless, not all individuals with ADHD have EF deficits (Rapport et al., 2001; Seidman, 2006) and it is likely that ADHD, like other psychiatric pathologies, is a heterogenous disorder both as regards its cause and its clinical presentation. Thus we can also observe impairments in ADHD in domains other than classically defined cognition such as deficits in brain reward systems that are relatively independent of EF impairments (Seidman, 2006). Although as a group, individuals with ADHD show impairment compared to controls, there is no reliable manner of identifying individuals with ADHD (Lange et al., 2014). A comparison of adults with either depression or ADHD showed that elements of the California Verbal Learning Test (CVLT), the Paced Auditory Serial Addition Test, and the Stroop Test discriminated between the groups. Although most of the ADHD patients were correctly classified, there were more frequent errors of classification in the MDD patients (Katz et al., 1998) demonstrating that neurocognitive testing cannot be used to distinguish between diagnostic groups. This may be attributable to the inability of specific neuropsychiatric tests to identify the functional deficits associated with specific cerebral areas (Wasserman and Wasserman, 2012)) possibly as a result of the interconnectivity of these areas which co-operate to produce a specific function.

Neurocognitive testing may, however, assist in assessing an individual's profiles and aid in developing personalized treatment plans.

Cognitive dysfunction is not commonly considered to be a characteristic of anxiety disorders. In a recent review, Alves and colleagues document decrements in memory tasks in panic disorder (Alves et al., 2013). Deficits in verbal memory, visual scanning, and visuoconstructional ability are found in social anxiety disorder (O'Toole and Pedersen, 2011). Impairments in EF, visuospatial and verbal memory, as well as verbal fluency have been identified (Shin et al., 2014) in obsessive compulsive disorder. The impact of anxiety on cognitive performance in the absence of true cognitive impairment is difficult to assess in these, as in other, disorders.

Personality disorders have also been associated with cognitive deficits (Burgess, 1992). A twin study generated data bolstering the hypothesis that EF deficits are linked to some forms of personality disorder (Coolidge et al., 2004). In a meta-analysis, individuals with borderline personality disorder (BPD) were found to show deficits on several cognitive tasks (Ruocco, 2005). Individuals with antisocial personality disorders show decrements in set-shifting, planning, and visual memory tasks (Dolan and Park, 2002). Characteristics of BPD such as suicidality have been shown to be associated with EF impairments (Mak and Lam, 2013). Conclusions regarding cognitive function in personality disorder need to be made with caution as various confounding variables may exist such as the presence of other medical or psychiatric disorders, or substance use. For example, the presence of ADHD, which is highly prevalent in individuals with antisocial personality disorder (Bergvall et al., 2001; Storebo and Simonsen, 2013), would need to be ascertained.

Deficits in cognition before onset and during the course of the disorder have been insufficiently explored in individuals with substance use disorders.

This brief overview suggests the omnipresence of cognitive deficits in psychiatric disorders highlighting the importance of research into this domain, particularly as regards its impact on clinical and functional outcomes. The prevalence of cognitive

dysfunction also underscores the need to develop clinically pertinent instruments for its evaluation.

Chapter 1.7 : Evaluation of cognition in psychiatric disorders

Despite the prevalence of cognitive deficits in various psychiatric disorders there is no established consensus on their evaluation in the clinical context. The gold standard of cognitive assessment involves access to the expertise of a neuropsychologist and requires several hours of evaluation. As a result, there has been a search for alternative means of assessment and screening tools. A review of the methods used to evaluate cognition in research trials relied on the criteria applied by Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project (test-retest reliability, utility, relationship to functional status, potential changeability in response to pharmacological agents, and tolerability and practicality for clinical trials) to rank the assessment tools used (Bakkour et al., 2014). Of 167 instruments, 30 were suitable : 27 had been studied in schizophrenia, 1 in MDD, and 2 in BD. This review highlights the need to identify common and valid tools to evaluate cognition in psychiatric pathology. A survey of psychiatrists found that although 59% reported evaluating cognition with an instrument in schizophrenia, only 38% did so in MDD, and 37% did so in BD (Belgaied et al., 2014). The same study showed that the instruments used were appropriate to the disorder in only 12% of cases for schizophrenia, 3% of cases for MDD and 0% for BD) (Belgaied et al., 2014).

Schizophrenia is the psychiatric condition in which cognition has been the most extensively studied. Hence, clinicians have access to a number of validated instruments (Schulz and Murray, 2016). Furthermore, an international initiative, The MATRICS Project generated a standardised neuropsychological battery specifically adapted to the cognitive profile of schizophrenia. Starting with 90 tests in 7 cognitive domains, the group selected 10 tests, the MATRICS Consensus Cognitive Battery (MCCB). The MCCB has good psychometric properties (Roseberry and Kristian Hill, 2014) and the MCCB global score correlates with functional measures such as the University of California at San Diego Performance-based Skills Assessment (UPSA) (Nuechterlein et al., 2008) as well as social functioning, educational and employment-history (Lystad et al., 2014).

Computerised neuropsychological batteries are common in psychiatric research (Barnett et al., 2010) and have been evaluated in schizophrenia. Integneuro (Silverstein et al., 2010), CogState (Maruff et al., 2009), The Mindstreams Computerized Cognitive Test Battery (Ritsner et al., 2006) and The Cambridge Neuropsychological Test Automated Battery (CANTAB) (Levaux et al., 2007; Sahakian and Owen, 1992) are capable of detecting impairment to a degree comparable to that of the MATRICS battery and generate results which are also correlated to the UPSA (Pietrzak et al., 2009). Nevertheless, these automated neuropsychological batteries require 90-210 minutes to administer spurring a search for abbreviated versions. The recourse to computerised assessment requires equipment which may be cumbersome and potentially intimidating to some patients. Finally, a potential future method harnessing computerised technology is the possibility of web-based cognitive screening (Medalia et al., 2005).

Clinicians are accustomed to using brief paper and pencil tests of cognition such as the Mini Mental State Exam (MMSE). In fact, the MMSE is widely used to evaluate cognition in the elderly (Ismail et al., 2010) and can be effectively used by general practitioners to discriminate between the absence of impairment and mild cognitive impairment (Pezzotti et al., 2008). The MMSE was more often in the impaired range (24 or less) in individuals with schizophrenia than in healthy controls (23 vs 0%) (Moore et al., 2004). A similar instrument, the Montreal Cognitive Assessment (MoCA) has gained popularity in the evaluation of cognition in the elderly because of its greater sensitivity (Ismail et al., 2010). The MoCA can also detect cognitive impairment in patients with schizophrenia (Wu et al., 2014). The MoCa was compared to the Brief Assessment of Cognition in Schizophrenia (BACS). The BACS, a validated, 35 minute cognitive battery (Bralet et al., 2008; Keefe et al., 2004), was unrelated to functional measures such as the UPSA, and the Global Assessment of Functioning (GAF)) while the MoCA proved to be correlated with the UPSA (Musso et al., 2014). Several other, equally brief, assessment tools which require only a paper and pencil but which may show greater sensitivity have been developed. The brief neurocognitive assessment (BNA) can be administered in

approximately 10 minutes. When compared to a full 90 minute neuropsychological battery in patients with schizophrenia, the BNA explained 76% of the variance in cognition. Both instruments were sensitive to treatment-related changes (Fervaha et al., 2014). The Brief Cognitive Assessment Tool (B-CATS) (Hurford et al., 2011), the brief cognitive assessment (BCA) (Velligan et al., 2004) and the Screen for Cognitive Impairment in Psychiatry SCIP (Pino et al., 2008; Purdon, 2005j) also require 10-15 minutes to administer. In a comparison of the Spanish version of the SCIP in patients with psychosis, bipolar disorder, and healthy controls the SCIP- S was more correlated to a complete battery than was the B-CATS (Cuesta et al., 2011).

Cognitive functioning can also be assessed with interview-based assessments. The Schizophrenia Cognition Rating Scale (SCoRS) interviewer ratings are reliable but suffer from reduced validity in the absence of third-party information (Keefe et al., 2015). Nevertheless, in stable patients, SCoRS global ratings were significantly correlated with scores of cognitive performance, symptoms, and psychosocial functioning (Keefe et al., 2006). As patients' severity of illness increased such correlations became less significant (Vita et al., 2013). Another interview-based measure of cognition, the Cognitive Assessment Interview (CAI), was both reliable and correlated to ratings of cognitive functioning (Ventura et al., 2010; Ventura et al., 2013). The Clinical Global Impression of Cognition in Schizophrenia (CGI-CogS), also interview-based, was correlated to third party ratings but not self-rating of psychosocial functioning (Ventura et al., 2008). The Positive and Negative Syndrome Scale (PANSS) is an interview based instrument used to assess the symptoms of schizophrenia. Several studies have identified a cognitive factor of the PANSS which is correlated to neuropsychological tests; however, this factor did not account for most of the neurocognitive functioning (Good et al., 2004).

The University of California Performance-based Skills Assessment (UPSA) tests cognitive functions through their application to standardised tasks of daily living. As expected, patients with schizophrenia perform less well than controls (Heinrichs et al., 2006). The abbreviated form, the Brief University of California San Diego

(UCSD) Performance-based Skills Assessment (UPSA-B), correlates with improved psychosocial functioning (Mausbach et al., 2010).

The evaluation of cognition in bipolar disorder has been inspired by the work done in schizophrenia. Thus, the MCCB has been evaluated in BD showing deficits in cognitive functioning. With the addition of two EF tasks, the MCCB was deemed a suitable instrument for the assessment of cognition in BD research (Van Rheenen and Rossell, 2014). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), like the Brief Assessment of Cognition in Affective Disorders (BAC-A) requires approximately 30 minutes to administer. The RBANS was significantly correlated with general cognitive ability (Hobart et al., 1999). The BAC-A detects impairment in memory and verbal fluency in individuals with BD, the latter being associated with scores on the Global assessment of function (GAF) (Bauer et al., 2015). In contrast with the findings in schizophrenia, the MMSE scores are situated in the normal range in euthymic BD, despite persistent functional impairment (O'Shea et al., 2010). Use of the SCIP in BD yields scores that correlate with those obtained with standard neuropsychological assessment (Gomez-Benito et al., 2013; Guilera et al., 2009).

Assessment of cognition in major depression is receiving increased attention, but there is as yet no accepted standardised battery as there is in BD. The MMSE lacks sensitivity when used to assess cognition in MDD classifying almost all who are impaired as cognitively intact, although sensitivity is somewhat improved with a cut-off score of 27 instead of the standard 24 (Rajji et al., 2009).

Several self-report instruments have been developed to aid in the evaluation of the cognitive deficits of depression (Fava et al., 2009; Fehnel et al., 2016; Hueng et al., 2011; Iverson and Lam, 2013). The Cognitive and Physical Functioning Questionnaire (CPFQ) is a 7 item, 6-point questionnaire that is correlated with measures of sleepiness, fatigue, apathy, neuropsychological functioning and depression (Fava et al., 2009). The British Columbia Cognitive Complaints Inventory (BC-CCI) is a 6-item questionnaire that has been validated in MDD (Iverson and Lam, 2013). The perceived deficit questionnaire which comprises 20

items, was initially developed for use in multiple sclerosis and refined for use in depression through the feedback of focus groups (Fehnel et al., 2016).

Cognition in ADHD is most often assessed through the use of self-administered questionnaires (SAQ). Three of the most frequently used SAQ were compared as screening tools for ADHD in college students. Scores on the Adult ADHD Self-Report Scale (ASRS), the Conners' Adult ADHD Rating Scale-Self-Report: Long Version (CAARS), and the Brown ADD Scales were correlated with each other but not with academic performance, although a weak correlation was found between the hyperactivity-impulsivity subscales of the CAARS (Fuller-Killgore et al., 2013). Individuals with ADHD perform less well than healthy controls (Advokat et al., 2007; Pollak et al., 2009) on continuous performance tasks and have been used to assess ADHD; however, they lack specificity both in children (Trommer et al., 1988) and adults (Riccio and Reynolds, 2001). It is possible that more challenging forms of the CPT may discriminate individuals with ADHD from normal controls (Lufi and Fichman, 2012). We can conclude that, at present, there is no clear consensus for the evaluation and pertinence of neurocognitive function in ADHD.

This brief survey of instruments for the evaluation of cognition in psychiatry allows us to conclude that there is a need for systematic research in this domain in order to identify standardised, appropriate tools for the assessment of cognition in clinical practice.

Chapter 1.8 : Self-evaluation and objective evaluation : are they related ?

The evaluation of cognition is clearly clinically pertinent. Yet the time constraints of clinical practice are such that it is unlikely that even brief instruments to evaluate cognition will be widely used. As a consequence there has been a determined search for self-administered questionnaires which can be completed by patients in the waiting room. The validity of this approach is belied by questions regarding the reliability of the self-evaluation of cognition. Discordance between patients' evaluation of cognition and their performance is well known to be prevalent in schizophrenia (Gould et al., 2015). The relationship of self-evaluation to performance in other psychiatric conditions is less clear. In schizophrenia, self-report of cognitive or psychosocial function is not correlated to objective performance and function or to clinician evaluation of these dimensions (Durand et al., 2015); however, clinicians' evaluations were correlated with daily function (Durand et al., 2015). The Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS) was developed by Stip as a self-report scale (Stip et al., 2003). Results on the SSTICS correlate with some domains of objective testing, as well as with assessment of cognitive impairment by a clinical rater (Lecardeur et al., 2009). In a review of the literature, Stip's group identified 14 different self-report scales for cognitive impairment in schizophrenia (Homayoun et al., 2011). They conclude that the relationship between such instruments and objective testing is variable although most studies with the SSTICS found some correlation between the two. Interestingly, a higher level of awareness of cognitive impairment seems associated with greater acknowledgement of the therapeutic effect of medication (Bayard et al., 2009) and better occupational outcome (Verdoux et al., 2010). Clinicians' evaluation of patients' cognitive performance is by no means infallible. For example, although clinicians judged 20-40% of inpatients to have normal memory, testing revealed significant impairments (Moritz et al., 2004). Though patients' rating of their cognition has little relation to their actual neurocognitive deficits, clinicians' ratings are only somewhat more accurate (Saperstein et al., 2012). Another study confirmed

the poor correlation between clinician and patient estimated cognitive performance and true cognitive performance (Medalia and Lim, 2004).

Again the literature is sparser regarding self-evaluation of cognition in psychiatric disorders other than schizophrenia. In a comparison of elderly individuals with bipolar disorders and matched controls, both groups reported similar levels of cognitive impairment although the bipolar group manifested greater deficits in attention and executive function (Schouws et al., 2012).

The perceived deficit questionnaire (PDQ) was adapted to major depression (Fehnel et al., 2016). Reported cognitive deficits on the PDQ surpass those found in objective testing (Lahr et al., 2007). In a web-based study, individuals with diagnosed depression indicated increasing levels of cognitive impairment on the PDQ as severity of depressive symptoms increased (Lawrence et al., 2013).

The PDQ has been studied in non-psychiatric populations. In rheumatoid arthritis the PDQ was unrelated to objective cognitive performance but significantly related to depression and fatigue (Shin et al., 2013). Similar results were found in a multiple sclerosis population (Christodoulou et al., 2005). Thus the 'subjective-objective' discordance in cognitive impairment is not specific to psychiatric populations.

Clearly self-assessment, although helpful, cannot take the place of objective testing of cognition.

Chapter 2 : Inflammation in psychiatric disorders

The immune system and inflammation have traditionally been considered to be the means by which the body defends itself against injury or infection. It is increasingly clear that the immune system plays a much larger role including the modulation of neuronal activity (Iori et al., 2016). Innate immunity comprises immune cells that use a fixed set of receptors to detect and interact with pathogens (Slavich and Irwin, 2014). The innate system can trigger a secondary reaction, adaptive immunity, which involves a specific response to pathogens (Slavich and Irwin, 2014). Toll-like receptors (TLR's) recognise patterns on pathogens and activate transcription factors -Nuclear factor-κB (NFKB) in the case of extracellular pathogens, and activate interferon regulatory factors (IFN) in the case of intracellular pathogens ; these in turn lead to the transcription of cytokines (Slavich and Irwin, 2014). Cytokines are large molecules produced by diverse immune cells that modulate the immune response (Kirkpatrick and Miller, 2013). They do not normally cross the blood-brain barrier (BBB) but influence the brain through diverse mechanisms. Cytokines may filter through the BBB when damage increases porosity. They may also be actively transported or potentially activate endothelial cells in the cerebral vasculature or adjacent macrophages which then secrete immunomodulatory molecules within the brain. Finally, cytokines can activate receptors on afferent nerves which then affect the brain (Haroon et al., 2012). Cytokines play a role in neurogenesis, neuronal pruning and plasticity as well as synaptic neurotransmission (Vezzani and Viviani, 2015). They can induce other molecules ; for example, IL-6 can increase levels of C-reactive protein (CRP) (Slavich and Irwin, 2014). Within the brain, microglia are key to the inflammatory reaction and can both attract and produce cytokines (Slavich and Irwin, 2014). Cytokines can produce a cluster of symptoms called 'sickness behaviour' which correspond to the manifestations of major depression (Lotrich, 2015). This has led to the concept of depression as resulting from an immune dysregulation (Maes, 1993; Smith, 1991). Supporting this concept is the observation that chronic mild stress leads to increased inflammation (Hughes et al., 2016) and the stress-immune interaction has been proposed as an aetiological model of depression

(Gold et al., 2015; Slavich and Irwin, 2014). Specific symptom profiles and clinical characteristics of MDD have been linked to the effects of the immune system. For example, women present greater increases of IL-6 and TNF- α following sleep deprivation and present a greater intensity of symptomatology in comparison to men (Derry et al., 2015). This greater immune reactivity has been proposed to underlie the greater prevalence of depression in women.

Table I : Cytokines and their roles

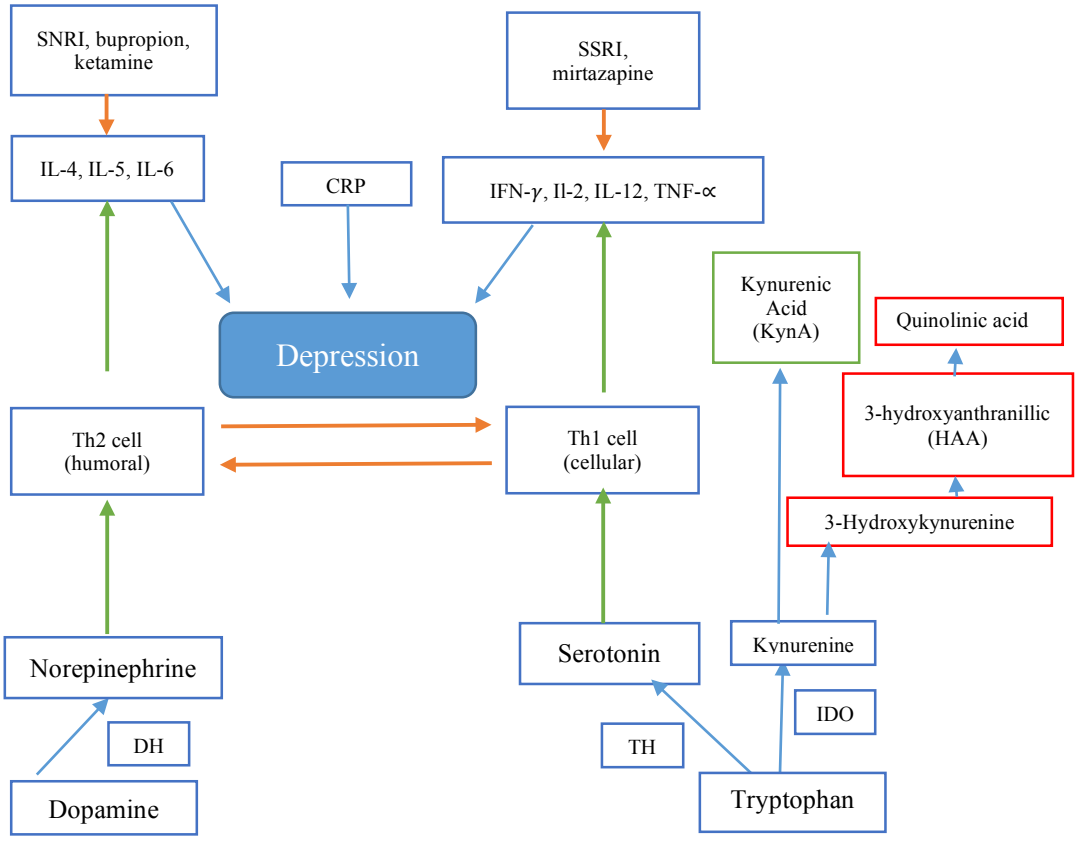
Cell-mediated immunity (pro-inflammatory)	IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IK-11, IL-12, IL-15, IL-16, IL-17, IL-18, IKL-21, IL-23, TNF-∝, TNF-$\boldsymbol{\beta}$,IFN-∝, IFN-$\boldsymbol{\beta}$, IFN-$\boldsymbol{\gamma}$
Humoral immunity (pro-inflammatory)	IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-15, IL-21, IL-25, TGF-β
Allergic immunity (pro-inflammatory)	IL-3, IL-4, IL-5, IL-9, IL-13, IL-25, IFN-γ, GM-CSF, SCF
Anti-inflammatory	IL-4, IL-5, IL-6, IL-10, IL-13, IL-19, IL-20, IL-22, IL-24, IL-26, TGF-β, IL-1RA, signalling by IL-1RII

Cell mediated immunity: IFN-γ is the major cytokine
Humoral immunity: mediated by B-cells and production of antibodies
Predominantly anti-inflammatory: IL-10, TGF-β
Both anti and pro-inflammatory : IL-6
Produced by innate cells and directing adaptive immunity and inflammation: IL-1, IL-6, tumor necrosis factor -∝
IL-1: interleukin 1
IL-1RA-I : interleukin 1 receptor antagonist
IL-1RII : IL-1 receptor type II
TNF−∝ F: tumor necrosis factor-∝
GM-CSF : granulocyte macrophage- colony stimulating factor
SCF: stem cell factor
From: Seruga and colleagues 2008 (Seruga et al., 2008)

In the CNS the main inflammatory cells are microglia. These cells can be activated in two ways. Classical or M1 activation leads to the synthesis of pro-inflammatory molecules such as IL-1β, TNF-α, Il-6, superoxide radicals, glutamate, and nitric oxide. M2 activation by cytokines such as IL-4, IL-13, or IL-25 leads to the synthesis of anti-inflammatory molecules such as IL-10, insulin growth factor 1(IGF-1), transforming growth factor-β (TGF-β) and neurotrophic factors (Reus et al., 2015a). Thus microglia, activated by inflammatory pathways, can contribute to either neurprotection or neurotoxicity in a contextually dependent fashion.

Inflammation has been linked to altered cerebral function, as well as to changes in brain volume which may contribute to the pathophysiology of depression (Byrne et al., 2016). For example, increases in CRP, IL-6, IL-1β, IL-1RA have been linked to decreased cerebral connectivity (Felger et al., 2015). Causes of inflammation such as psychosocial stress, childhood trauma, diet, lack of exercise, 'leaky gut syndrome', atopic disorders, chronic dental diseases, sleep deprivation and vitamin D deficiency (Berk et al., 2013) may contribute to the development and persistence of psychiatric disorders.

Figure I: Cytokine-neurotransmitter interaction in depression



Cytokines induce IDO which leads to increased synthesis of kynurenine from tryptophan. Tryptophan is then less available for synthesis into serotonin
Kynurenine is metabolised by astrocytes into kynurenic acid which is neuroprotective or by microglia into 3-hydroxykynurenine (3-HK), 3-

hydroxyanthranillic acid (3-HAA) and quinolinic acid (Quin) which are neurotoxic
IDO:Indoleamine Oxidase
DH: Dopamine hydroxylase
PH: phenylalanine hydroxylase,
TH:tyrosine hydroxylase
TPH:tryptophan hydroxylase
TYR:tyrosine
5-HT:5-hydroxytryptophan

Modified from (Hashimoto, 2015; Reus et al., 2015b; Swardfager et al., 2016)

Chapter 2.1: Inflammation in schizophrenia

Altered immunity has long been identified in schizophrenia (DeLisi and Wyatt, 1982; Sperner-Unterweger and Fuchs, 2015; Zakharyan and Boyajyan, 2014). Further, genetic studies have shown linkage to schizophrenia in a region related to immune function (Muller et al., 2015). Nevertheless, the nature and relevance of inflammation in this condition as in other psychiatric disorders remains unclear.

Pro-inflammatory cytokines are increased in schizophrenia. Higher levels of IL-6 are found in new-onset schizophrenia (Coughlin et al., 2016), chronic schizophrenia (Goldsmith et al., 2016) and in schizophrenia of undefined duration (Neelamekam et al., 2014; Schwieler et al., 2015; Song et al., 2014b). Despite this, no polymorphisms of the IL-6 and IL-6R have been identified in schizophrenia (Kapelski et al., 2015). In individuals at risk for psychosis who were not taking cannabis IL-6 was increased over control levels (Stojanovic et al., 2014) suggesting that such increases may predict an unfavourable evolution. In a meta-analysis, Guo and his group included 21 studies and concluded that while in vitro INF-γ and IL-2 production was lower in patients with schizophrenia compared to controls, serum levels are not different in the two groups (Guo et al., 2015). In a study of cytokines in chronic schizophrenia, elevated levels of serum TNF-α, IL-6 and IL-18 were detected (Luo et al., 2014). Although increased IL-18 was confirmed in some studies (Xu et al., 2016), others were unable to replicate this finding (Zhang et al., 2016a). Nevertheless, Zhang and colleagues found increased levels of IL-18 and PANSS scores to be associated in individuals carrying the C allele of the IL-18 gene. Elevated levels of TNF- α and IL-1β were also found by Song and colleagues (Song et al., 2014b). In contrast, Lv and colleagues found lower TNF-α levels in patients with chronic schizophrenia (Lv et al., 2015). IL-3 levels were significantly increased in patients with chronic schizophrenia compared to healthy control subjects and were correlated with the PANSS general score as well as with the depressive subscore (Xiu et al., 2015). The cytokine IL-23, which is involved in the IL-17 pathway, was found by Borovcanin to be increased in individuals with schizophrenia either in the

first episode or during relapse (Borovcanin et al., 2015). Dimitrov and colleagues confirmed the involvement of the IL-17 pathway in a study of veterans with schizophrenia (Dimitrov et al., 2013). Treatment did not modify the raised IL-23 levels (Borovcanin et al., 2015; O'Connell et al., 2015). Il-12, which may have both pro and anti-inflammatory properties (Chang and Radbruch, 2007), is increased in schizophrenia compared to controls, and this difference is even more marked in women (Bedrossian et al., 2016). Overall, a preponderance of data confirms a pro-inflammatory state in schizophrenia.

Zhang and his group examined the interaction of cytokines with brain derived neurotrophic factor (BDNF) ; they found lower levels of BDNF and TNF- α , and higher levels of IL-2, IL-6, and IL-8 (Zhang et al., 2016b). There was also a significant correlation between BDNF and both IL-2 and IL-8 levels; furthermore, low BDNF and TNF- α levels taken together were associated with poor performance on the PANSS cognitive factor (Zhang et al., 2016b). A study examining mRNA production detected increased levels of IL-6, TNF- α, IL-1R1, TNFR1, and TNFR2, suggesting increased transcription of pro-inflammatory cytokines in schizophrenia (Pandey et al., 2015b).

Meta-analyses largely support individual observations. A recent publication identified 68 studies which examined cytokine levels in psychiatric disorders. Forty of these were in schizophrenia. Interleukin-6, TNF- α, sIL-2R, IL-1RA were significantly increased in the acute phase of schizophrenia (Goldsmith et al., 2016). Interleukin 6, IL-18, TNF α, and sIL-2R remained increased in individuals with schizophrenia after controlling for identifiable causes of inflammation (Al-Hakeim et al., 2015). A meta-analysis conducted in 2014 screened 4651 studies of medication naive patients with first episode psychosis and retained 21 for analysis. These studies included 570 patients, 683 controls and 20 cytokines and cytokine receptors. Increased IL-1β, sIL-2R, IL-6, and TNF- α levels were found (Upthegrove et al., 2014).

Treatment of chronic schizophrenia is associated with a reduction of IL6 and an increase in sIL-2R (Goldsmith et al., 2016). In another study, treatment with

aripiprazole led to decrements in CRP, insulin, IL-1 β, IL-6, TNF- α, sTNF-R1, IL-12, IL-23, IL-1Ra, TGF-β1, IL-4, IFN-γ and increased IL-10. IL-10, an anti-inflammatory cytokine, is inversely correlated with PANSS scores (Sobis et al., 2015; Xiu et al., 2014). A study of antipsychotic-naive, first-episode schizophrenia patients found increased levels of IL-1RA, IL-10 and IL-15; furthermore, after treatment with atypical antipsychotics IL-1RA and IL-10 were reduced (de Witte et al., 2014). Ajami and colleagues, similarly observed decreased TNF- α and increased IL-10 following treatment with clozapine and risperidone (Ajami et al., 2014). Al Amin and colleagues, using a different paradigm, found increases in the levels of the anti-inflammatory cytokines, IL-4 and IL-10, and a decrease in the pro-inflammatory IFN-γ following treatment with antipsychotics (Al-Amin et al., 2013). A meta-analysis of 23 studies and 762 subjects with schizophrenia further confirms an anti-inflammatory effect of treatment, showing increased plasma levels of sIL-2R, and reductions of IL-2 and IL1β (Tourjman et al., 2013). This personal work is reported in detail in Chapter 4.5. In a study of drug naive individuals with schizophrenia baseline levels of IL-1 β, IL-6, and TNF- α were increased. The first month of risperidone treatment was associated with lower levels of IL-1β. This effect was no longer seen after 2 months of treatment; in addition, levels of IL-6, and TNF- α increased over time (Song et al., 2014a). This raises the possibility that the long-term adverse effects of medication, such as weight gain and metabolic syndrome, may abolish initial anti-inflammatory effects. Finally, Noto and colleagues found that resistance to treatment is associated with a specific pro-inflammatory profile (increased sTNF-R1, sTNF-R2 and MCP-1)(Noto et al., 2015).

There are many confounding factors which complicate the interpretation of the literature regarding inflammation and which are not always controlled for in the studies in this field. For example, obesity may be a confounding factor in studies of inflammation both in treated and untreated individuals with schizophrenia (Klemettila et al., 2014; Sirota et al., 2015). Aspects of illness such as tardive dyskinesia (TD) may also be related to inflammation; for example, IL-2 levels were significantly correlated with the Abnormal Involuntary Movement Scale score in TD

patients (An et al., 2015). Tardive dyskinesia may in turn be linked to duration and dose of treatment. Gender, age and psychosocial stressors may be other such factors.

In their review of neuroimmune interactions, Khandaker and Dantzer suggest that the symptoms of schizophrenia may emerge, at least in part, as a result of low-grade inflammation (Khandaker and Dantzer, 2016). A meta-analysis of neuroimaging studies found evidence of microglial activation and neurodegeneration in individuals with schizophrenia ; this observation was also associated with cases manifesting increased transcription of pro-inflammatory cytokines (Najjar and Pearlman, 2015). This may suggest that a genetic and physiological vulnerability to chronic inflammation may contribute to the structural and functional cerebral abnormalities found in neuroimaging studies of schizophrenia (Fineberg and Ellman, 2013).

This hypothesis is further supported by additional data showing a relationship between a polymorphism of IL-6 and reduced hippocampal volume (Kalmady et al., 2014). Given the effect of cytokines on neuroplasticity, it has been proposed that a chronic inflammatory state may lead to neurodegeneration in schizophrenia and also to the cognitive and negative symptoms seen in the disorder. The mediators of immunity may thus be promising candidates for treatment intervention (Mansur et al., 2012).

Chapter 2.2: Inflammation in bipolar disorder

There has been a recent flourishing of interest in the role of inflammation in bipolar disorder. Several reviews and meta-analyses describe findings of increased inflammation in bipolar disorder and its implication. Overall there is indication of widespread alterations in immunity during mania, depression (Muneer, 2016) and euthymia (Rosenblat and McIntyre, 2016).

Several theories as to the underpinnings of the relationship of inflammation and bipolar disorder have been advanced. For example, an abnormally reactive immune system or a more porous BBB (Patel and Frey, 2015), or the direct effect of cytokines on neurotransmission (Rosenblat et al., 2014). The influence of the cytokine changes seen in bipolar disorder on tryptophan metabolism may also contribute to mood disorder pathology (Anderson and Maes, 2015). A recent investigation of BD I showed increased IL-6, and IL-8; although these observations were no longer significant after corrections for confounding factors, CRP was decreased (Jacoby et al., 2016). This decrease in CRP was seen exclusively in the depressive phase. In adolescents and young adults (Goldstein et al., 2015; Wang et al., 2016) clinical parameters such as longer illness duration, suicide attempts, and substance use disorders are correlated to CRP. Dargel and colleagues included 11 studies in a meta-analysis of CRP, arriving at the conclusion that CRP is increased in BD (Dargel et al., 2015). This result contrasts with Dickerson's study which found CRP to be elevated in mania and the euthymic state but not in the depressed state. A systematic meta-analysis conducted in 2013 found sIL-2R, TNF- α, sTNFR1, sIL6R, and IL-4 were increased in BD (Munkholm et al., 2013). The same study found no differences between BD and controls for IL-1, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, IL-1 β, IL-1RA, IFN-γ, TGF- β1, and sTNFR2. In a global comparison of BD and controls, cytokine levels were not significantly different (Tsai et al., 2014) ; however, BD cases in an abnormal mood state did show increased levels of TNF-α, sTNFR1/sTNFR2, IL-1β, IL-6, IL-10, IL-18, IL-4, IFN-γ and other inflammatory factors. Similar results were found by Bai and colleagues (Bai et al., 2014) who observed increased cytokines in BDI and II. Intriguingly, BD II and patients in the

depressive state manifested lower levels of sTNF-R1. In some studies the changes seen in BDI were greater than those seen in BDII (Wang et al., 2016). In a study of BD, schizophrenia, and MDD, IL-6, TNF- α, sIL-2R, and IL-1RA were increased in all three groups in the acute phase (Goldsmith et al., 2016). A pleiotropic pro-inflammatory cytokine, IL-33, and sST2, a soluble receptor which mediates some of IL-33's actions, are both increased in BD (Barbosa et al., 2014). Alteration in the regulation of the immune response is also evident in bipolar disorder (Elhaik and Zandi, 2015; Wieck et al., 2016). It is conceivable that this altered regulation may be related to the increased activation of immune cells seen in BDI (Barbosa et al., 2014). Euthymic patients with BD and healthy controls undergoing a social stress test manifested increased IL-2 and decreased sTNFR1 following the test; these increases were greater in the BD group (Wieck et al., 2014).

Transcription of mRNA of pro-inflammatory cytokines is also increased in bipolar disorder (Pandey et al., 2015a) and there is some indication of genetic alterations associated with the changes in immunity seen in BD. Levels of three inflammatory markers which were increased in mania were found to be associated with methylation of a gene coding for an enzyme involved in the synthesis of steroid hormones (Sabunciyan et al., 2015). In addition, in BD genes coding for inflammatory pathways are characterised by a greater number of variants which may point to a greater vulnerability of the inflammatory process in this condition (Drago et al., 2015).

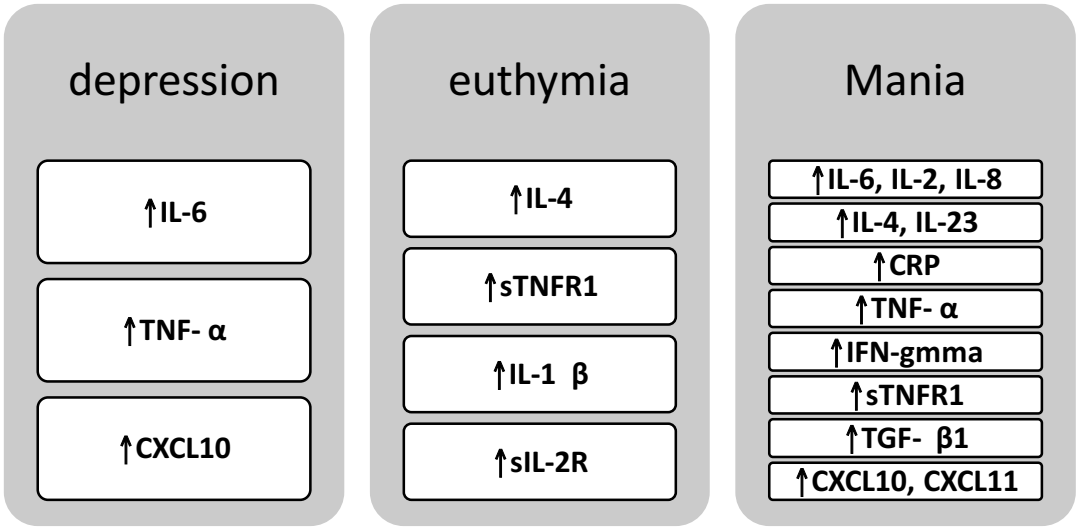
Treatment of BD with mood stabilisers such as lithium has been shown to have an anti-inflammatory effect (Rosenblat and McIntyre, 2016). Lithium decreases cyclooxygenase-2 expression, IL-1 β, TNF -α, INF-γ and increases IL-2, IL-4, and IL-10 (Nassar and Azab, 2014). Increased inflammatory markers found in mania are decreased following treatment (Li et al., 2015; Uyanik et al., 2015). Goldsmith showed that IL-1RA levels are increased in mania and decreased following treatment (Goldsmith et al., 2016). Interleukin 8 (IL-8) concentrations were found to be higher in patients with bipolar disorders compared to controls and were correlated to treatment with lithium and antipsychotics (Isgren et al., 2015).

The addition of anti-inflammatory agents to valproate resulted in a higher remission rate of bipolar mania (Arabzadeh et al., 2015). A review of adjunctive treatment with anti-inflammatory agents in bipolar disorder identified 16 articles (Ayorech et al., 2015). Of the agents studied (omega-3 fatty acids, celecoxib, n-acetyl cysteine) the data was strongest for n-acetyl cysteine (NAC). Another review which included 10 randomised controlled trials of anti-inflammatory agents for the treatment of bipolar depression also included pioglitazone. Overall, anti-inflammatory agents had a moderate effect size, improving depressive symptoms (Rosenblat et al., 2016). Again the strongest effect in this review was for NAC.

The inflammatory profile of bipolar disorder is inconsistent. At the very least, it varies by phase (see table). There is some suggestion that it may vary by type of bipolar disorder. In rapid cycling bipolar disorder IL-6 and IL -18 are increased in the hypomanic and manic phases compared to levels seen in the depressed or euthymic phases or in healthy controls (Munkholm et al., 2015). Haenisch and colleagues found that mixed states show greater alterations of haptoglobin, chemokine CC4 and matrix metalloproteinase 7 (Haenisch et al., 2015). Transcription of the chemokine ligand 24 (CCL24) was shown to be consistently increased in MDD compared to healthy controls (HC) and BD, while that of chemokine receptor type 6 was decreased in MDD compared to HC (Powell et al., 2014).

Bipolar disorder and schizophrenia seem to have differing inflammatory profiles (Morch et al., 2016). Morch and colleagues observed increases of sTNF-R1 and IL-1Rα in comparison to HC. Increased sTNF-R1 was seen in schizoaffective disorder and affective spectrum disorder. For example, lower counts of natural killer cells are found in schizophrenia but not in bipolar disorder compared to HC (Karpinski et al., 2016). Bipolar disorder also seems to differ from depressive disorder; for example, BDII is characterised by higher CRP levels (Chang et al., 2016).

Table II: Inflammatory markers in bipolar disorder



Chapter 2.3 : Inflammation in depression

There is a preponderance of data supporting the observation of increased levels of cytokines in major depression. Recent reviews identify increases in MDD of the cytokines IL-6, IL-18, sIL-2R and TNFα (Al-Hakeim et al., 2015; Fonseka et al., 2015; Noto et al., 2014), IL-1, IL-6, TNf-∝, CRP, and MCP-1(Young et al., 2014). The most powerful associations seem to be with IL-6 and CRP (Haapakoski et al., 2015). A recent population study showed CRP and TNF-∝ to be increased in MDD. This was associated with indicators of endothelial dysfunction (van Dooren et al., 2016). Nevertheless, not all investigations come to the same conclusion, suggesting a complexity that has yet to be elucidated. For example, Bahrini and colleagues found no increases in CRP in untreated MDD without concurrent inflammatory medical conditions, although IL-6 was increased (Bahrini et al., 2016). A large populational study found that plasma CRP' was associated with MDD (Wium-Andersen et al., 2014). Obesity may contribute to the inflammatory profile found in MDD. Shelton found that adjusting for body mass index (BMI) abolishes the differences between MDD and HC in CRP and TNF-∝ but not in IL-6 levels (Shelton et al., 2015). Chemokines, a subpopulation of cytokines secreted by cells and exerting an effect on chemotaxis, have also been shown to be altered in depression. Specifically, CCL2 and MCP-1 are increased in this population (Eyre et al., 2016).

Additional alterations in immune functioning have been noted in depression; for example, abnormalities in the maturation of T cells and natural killer cells (NKC) have been documented in MDD populations (Grosse et al., 2016). The neutrophil to lymphocyte ratio (NLR) is increased in MDD (Demir et al., 2015) and predicts higher scores on the Hamilton depression rating scale (HAMD) (Aydin Sunbul et al., 2016). It is well established that a significant portion of patients treated with interferon-∝ (IFN-∝) develop depression. Hepgul and colleagues showed that these patients show a distinct profile as pertains to the expression of genes involved in inflammation, neuroplasticity and oxidative stress pathways (Hepgul et al., 2016).

Inflammation is also a correlate of poor prognosis. In several populational studies higher levels of CRP were associated with the development of depression (Liu et al.,

2014b; Zalli et al., 2016). Patients with both MDD and obesity have a different profile of inflammatory markers compared to those with MDD alone or obesity alone (Schmidt et al., 2014). Inflammatory markers associated with metabolic syndrome are linked to a more chronic course of depression (Topic et al., 2013; Vogelzangs et al., 2014). In a large study spanning 5 years the presence of higher levels of IL-6 and CRP were predictive of depressive symptoms at 5 years as well as their persistence over time (Zalli et al., 2016).

The symptom profile and course of MDD may, in part, be linked to the activity of cytokines. For example, similar inflammatory mechanisms may lead to both depression and pain (Burke et al., 2015; Leonard, 2015). In the same vein, somatoform symptoms are associated with increased levels of TNF-α (Dannehl et al., 2014). Suicidal behaviours are linked with increased IL-6 and decreased IL-2 (Marini et al., 2016). CRP is higher in BDII than in MDD both at baseline and after treatment (Chang et al., 2016).

The causal relationship between MDD and inflammation has yet to be completely elucidated; nonetheless, there are several pathways which can explain the co-occurrence of depression and a pro-inflammatory status. The inflammatory changes seen in major depression interact with neurotransmitter systems in such a way as to reduce the synthesis of monoamines (Leonard, 2014; Swardfager et al., 2016). In turn monoamines influence the activity of cytokines (Hashimoto, 2015). Beyond the monoamines, inflammation can affect other neurotransmitters. For example, increased CRP in MDD is associated with increased glutamate in the basal ganglia (Haroon et al., 2016). Cytokines can also activate indoleamine 2,3 dioxygenase (IDO), which degrades tryptophan thereby increasing the production of kynurenine and its metabolites. This has the effect of decreasing tryptophan and therefore serotonin (Meier et al., 2016). Kynurenine can be metabolised into Kynurenic acid (KynA), which is considered to be neuroprotective, or into 3-hydroxykynurenine (3-HK), 3-hydroxyanthrallic acid (3-HAA), and quinolinic acid (QA) which are considered to be neurotoxic. The ratio of KynA/QA is reduced in MDD ; furthermore, kynurenine concentration, and the kynurenine to tryptophan ratio are

correlated to decreased striatal volumes in MDD (Savitz et al., 2015a). In addition, a higher KynA/QA ratio is correlated to the number of months in remission (Savitz et al., 2015c) as well as larger volumes of the hippocampus and amygdala (Savitz et al., 2015b). Thus a pro-inflammatory context may contribute to the cerebral changes known to be characteristic of MDD.

Genetic differences underlying altered inflammation in MDD have yet to be elucidated but may contribute to an altered reactivity of the immune system and vulnerability to depression. In one study, fibroblasts of MDD patients had similar levels of transcription of inflammatory genes at baseline but once these cells were stimulated with IL-6 they manifested reduced transcription (Money et al., 2016).

The recognition of the presence of inflammation in depression has potential implications for its treatment (Hashimoto, 2015; Leonard, 2014). Treatment of depression with antidepressants generally reduces markers of inflammation (Basterzi et al., 2005; Crnkovic et al., 2012; Himmerich et al., 2010a; Himmerich et al., 2010b; Kubera et al., 2001a; Kubera et al., 2001b; Kubera et al., 2001d; Lanquillon et al., 2000; Sluzewska et al., 1995; Tuglu et al., 2003; van West and Maes, 1999; Walker, 2013). A recent meta-analysis showed that antidepressants decrease IL-6 (Strawbridge et al., 2015). Selective serotonin inhibitors (SSRIs) have been shown to exert anti-inflammatory effects (Branco-de-Almeida et al., 2011; Diamond et al., 2006; Maes et al., 1999; Martensson and Nassberger, 1993; Rawdin et al., 2013; Strumper et al., 2003; Taler et al., 2007; Xia et al., 1996) including a reduction of cortisol which is in turn correlated with a reduction of pro-inflammatory cytokines (Hernandez et al., 2013). These antidepressants also have an inhibitory effect on microglial and astroglial proliferation (Czeh and Di Benedetto, 2013) and their production of inflammatory molecules (Hashioka et al., 2007; Horikawa et al., 2010; Hwang et al., 2008). The anti-inflammatory effects of all SSRIs are not equivalent, with some exerting greater effects than others (Tynan et al., 2012) . Escitalopram is associated with reductions of neurotoxic metabolites in the tryptophan -kynurenine pathway (Strawbridge et al., 2015). In a study of cognitive behaviour therapy Toll-like receptor 4 (TLR-4) RNA was found to be increased in monocytes from

individuals with MDD, as were NF-kβ and IL-6 (Keri et al., 2014). Following treatment with cognitive behaviour therapy, improvement in depressive symptoms was associated with reductions in inflammatory markers, although IL-6 and CRP were unchanged. Globally, pharmacologic treatment of depression is associated with a reduction of pro-inflammatory markers; nevertheless, not all studies found an effect of antidepressants on inflammation (Jazayeri et al., 2010; Maes et al., 1995b).

Levels of inflammation, as indicated by CRP, are predictive of differential drug response in a study by Uher and colleagues (Uher et al., 2014). Thus, lower levels of CRP predicted response to escitalopram, while higher levels predicted response to nortripyline. Strawbridge and colleagues' meta-analysis concluded that TNF-$\propto$ was associated with treatment resistance (Strawbridge et al., 2015). There is some evidence that certain genetic profiles of genes involved in inflammation may also be predictive of response to intervention, although this remains to be confirmed (Hung et al., 2016; Maciukiewicz et al., 2015).

The addition of anti-inflammatory agents to antidepressants is associated with a reduction of depressive symptoms as well as of inflammatory markers. Celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, reduces the levels of pro-inflammatory cytokines, but also affects glutamatergic neurotransmission and tryptophan/kynurenine metabolism. As in schizophrenia, celecoxib shows a therapeutic effect in MDD (Muller, 2013). Celecoxib, added to antidepressant treatment, reduces the symptoms of depression as well as IL-6 concentrations (Abbasi et al., 2012; Muller et al., 2006). The experience with aspirin (ASA), added to SSRIs, has been contradictory accelerating response to antidepressants in one study (Mendlewicz et al., 2006), but in another small study causing worsening and intolerable side-effects (Ghanizadeh and Hedayati, 2014). Infliximab, an anti-TNF-α agent, alone or added to an antidepressant in treatment-resistant depression (Maas et al., 2010), and adjunctive minocycline (Levine et al., 1996; Miyaoka et al., 2012) led to greater improvement of depressive symptoms compared to adjunctive placebo in those individuals with CRP higher than 5 mg/L (Raison et al., 2013). Finally, the administration of prednisone in treatment-resistant depression is associated with

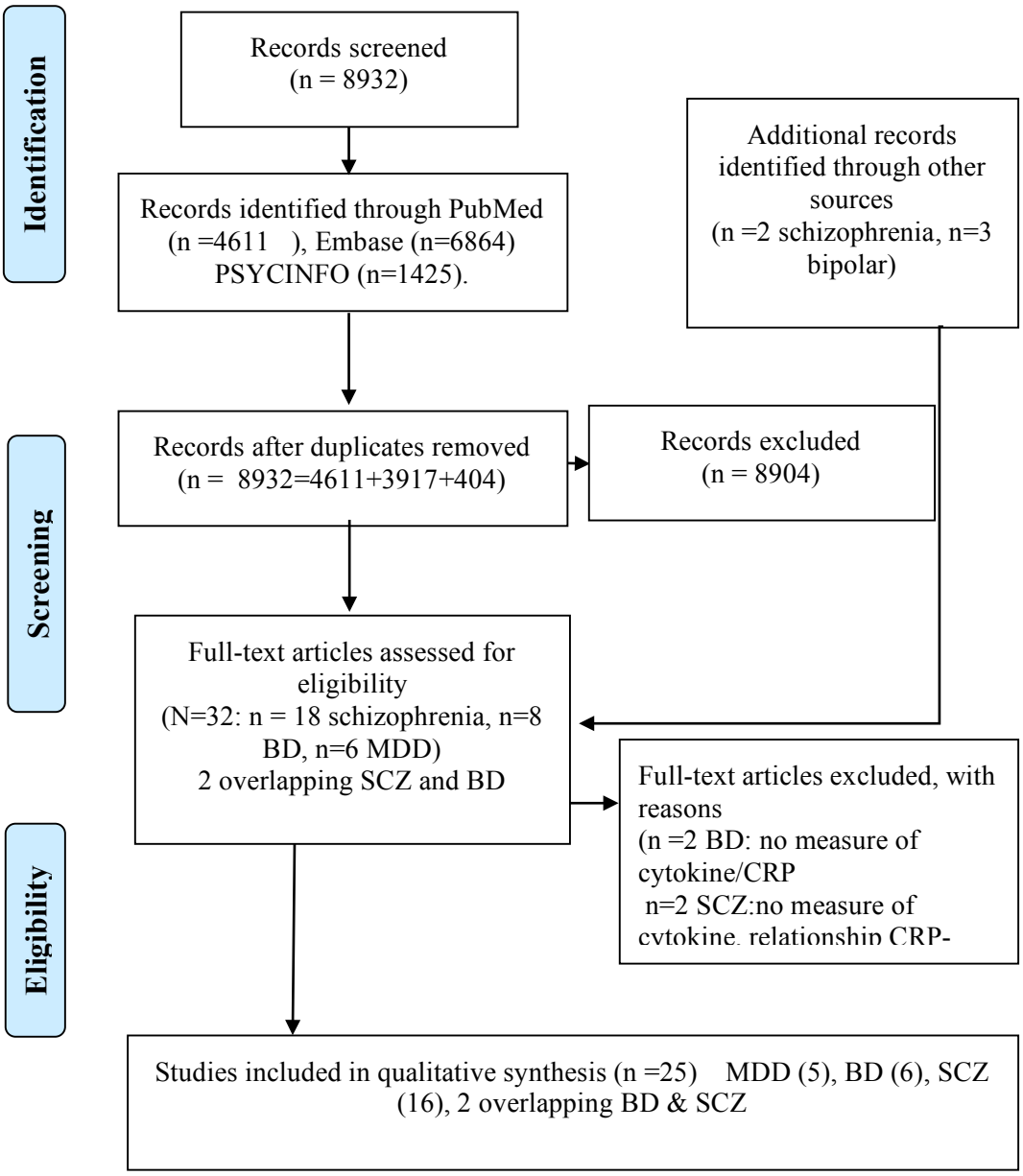
improvement of symptoms (Bouwer et al., 2000). In a populational study, prophylactic use of aspirin did not seem to prevent the occurrence of MDD (Glaus et al., 2015). Thus, not all anti-inflammatory agents can be expected to produce the same results in MDD and their specific effect on the inflammatory cascades must be taken into account in assessing their therapeutic potential (Maes, 2012).

Chapter 3 : The Relationship between inflammation and cognition

Inflammation and cognitive deficits are both prevalent and characteristic of many, if not most psychiatric disorders. It is possible that their co-occurrence is not random but in fact causal. In this section we present a review of the literature exploring this co-occurrence and its implications.

A search of PubMed, Embase, and Psycinfo was conducted on February 23, 2016. The search was limited to French or English publications in the past 10 years. The search terms entered were: inflammation or cytokines or C-reactive protein or tumour necrosis factor-alpha or interleukin 1 or interleukin 2 or interleukin 6 and cognition or cognition disorders or neurocognition or cognitive or neurocognitive or metacognition or metacognitive. The results are presented in the PRISMA flow diagram.

Figure II: Cognition and inflammation literature review flow chart



Chapter 3.1 : Inflammation and cognition in schizophrenia

The literature search identified 16 articles of studies with at least one cognitive measure and one measure of an inflammatory marker. Two additional studies were identified as they were referenced in articles on inflammation in schizophrenia. Invariably, as markers of inflammation increased, cognitive performance decreased. This was true in individuals with established schizophrenia, as well as in first episode patients. Intriguingly, this relationship was not found in control subjects. Different markers were correlated to decreased cognition in BD and in schizophrenia raising the possibility to be confirmed that although inflammation may be at play in both disorders, there may be unique profiles of immunity and cognitive vulnerability.

Table III: Cognition and inflammation in schizophrenia

Inflammatory markers	Cognitive test	Citation	Severity	Note	Age	Illness duration (yrs)	N		
CRP	**RBANS**	(Dickerson et al., 2007)	PANSS=71,5		18-65	19.1	SCZ/SA =413	↑CRP	↓RBANS
CRP	**RBANS**	(Dickerson et al., 2012)	PANSS=72,3	Strongest effect: HSV-1+ CRP.	18-65	18.8	SCZ/SA =588	↑CRP	↓RBANS
CRP	**MMSE**	(Diyanoosh et al., 2012)	Hospitalised		18-65	15,4	SCZ=75	↑CRP	↓MMSE
CRP IL6	**RAVLT, TMT, VF, Stroop, WAISs, (Sim, DSC, DSf/b)**	(Frydecka et al., 2015)	PANSS= 75,8-87,9		37,84± 11,6	12,2	SCZ=151 HC=194	↑CRP ↑IL6	↓RAVLT ↓Stroop, TMTA, DSC, DSf, RAVLT, VF, TMTB
CRP IL1ra, IL6 sTNF-R1	**WAIS, LM, I/DR, CVLT, DFR**	(Hoseth et al., 2016)	PANSS=45 PANSS=58	Association found in all groups	32 30 35		SCZ =109 BD=117 HC=236	↑sTNF-R1	↓VM ↓Logical MEM
CRP	**D-KEFS:TMT, CWI, LF**	(Joseph et al., 2015)	SAPS-4,3 SANS-7,2	No association Stable outpatients	49,4±10,8 50,2±11,5	23,6	SCZ=65 SA=23 HC=71		
CRP	**TMT A/B, Stroop, CF, SG, DSC**	(Micoulaud-Franchi et al., 2015)	PANSS=68,46		33,74±9,46	12,18	SCZ=55	↑CRP	↓SG ↓stroop
IL2	**NP, VL, VF,WM, SS, DS, EF, InhInt**	(Asevedo et al., 2014)	PANSS=61,38±14,29	SZ ↓ IL-2 Few cognitive deficits found2015	33,17±9,73 34,65±10,64	11,8	SCZ=29 HC=26	↑IL2	↑DS, NVI
IL2	**PANSSc**	(Tan et al., 2015)	PANSS=77±19,9	↑IL-2 in chronic SCZ Mean age of onset 28	45,9±6,3 45,2±7,8		SCZ=160 HC=60	↑IL2	↓PANSSc
IL2, IL6, IL8 TNF	**PANSS cognitive factor**	(Zhang et al., 2016b)	PANSS=73,5±17,2	Chronic SCZ : ↓ ↑ BDNF,TNF- α, higher IL-2, IL-6, IL-8 correlation between BDNF, IL-2, IL-8	47,5±4,4 47,7±4,5	23,2	SCZ=92 HC=60	↓BDNF + ↓TNF	↓PANSSc
IL10	**PANSSc**	(Xiu et al., 2014)	PANSS=	SCZ cor ↓ IL-10 IL-10 InCor PANSSn FEDN	25,8±9,4 28,8±8,4	23,4	SCZ=128 HC=62	↑IL10	↓PANSSc
IL-10 IL10 -592 A/C PP	**RBANS**	(Xiu et al., 2016)	PANSS=72,5	FEDN Assn linked to A allele and FEDN, No assn in HC Genes most co-expressed with IL10 were associated with SVT Age of onset 25,1	26,4±9,1 27,9±11,8		SCZ=256 HC=540 Brain sample= 577	↑IL10	↑RBANS, attn., lang
IL18	**RBANS**	(Wu et al., 2016)	PANSS=59,8±15,7	↑IL18 in SCZ	46,2±11,2 45,4±9,3	21,5	SCZ=70 HC=75	↑IL18	↑RBANS total ↑Attn ↑i&dMem
IL-1 β mRNA	**Verbal fluency**	(Fillman et al., 2015)	PANSS=63,2±19,5	↑ IL-1 β mRNA in SCZ	33,6±2-40 32,5±22-48	11,7	SCZ/SA=43 HC=43	IL-1β mRNA	↓VF
IL18	**RBANS**	(Zhang et al., 2013)	PANSS=82,4±17,4	FEDN RBANS ↓ SCZ Age of onset 26,5	29,2±9,6 28,7±9,1		SCZ=77 HC=75	↑IL18	↓VSCd in patients
IL-1Ra sTNF-R1 sCD40L IL-6 vWF CRP	**Wechsler Abbreviated Scale of Intelligence (WASI)**	(Hope et al., 2015)	BD PANSS=60 YMRS=5,5 IDS=16 HC PANSS=45 YMRS=2,9 IDS=5,6	Correlated to cognition in total sample:sTNFR1, IL1RA, sCD40L	36±10 33±10 36±12	5±7	SCZ=121 BD=111 HC=241	↑IL1Ra sTNF-R1 sTNF-R1	↓General CGN

Chapter 3.2 : Inflammation and cognition in bipolar disorder

Bipolar disorder is associated with a pro-inflammatory status. As in schizophrenia, inflammation has been observed in BD. Recent reviews examining the association of inflammation and cognition in bipolar disorder. Bauer and colleagues found 10 studies showing that increased levels of peripheral inflammatory cytokines, oxidative stress or BDNF were correlated with reduced cognition (Bauer et al., 2014). A subsequent investigation identified 8 studies involving 555 individuals with BD; YKL40, IL-6, sCD40L, IL-1Ra, hsCRP and TNF-α levels were inversely correlated with cognitive performance (Rosenblat et al., 2015). We were able to find 6 studies conducted over the past 10 years in which at least one cognitive measure and one inflammatory marker were captured. In all samples of bipolar disorder, increased concentrations of inflammatory markers were associated with reduced cognitive performance. In most cases bipolar patients were euthymic.

The association noted between inflammation and cognitive function may indicate a direct relationship but may also be the result of influences which affect both dimensions (Depp et al., 2016).

Rolstad and colleagues measured inflammatory markers (MCP-1, sCD14, YKL-40) in the CSF of euthymic individuals with bipolar disorder; only YKL-40 influenced cognition, explaining 42,8% of the variance of executive function (Rolstad et al., 2015).

Table IV: Inflammation and cognition in bipolar disorder

Inflammatory cytokines	Cognitive test	Citation	Severity	Note	Age	Illness duration	N		
TNF-∝ sTNFR2 sTNFR1	MMSE, FAB	(Barbosa et al., 2012)	YMRS=1,08±1,53 HAMD=1,52±1,64		50,88±9,11 48,04±7,08	27,88±11,8	BDI=25 HC=25	↑TNFa ↑sTNFR2	↑inhibitory control ↓motor programming
TNF	RBANS, TMTA, WAISi, LNS	(Dickerson et al., 2013)	YMRS=14±9,2 HAMD=22,3±10,7	Age of onset 16,1	36,3±13,4		BDIm=29 BDId=41 BDIx=23 BDII=14	↑CRP	↓RBANS total, MEMi, ATTN, LANG, TMTA
TNF	RAVLT NPB WCST	(Doganavsargil-Baysal et al., 2013)	Euthymic		39,46±11,62 38,33±10,8	12,48±8,63	BDI=54 HC=18	↑TNFa	↓RAVLTd
IL1ra, IL6 sTNF-R1, CRP	WAIS, LM, I/DR, CVLT, DFR	(Hoseth et al., 2016)	PANSS=58±21 PANSS=45±11	Association found in all groups	32 30 35		SCZ =109 BD=117 HC=236	↑sTNF-R1	↓VM Learning/ recall
IL-1Ra, sTNF-R1 OPG, vWF , CRP IL6, CD40L	WASI	(Hope et al., 2015)	BD PANSS=60 YMRS=5,5 IDS=16 HC PANSS=45 YMRS=2,9 IDS=5,6	Correlated to cognition in total sample:sTNFR1, IL1RA, sCD40L	36 33 36	5±7	SCZ=121 BD=111 HC=241	↑IL1Ra, sCD40L sTNF-R1	↓Genral CGN
IL-6	CVLT WM Verbal ability, WAIS III	(Hamdani et al., 2015)	YMRS=4,73 MADRS=9,03	Euthymic BD Among deteriorated patients the IL-6 mRNA expression was twice greater	46,1±13 38,1±15,2	18,24±13,1	BD=42 HC=36	↑IL-6 mRNA in those + T. Gondi	↑Cognitive deterioration index

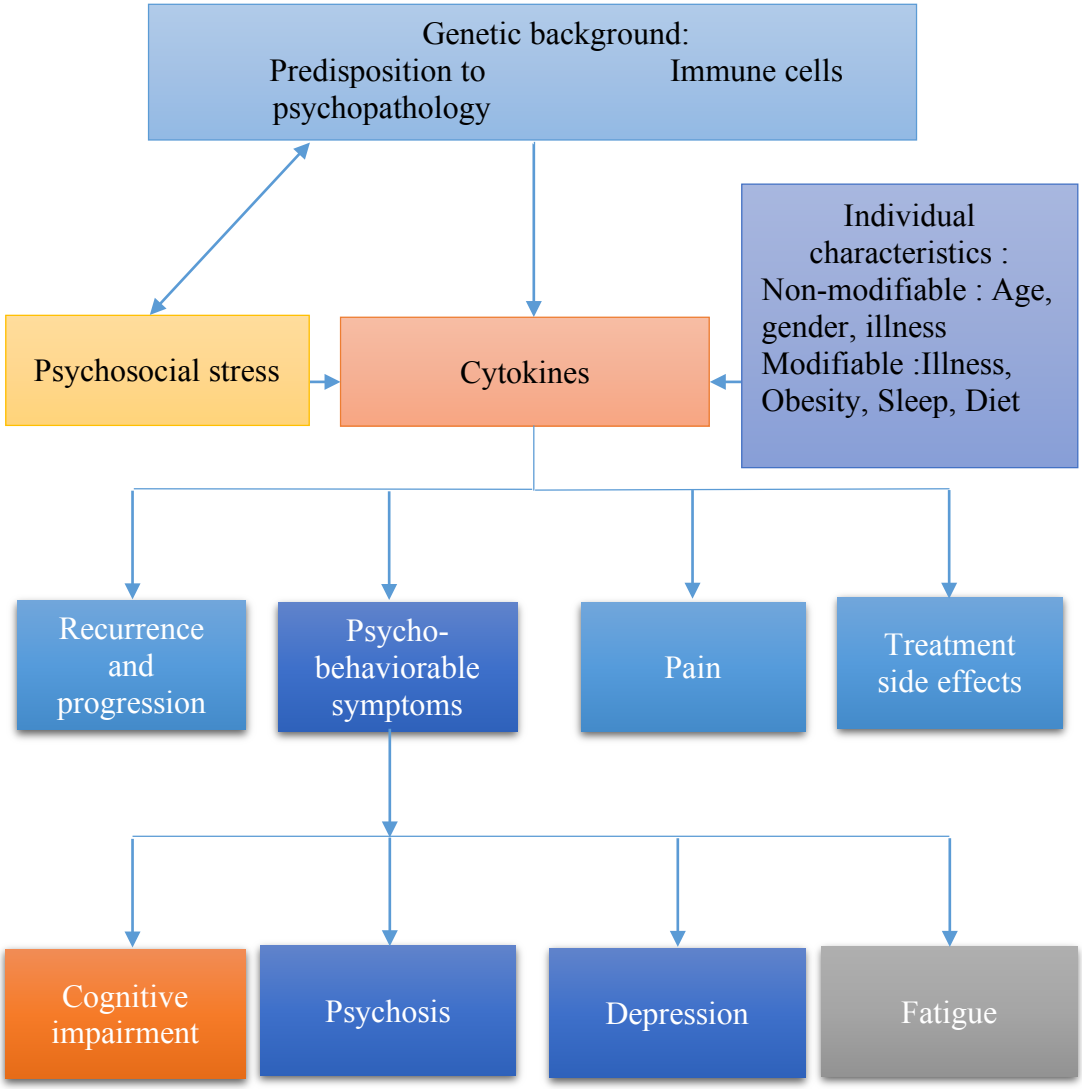
Chapter 3.3 : Inflammation and cognition in major depression

Major depression like bipolar disorder and schizophrenia is characterised by cognitive dysfunction. This is so much the case that difficulties in concentration are included in the diagnostic criteria of depression. Accumulating evidence implicates inflammatory processes and oxidative and nitrosative stress in the pathology of major depression (Galecki et al., 2015; Talarowska et al., 2014) and in particular with the neurodegenerative processes which characterise it (Carvalho et al., 2014; Liu et al., 2014a). This association is more evident in clinically defined samples (Howren et al., 2009). Our review of the last decade of publications regarding inflammation, cognition and major depression identified 5 studies with at least one measure of inflammatory cytokines and one measure of cognition.

Table V: Cognition and inflammation in major depression

Cognitive test	Inflammatory marker	Citation	Severity	Note	Age	Illness duration	N		
CPT, FTT, WCST	CRP	(Chang et al., 2012)	HAMD : 9,2±8,4	Rx free ↑CRP after 6 wks ven/pzc Bl CRP : corr FTT before/after, WCST after Rx	38,8±12,4		149	↑CRP	↓FTT ↓WCST
Multiple	hsCRP IL6	(Krogh et al., 2014)	HAMD: 18,9±3,9 0,9±1,3	3 mo exercise or control gp ↑IL-6, hsCRP in MDD but not after adjustment for lifestyle	41,6±11,5 40,3±13,1		112	MD :↑IL6 ↑CRP All : ↓IL6	↑Serial 7s ↓TMT-A ↓DF ↓VF
CVLT VR, ROCD, MTXR, Stroop, WCST, DSST, TMTA/B, MMSE	CRP IL6	(Elderkin-Thompson et al., 2012)	HAMD= 18,7±2,9	IL-6 levels not different in MD and HC	69,7±7,9 69,2±7,1	6,5 yrs	MD:45 HC:42	↑IL6 CRP	↓encoding, recall no association
Logical Memory Scale	IL6 TNFa	(Grassi-Oliveira et al., 2011)	BDI= 28,5±11,26	Women with Recurrent MDD	39,2±	11,5±5,8	MD:30	↑IL6	↓Immediate, delayed verbal recall
TMTA DF VF	CRP IL-6	(Krogh et al., 2014)		3 month exercise intervention or exercise control group ↗IL-6, hsCRP in MDD, NS after adjustment for lifestyle At 3months : IL-6, hsCRP unchanged			MD:112 HC:57	↑IL6 ↑CRP ↓IL-6 ↓CRP	↑serial seven ↓TMTA, ↓VF ↑TMTA

Figure III : Inflammation, psychiatric disorders, and cognitive impairment



Modified from (Seruga et al., 2008)

Chapter 4: Personal contribution

In view of the importance of cognition to the assessment of individuals suffering with psychiatric disorders, development of a personalized treatment plan, and the clinical course of illness, our group undertook the validation of a French version of the Screen for Cognitive Impairment in Psychiatry. In the second phase of the study the SCIP was administered in the clinical setting in order to assess the feasibility of using it routinely in an unselected population of patients. The results of the administration of the SCIP in a group with ADHD and another group with MDD are presented. Although the scope of this study was narrow, its results provide important information. The findings in the MDD group highlight the link between cognition and function in MDD. Despite the intuitive conviction that this must be the case, there exists very little data supporting this link in MDD. The results found in the ADHD population are equally pertinent in that they show that cognitive deficits of significant magnitude can be demonstrated in a clinical population with this condition. Once more a link was found between cognitive impairment and function. The comparison of assessment of cognitive performance through actual testing and through a self-report scale underscores the discordance between these two methods of evaluation and the importance of not relying on self-report alone. This study generated four manuscripts, one of which is published and 3 of which have been submitted. These are presented below in chapters 4.1 through 4.4.

In the exploration of factors which may modify cognition, inflammation is an obvious candidate. A literature review of the effect of antipsychotics on inflammatory markers in schizophrenia is presented in chapter 4.5. It demonstrates that antipsychotics increase sIL-2R and reduce IL-1β and IFN-γ. This review contributes to the understanding of the mechanisms of action of antipsychotics, as well as to the nature of inflammation in schizophrenia.

We are in the process of collecting data regarding the relationship of cognition, inflammation and cerebral connectivity which will continue the thrust of this work.

Chapter 4.1: Article 1 - Validation of a french version of the Screen for cognitive impairment in psychiatry

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Reprint

French Validation of the Screen for Cognitive Impairment in Psychiatry (SCIP-F)

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Abstract

Background: Measuring cognition in clinical practice is clearly essential to the appropriate characterisation of patients' clinical status and to the development of a personalised care plan. The Screen for Cognitive Impairment in Psychiatry (SCIP) has been developed in order to provide a brief and accessible tool allowing the evaluation of cognitive function in psychiatric conditions.

Objective: We present a validation of a French version of the SCIP. *Method*: Translation from English into French is carried out using the accepted back-translation method. Seventy-two healthy volunteers are characterised by demographic questionnaires and a neuropsychological battery. The French version of the SCIP is then administered on two separate occasions separated by at least a one-week interval.

Results: High internal consistencies as well as strong correlations with comparable neuropsychological tests are obtained. A normalised Cronbach's $\alpha = 0.66$ is obtained.

Conclusions: The French version of the SCIP (SCIP-F) yields results comparable to the English version. The SCIP represents an essential tool for the preliminary evaluation of cognition. Its characteristics, brevity and the lack of need for a technological platform, allow for its integration into clinical practice. Further testing of SCIP-F in various psychiatric conditions will yield valuable information on its potential in clinical settings.

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Keywords

Screen for Cognitive Impairment in Psychiatry, Cognitive Deficits, Neuropsychological Assessment, Cognitive Screening, Patient-Centered Approaches

1. Introduction

The notion that cognitive functions contribute to functional outcomes has become increasingly apparent in various psychiatric disorders. Impaired functional outcomes are predicted by decreased cognitive performance in schizophrenia(Milev et al., 2005; Velligan et al., 1997), bipolar disorder (Martinez-Aran et al., 2002; Martinez-Aran et al., 2007; Zarate et al., 2000), attention deficit disorder (Biederman et al., 2004; Thorell, 2007), and alzheimer disease (Boyle et al., 2003). Cognitive impairment has also been associated with decreased treatment adherence in psychotic disorders (Vieta, 2005) and non-psychiatric illnesses (Alosco et al., 2012). Furthermore, cognitive deficits are associated with reductions in work performance (Bell and Bryson, 2001), and daily activities (Cameron et al., 2010; Pereira et al., 2008), as well as with deterioration of self-care in medical illness (Cameron et al., 2010). Various health practitioners and clinicians rely on the assessment of cognitive functioning to improve diagnostic accuracy, to assess the evolution of disorders, and, sometimes, to measure the response to medication.

Cognitive functioning is classically assessed via comprehensive neuropsychological testing. This mode of assessment remains the gold standard against which other evaluations of cognition are measured. Unfortunately, access to traditional neuropsychological testing is limited by a number of constraints: the availability of neuro- psychologists, the time required for testing, as well as the associated costs. As new data reveals the importance of measuring cognitive functioning in psychiatric disorders, researchers have explored ways in which to screen for putative cognitive deficits, which may guide decision-making as to the necessity for classical methods of assessment of cognition. A plethora of computer assisted neuropsychological batteries has been developed (Fray and Robbins, 1996; Pietrzak et al., 2009) ; however these require expensive equipment and are usually administered by staff in a dedicated space. As a result, computerized testing has not yet been routinely incorporated in clinical practice.

A major challenge has been the development of brief, easily mastered tests that can be used as screening tools to determine the need for more in-depth

neuropsychological assessment, can be administered by clinicians from various backgrounds, are inexpensive, and can be administered in different clinical settings. Examples of such tests currently used in clinical practice are the Mini-Mental State Examination (MMSE; (Folstein et al., 1975)) and the Montreal Cognitive Assessment (MoCA; (Nasreddine et al., 2005)). These tests are used primarily to screen for severe cognitive deficits, and do not have the sensitivity to measure subtle changes found in schizophrenia or mood disorder (Alpert et al., 1995). Other screening tests, which have been developed, are the Neurobehavioral Cognitive Status Examination (NCSE; (Kiernan, 1995)), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; (Randolph et al., 1998)), and the Brief Assessment of Cognition in Schizophrenia (BACS; (Keefe et al., 2004)). These screening tools have been developed for specific populations such as the elderly and patients afflicted with schizophrenia and may not be applicable for the general psychiatric population. More importantly, although nominally brief, the RBANS and the BACS require 40 minutes or more to administer.

In 2005, Scot Purdon developed the Screen for Cognitive Impairment in Psychiatry (SCIP), an assessment tool that possessed a number of advantages with respect to other instruments (Purdon, 2005a). This test is intended for administration by a clinician with a minimum of training, and requires, on average, no more than 15 minutes to complete. Because it is a simple paper and pencil test, it is inexpensive and can be used in different settings, including at the patient's bedside. Three different versions of the SCIP have been developed (Purdon, 2005a), allowing for retesting and thus for following the impact of illness or medication on cognitive function. These features have made this test an instrument of interest for clinicians who wish to screen for potential cognitive deficits and direct their patients to the appropriate resources. German (Czekaj et al., 2012), Spanish (Pino et al., 2008), and Japanese (Hirabayashi et al., 2006) versions have already been validated. The Spanish version has been tested in psychosis and schizophrenia (Cuesta et al., 2011; Nieto et al., 2012), and in bipolar disorder (Guilera et al., 2009).

A cognitive test should possess several qualities (Bland and Altman, 2002). It should be valid, providing results that correlate with classical neuropsychological testing. It should be reliable, offering similar results for the same subject. The degree of practice effect, that is the improvement of result in the same individual because of prior exposure, should be minimal. The original English version of the SCIP possesses these characteristics. It shows no main effect of sex; although a difference was found on one of the five subtests in one of the versions of the SCIP. An effect of practice is observed on the working memory, verbal fluency and visuomotor subtests in the original English version. Globally, the SCIP does not replace a complete neuropsychological battery, but can be a useful tool for screening cognitive impairment in psychiatric populations and following therapeutic effects.

Objectives

The need for a screen of cognitive function in French has led us to develop a validated French version of the SCIP. We report in this paper the results of this validation.

2. Material and Methods

2.1. Participants

This study was approved by the Institutional Review Board of the Institut Universitaire en Santé Mentale de Montréal (IUSMM) following established guidelines. All participants provided written informed consent after study procedures were explained. The work described was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Seventy-two individuals with a college level education who were fluent in French participated in this study. Inclusion criteria included the capacity to give informed consent and the absence of psychiatric, neurological illness, or other conditions which could be expected to affect cognitive function. Participants were recruited through posters displayed in a local university, the IUSMM and the website of the

IUSMM. Participants who could not attend two testing sessions of the SCIP were also excluded.

2.2. Instrument

2.2.1. Screen for Cognitive Impairment in Psychiatry

The SCIP is composed of five subscales that assess short and long term verbal learning memory, working memory, verbal fluency, and psychomotor velocity (Purdon, 2005a). Similar subscales exist in validated neuropsychological tests. Three alternative versions of the SCIP have been developed.

The verbal learning and delayed recall subtest (Verbal Learning Test, VLT) consists of a list of ten words which is read three times to the participant, who is asked to repeat the words in any order following each reading (Verbal Learning Test-Immediate Recall, VLT-I). After five minutes, the subject is once again asked to recall as many of the words in the list as possible (Verbal Learning Test-Delayed Recall, VLT-D) without it being read beforehand. The three different versions of this subtest include different series of words. The score of the VLT-I and VLT-D is equivalent to the number of words remembered during every trial. The verbal learning and de layed recall subscale is based on the Rey Auditory Verbal Learning Test (RAVLT; (Rey, 1964)).

The working memory subscale using triads of consonants is similar to the Brown-Peterson Consonant Tri- gram test (CTT; (Brown, 1958)). It consists of a sequence of 3 consonants that are read to the participant, followed by a given number. Before repeating the three consonants, the participant must count backwards from the given number for a specific period of time of 0, 3, 9, or 18 seconds. This subscale assesses working memory using an interference task, and is scored based on the number of consonants remembered. Twenty-four randomly distributed triads of consonants have been included in the SCIP, 8 for every version of the SCIP. The first 2 triads have no delay or interference (the subject has to repeat the sequence of consonants immediately and without performing any interfering task), while the remaining 6

have been divided into pairs, each of which having a differing delay of 3, 9, or 18 seconds.

The Verbal Fluency Test (VFT) consists of generating as many words as possible that start with a given letter, during a 30 seconds lapse of time. Each version of the SCIP has 2 specific letters and the score is based on the total number of words produced. This task is similar to the Controlled Oral Word Association Test (COWAT; (Peterson and Peterson, 1959)). The Information Processing Speed (Visuomotor Tracking Test, VMT) subtest requires the participant to write the Morse code version of a series of letters within 1 minute. This task requires copying the Morse characters in blank spaces as fast as possible. The score is based on the number of accurate codes generated.

2.2.2. Psychometric Assessment

To estimate intellectual functioning level, participants completed the four subtests (Blocs, Matrix, Similarities, and Vocabulary) of the Wechsler Abbreviated Scale for Intelligence (WASI; (Wechsler, 1997)). Some subtests from the Wechsler Adult Intelligence Scale (Wechsler, 1999) were administered including those contributing to the Speed Processing Index (SPI) (Digit-Symbol Coding and Symbol Search) and of the Working Memory Index (WMI) (Digit Span and Letter-Number Sequencing) in order to examine their relationship with the VMT and WMT subtests of the SCIP, respectively. The Verbal Fluency subtest from the Delis-Kaplan Executive Functions System (D-KEFS; (Delis et al., 2001)), which is very similar to the VFT in its administration, was used. Finally, participants completed the California Verbal Learning Test (CVLT; (Delis et al., 2000)), a test assessing verbal learning and memory in which a wordlist is read five times and participants have to recall immediately after each reading as many words as they can. They must repeat the list in a free recall then a cued recall, right after the five readings and 20 to 30 minutes afterwards.

2.2.3. French Version of the Screen for Cognitive Impairment in Psychiatry

The SCIP was translated to French following the inverse translation design. The scale and instructions were translated by a bilingual psychiatrist (S. V. Tourjman) from Quebec, Canada, whose mother tongue is English and by a neuropsychologist (Josée Gagné) whose mother tongue is French. A first back translation was carried out by a bilingual research assistant (Mara Du Bow) whose mother tongue is English. Discrepancies were scarce and addressed by consensus. A second back translation was carried out by a bilingual psychiatrist from Quebec (René Desautels), whose mother tongue is French. Both individuals involved in the back translation were blind to the original English version. The final French translation of the 3 versions of the SCIP was compared to the original English versions, and no differences in the meaning of the different items or the subtests instructions have been found. All the words employed for VLT were literally translated. For the VFT the letter "W" was replaced by the letter V, since the letter W is not employed as often in French as in English. The number of words generated from the letters in each of the French versions was comparable to the other French versions as well as to the English version.

2.3. Testing Procedure

Participants completed questionnaires in order to capture demographic data. A traditional neuropsychological battery was administered. The neuropsychological tests used were selected by two of the authors (MB, MNC) who are neuropsychologists and researchers in the field of cognitive development. Participants were tested with the SCIP on two occasions separated by at least a one-week interval. The order of testing was random and included all six possible permutations of the different versions of the SCIP (version 1:2, 1:3, 2:1, 2:3, 3:1, 3:2). Evaluations were administered by a psychology undergraduate student and a clinical assistant with training as a physician after observing several evaluations administered by a neuropsychologist and then being supervised until judged autonomous.

2.4. Statistical Analyses

Data analyses were performed using the Statistical Package for the Social Sciences Version 9.3 (SAS Institute Inc., Cary, NC). The three alternative forms of the SCIP were analysed with regards to consistency, practice effects, and comparability with results on the classical neuropsychological battery. The three versions of the SCIP were compared considering only those that were passed during the first assessment. Gender differences were analyzed with multivariate mixed analyses of variance. Univariate analyses of variance were performed when main effects emerged as being significant. Cronbach's α coefficient was calculated in order to determine the internal consistency between the subtests. Test-retest reliability was assessed calculating the intra-class correlation coefficient (ICC) between the first and the second administration of equivalent SCIP versions. To verify the internal validity of the SCIP, we performed a factor analysis, using the principal component analysis method with a varimax rotation. Finally, Pearson's correlation coefficient between the SCIP total score and the global *z* score from the neuropsychological battery was calculated. For all analyses, the statistical threshold was set at $p < 0.05$.

3. Results

All participants were able to complete the SCIP. Demographic data are presented in

Table 1. The average age was 26 and spanned from 18 to 48 years of age. Most of the sample had a college or more advanced diploma and the majority were students.

Table 1. Demographics.

Descriptive	
Age, M (Range)	26 (18 - 48)
Years of schooling, M (Range)	17 (12 - 27)
Sex (Men/Women), %	35/37
Ethnicity, White, %	76.4
Right-handed, %	82.86
Single, %	81.94
Employed, %	22.2
Student, %	77.8
Education High school diploma, %	8.3
College, %	50
Undergraduate degree, %	34.7
Graduate degree, %	6.9

3.1. Screen for Cognitive Impairment in Psychiatry Versions

No significant differences in the subjects'global performance were found between the three versions of the SCIP ($p > 0.05$).

3.2. Sex Differences

Results yielded interactions between sex and SCIP version ($p < 0.05$), showing a significant difference between ratings for the version 1, where women scored higher than men. No differences were found for the versions 2 and 3 of the SCIP between men and women. Considering sex as separate groups, men scored lower on the version 1 compared to versions 2 and 3 of the SCIP, which were equivalent. Women showed no significant differences between the 3 versions of the SCIP.

When gender and subtests were evaluated, it was found that for the subtest VLT-I, men scored similarly for the versions 2 and 3, but lower for the version 1. Men also scored lower than women for VLT-I. For VLT-D, men scored lower for version 3 compared to versions 1 and 2, where they scored similarly. Men also scored lower than women on this subtest. WMT showed no effect of gender or version, so this subtest can be considered as equivalent between the 3 versions and for both genders. For VFT, an effect of version was observed where participants of both genders scored higher in the version 2, but no differences between the sexes were observed. VMT was higher for women in all the different versions, but no effect of version was detected.

3.3. Practice Effect

No effect of practice for the subtests VLT-I ($F_{(1,59)} = 0.02$, $p = 0.9$), VLT-D ($F_{(1,6)} = 1.01$, $p = 0.3$), and VFT ($F_{(1,6)} = 1.44$, $p = 0.2$) were observed. By contrast, significant differences for WMT ($F_{(1,6)} = 14.50$, $p < 0.01$) and VMT ($F_{(1,6)} = 9.54$, $p < 0.01$) were found, where higher scores were observed in favour of the versions administered at time 2.

3.4. Test-Retest Reliability

Test retest reliability between the first and the second administration of the SCIP was assessed with the calculation of the ICCs core, which yielded a high score. The ICCs ranged from 0 to 6 for the WMT subscale to 0 to 8 to the VMT subscale. The sum of the subscale scores achieved an ICC of 0.9. The ICCs also showed high scores for VLT-I (ICC = 0.7), WMT and VLT-D (ICC = 0.8), VMT (ICC = 0.8) and VFT (ICC = 0.7).

3.5. Internal Coherence

Using a varimax rotation analysis of the main components, 2 factors were obtained for version 1 and 2, with 4 (VLT-I, VLT-D, VMT, WMT) and 3 (VLT-I, VLT-D,

VMT) subtests respectively loading heavily on factor 1. Only one factor comprising of all SCIP subtests was found for version 3. Taking all versions as a whole all subtests load onto one factor suggesting coherence between them.

3.6. Internal Consistency

Results yielded Cronbach's α coefficients of 0.44 for VLT-I, 0.46 for VLT-D, 0.50 for VMT, 0.71 for VFT, and 0.50 for WMT. A weak correlation between the total scores and VFT Cronbach's α coefficient was found, and the rejection of this subtest, increased the Cronbach's α coefficient to 0.73. Normalised α's yielded a score of 0.66.

3.7. Standardized Scores

Z scores were calculated by dividing the difference between the obtained scores and the expected score by the standard deviation. Mean Z scores for the SCIP were not different from the expected score of zero implying that the sample tested was comparable to the original normative data for the SCIP (**Table 2**).

3.8. Correlations with Neuropsychological Testing

The SCIP was correlated with scores on traditional neuropsychological tests. As expected, the three versions of the SCIP correlated with most of the neuropsychological tests administered, such as subtests of the Wechsler Adult Intelligence Scale (WAIS-III), the California Verbal Learning Test and Verbal fluency of the Delis-Kap- lan Executive Functions System, (see **Table 3**), since the SCIP score consists of the sum of the same functions tested by these tests. Total score for the SCIP version 1 was significantly correlated to all but the following tests of the neuropsychological battery: sequences, symbols, list b. The SCIP version 2 total score was related to all but the recognition false positives score of the

neuropsychological battery. Finally, the total score of the SCIP 3 was related to all but the arithmetic and similarities subtest and to the working memory subscale.

3.9. Validity

Next, the correlations of interest are reported in **Table 4** showing how each score of the SCIP correlated with existing neuropsychological tests that measure the same abilities. As expected, in all three versions of the SCIP, VLT-I correlated with Recall 5 and Immediate Free Recall of the CVLT and VLT-D correlated with Delayed Free Recall and Delayed Cues Recall assessing learning abilities of a list of words and its retention after a delayed recall.

WMT is supposed to be a measure of working memory and indeed all versions correlated with Digit Span of the WAIS-III but surprisingly version 1 did not correlate with Letter-Number Sequence, while versions 2 and 3 did. However, all 3 versions correlated with the Working Memory Index of the WAIS-III. VFT is supposed to assess verbal fluency abilities. Indeed, it correlated with all three version of the Verbal Fluency test from the D-KEFS. Finally, all three versions of VMT, which is supposed to assess visuo-motor processing speed, correlated with Digit Symbol Coding, and with PSI, though only version 3 of VLT correlated with Symbol Search subtest. No other tasks of the SCIP were correlated with some of the neuropsychological subtests, which is not surprising since only some of these functions relate to each other.

Table 2. Standardized scores for the French validation of the screen for cognitive impairment in psychiatry (SCIP-F).

	Mean	SD	P^*
SCIP 1	−0.07	0.8	0.6
SCIP 2	0.08	0.7	0.48
SCIP 3	0.03	0.7	0.8

*Z score is thus not different from expected score of $Z = 0$.

Table 3. Correlations between French validation of the screen for cognitive impairment in psychiatry (SCIP-F) standardized scores and neuropsychological battery results.

	SCIP-F 1	SCIP-F 2	SCIP-F 3
Block Design	0.565***	0.312*	0.319*
Digit Span	0.412**	0.540***	0.367*
Vocabulary	0.446***	0.610***	0.413**
Matrix Reasoning	0.505***	0.361*	0.388*
Letter-Number Sequencing	0.123	0.434**	0.368*
Digit-Symbol Coding	0.371*	0.525***	0.401**
Arithmetic	0.482**	0.402**	0.251
Similarities	0.407*	0.292†	0.272†
Information	0.542***	0.375*	0.315*
Symbol Search	0.289*	0.348*	0.513***
Performance IQ	.640***	0.500***	0.504***
Verbal IQ	0.486**	0.527***	0.382*
Working Memory Index	0.351*	0.456**	0.292†
Processing Speed index	0.550***	0.561***	0.517***
Verbal Fluency	0.446**	0.518***	0.419**
Trial 5 (California Verbal Learning Test)	0.585***	0.656***	0.703***
Trial B (California Verbal Learning Test)	0.371*	0.297†	0.445**
Immediate Free Recall dv	0.612***	0.605***	0.606***
Immediate Cued Recall dv	0.576***	0.532***	0.620***
Delayed Free Recall dv	0.676***	0.603***	0.567***
Delayed Cued Recall dv	0.558***	0.586***	0.579***
Recognition Hits dv	0.290†	0.482**	0.4661**
Recognition False Alarm dv	−0.327*	−0.370*	−0.382*
Recognition False Positive dv	0.327*	0.370*	0.382*

Note: †$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.00$.

4. Discussion

The present study successfully validated a French version of the Screen for Cognitive Impairment in Psychiatry (SCIP-F). The *Z* scores of the SCIP-F are comparable to the scores obtained in the original English versions of the SCIP despite a greater heterogeneity in the sample confirming comparability of the French and English versions of the SCIP. The main advantages of the SCIP compared to traditional neuropsychological batteries are the ease and rapidity of administration of the test (around 15 minutes), and the requirement of inexpensive materials (pencil, paper and clock) that can be used in different settings without special requirements. The

feasibility of using the SCIP-F in clinical settings is currently being evaluated in several clinical populations.

The validity of the SCIP-F is confirmed by the correlation of the subtests of the SCIP-F with related tasks in the neuropsychological battery. Thus the verbal learning tests are correlated with the CVLT, which is a validated test to assess verbal learning and memory. The WMT which tests working memory is correlated with the working memory index of the WAIS-III and the subtest of Digit Span, but version 1 did not correlate with Letter- Number Sequence though version 2 and 3 did. The verbal fluency task of the SCIP-F correlates with the verbal fluency subtest of the D-KEFS battery. Finally the visuomotor task is correlated with the Coding subtest of the WAIS-III which tests the same function, that is mainly visuo-motor processing speed. This task is also correlated with the speed processing index on all versions, and with the symbol search task on version 3. Therefore, the SCIP-F yields good validity since all abilities that are supposed to be assessed by it correlate with well validated neuropsychological tests in their French version.

Table 4. Correlations matrix for the French validation of the screen for cognitive impairment in psychiatry (SCIP-F) and the neuropsychological battery.

	1 VLT1	1 WMT	1 VFT	1 VLT2	1 VMT	2 VLT1	2 WMT	2 VFT	2 VLT2	2 VMT	3 VLT1	3 WMT	3 VFT	3 VLT2	3 VMT
Block Design	0.434**	0.378*	0.179	0.443**	0.398*	0.233	0.081	0.002	0.343*	0.386*	0.080	−0.017	0.323*	0.237	0.436**
Digit Span	0.360*	0.474**	0.170	0.182	0.148	0.263†	0.466	0.477**	0.221	0.352*	0.205	0.584***	0.204	0.118	0.207
Vocabulary	0.508**	0.491**	−0.037	0.263	0.206	0.540***	0.375*	0.289†	0.477**	0.315*	0.304	0.196	0.268	0.354•	0.284†
Matrix Reasoning	0.311†	0.227	0.201	0.556***	0.348*	0.177	0.421**	0.218	0.139	0.218	0.255	0.293†	0.277†	0.348*	0.180
Letter-Number Sequencing	0.144	0.219	−0.037	−0.002	0.066	0.180	0.578**	0.198	0.178	0.259†	0.248	0.506***	0.100	0.207	0.241
Digit-Symbol Coding	0.168	0.288†	0.112	0.069	0.552***	0.275†	0.267†	0.158	0.376*	0.705***	0.125	0.307	0.118	0.160	0.643***
Arithmetic	0.370*	0.271	0.148	0.335*	0.437**	0.109	0.291†	0.502***	0.193	0.211	0.072	0.304†	0.193	0.103	0.218
Similarities	0.337*	0.113	0.206	0.293†	0.379*	0.200	0.149	0.144	0.307*	0.131	0.247	0.054	0.108	0.336•	0.167
Information	0.371*	0.365*	0.308†	0.370*	0.314†	0.419**	0.259†	0.162	0.305*	0.070	0.211	0.140	0.293†	0.323•	0.129
Symbol Search	0.351*	0.147	0.122	0.300†	0.028	0.178	0.184	0.376*	0.158	0.273†	0.315*	0.370*	0.120	0.317*	0.610***
Performance IQ	0.444**	0.383*	0.225	0.580***	0.445**	0.378	0.219	0.116	0.472**	0.469**	0.315*	0.063	0.448**	0.461**	0.408**
Verbal IQ	0.475	0.390*	0.094	0.288†	0.325*	0.417**	0.332*	0.267†	0.448**	0.239	0.319*	0.117	0.213	0.407**	0.236
Working Memory Index	0.302†	0.321*	0.061	0.170	0.227†	0.104	0.518***	0.372*	0.189	0.284†	0.190	0.466**	0.056	0.128	0.201
Processing Speed Index	0.331*	0.383*	0.267	0.264	0.537***	0.362•	0.247	0.211	0.386*	0.708***	0.243	0.370*	0.298†	0.275†	0.579***
Verbal Fluency	0.413**	0.241	0.472**	0.171	0.178	0.260†	0.298†	0.444**	0.370*	0.315	0.198	0.082	0.602***	0.266†	0.283†
Recall 5 (CVLT)	0.565***	0.329*	0.200	0.542***	0.269	0.479**	0.581***	0.072	0.596***	0.364*	0.691***	0.182	0.332*	0.809***	0.346*
List B (CVLT)	0.455**	0.135	0.120	0.388*	0.118	0.271†	0.259†	−0.003	0.348*	0.0395	0.510***	0.114	0.160	0.429†	0.262†
Immediate Free Recall dv	0.420**	0.351*	0.368*	0.533***	0.325*	0.455**	0.439**	0.004	0.601***	0.453**	0.518***	0.103	0.393*	0.700***	0.325*
Immediate cued recall dv	0.417**	0.248	0.434**	0.555***	0.238	0.267†	0.471**	0.073	0.504***	0.376	0.556***	0.176	0.410**	0.692***	0.268†
Delayed Free Recall dv	0.508**	0.374*	0.386*	0.591***	0.347*	0.436	0.468**	−0.016	0.582***	0.478**	0.422**	0.132	0.346*	0.624***	0.386*
Delayed Cued Recall dv	0.415**	0.243	0.469**	0.495**	0.215	0.356*	0.491***	0.025	0.605***	0.377*	0.539***	0.108	0.384*	0.669***	0.253
Recognition Hits dv	0.189	0.258	0.263	0.281†	−0.037	0.446**	0.393**	0.104	0.396**	0.219	0.436**	0.225	0.349*	0.563***	0.024
Recognition False Alarm dv	−0.179	−0.114	−0.290	−0.335*	−0.160	−0.386*	−0.058	0.114	−0.500***	−0.395**	−0.212	−0.135	−0.352*	−0.428**	−0.189
Recognition False Positive dv	0.179	0.144	0.290	0.335*	0.160	0.386*	0.058	−0.114	0.500***	0.395**	0.212	0.135	0.352*	0.428**	0.189

Note: †$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; Abbreviations: VLT: verbal learning task, WMT: nworking memory task, VFT: verbal fluency task, VMT: visuomotor task.

Internal consistency showed good correlation between total scores and the subtests VLT-I, VLT-D, WMT and VFT, and a weaker correlation to VFT. Test-retest

reliability showed a good correlation between the first and the second administrations of the SCIP-F. No practice effect was observed for VLT1, VLT2 and VFT subtests, but an improvement in the scores was obtained during the second administration for WMT and VMT, similarly to that seen in the Spanish version. Such practice effects are commonly reported in neuropsychological testing and must be taken into account in the design of studies focusing on cognition and on repeated testing in a clinical context.

4.1. Limitations and Future Directions

The SCIP does not cover important cognitive domains that are frequently affected in mental disorders. Moreover, the SCIP-F was administered by a non-psychiatrist physician rather than by psychiatrists for the English and the Spanish versions. Despite this limitation, results were comparable to the English version underscoring the ease of use of this instrument. Further research should address the relationship of performance on the SCIP to func- tional outcomes, thus further elucidating the clinical utility of this instrument.

4.2. Conclusion

The SCIP-F has the potential to be a very useful test in screening psychiatric patients for cognitive deficits, assisting clinicians in deciding who will benefit from a full neuropsychological assessment and in establishing an individualized treatment plan. It does not constitute nor can replace a complete and thorough neuropsychological exam. This study is performed by non psychiatrist professionals, so it provides information regarding the feasibility of the administration by other professionals. In conclusion, the SCIP constitutes a fast and inexpensive cognitive screening tool and current evidence supports the use of alternative forms such as our successfully validated SCIP-F.

Conflict of Interest

This study was possible as a result of a grant from +Prend soins de toi+.

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Chapter 4.2: Article 2 - Self-evaluation and objective assesment of cognition in major depression and attention deficit disorder: implications for clinical practice

SUBMITTED TO COMPREHENSIVE PSYCHIATRY

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Abstract

Introduction: One of the major challenges associated with the assessment of cognitive functioning in psychiatric populations is the choice of an evaluation tool. Access to cognitive assessment is often limited by issues of expense and by the lengthiness of the testing procedure. As a result, an interest emerged in the development of self-administered questionnaires to assess an individual's perception of their own cognitive functioning. These questionnaires could be more easily used for screening as part of a routine psychiatric consultation. However, few studies have compared the results of the novel subjective measures with established objective tests of cognitive skills, and most have focused on psychopathologies marked by major and apparent cognitive impairments.

Objective: The main goal of this study was to investigate the relationship between objective and subjective cognition in patients with major depression (MDD) and attention-deficit/hyperactivity disorder (ADHD) both associated with subtle cognitive impairments on neuropsychological testing.

Methods: First, we compared performance of patients with MDD and ADHD to that of healthy controls (HC) on objective and subjective measures of cognition. Then, we evaluated the association between objective and subjective measures of cognitive functioning in the three groups of participants.

Results: Patients with MDD and ADHD performed worse than HC on neuropsychological tests and reported more cognitive difficulties in their daily life. Only a moderate correlation was observed between objective and subjective measures of cognition in individuals with MDD and ADHD. Subjective cognitive measures were more closely correlated with functioning than objective measures.

Conclusion: These findings suggest that neuropsychological testing and self-reported scales of cognition are not interchangeable but rather give information about different constructs. The evaluation of cognitive functioning should ideally include both objective and subjective measures of cognition.

Keywords: Screen for Cognitive Impairment in Psychiatry; cognitive deficits; neuropsychological assessment; cognitive screening; major depressive disorder; attention-deficit/hyperactivity disorder

1. Introduction

Numerous neuropsychological studies have examined the role of cognition in psychopathology, revealing that most psychiatric disorders are associated with some degree of cognitive impairment. The majority of this research has focused on psychopathologies marked by prominent cognitive deficits, such as schizophrenia (Gold and Harvey, 1993; Green et al., 2004; Keefe et al., 2005). However, cognitive profiles of other psychiatric conditions associated with subtle impairments have not been well characterized. For example, some neuropsychological studies have detected mild impairments in executive functions, memory, attention and speed processing in individuals diagnosed with major depression disorder (MDD)(Beblo et al., 1999; Den Hartog et al., 2003; Fossati et al., 2002; Porter et al., 2003).

By contrast, other studies have not reported differences in cognitive performance between people with MDD and healthy controls (Berger et al., 2002; Fischer et al., 2008). Having strong comorbidity with MDD (McGough et al., 2005; Sobanski, 2006), attention-deficit/hyperactivity disorder (ADHD) is another example of a psychopathology associated with inconsistencies in neuropsychological findings, for which executive, attentional and memory deficits have been reported (Barkley, 1997; Marchetta et al., 2008; Tucha et al., 2009; Tucha et al., 2005; Walker et al., 2000), but not always replicated (Nigg et al., 2005).

Regardless of their symptom severity, cognitive deficits in patients suffering from MDD or ADHD undermine adaptive capacity and general functioning (Biederman et al., 2004; Jaeger et al., 2006; Thorell, 2007). Although this has contributed to heightened interest in cognitive measurement strategies that could be applied within clinical settings that provide treatment to individuals with MDD or ADHD, access to a highly trained clinical neuropsychologists is often limited in psychiatric settings, and comprehensive evaluations with a battery of objective tests is difficult to secure (Biederman et al., 2008; Pennington and Ozonoff, 1996). This has prompted the development and validation of questionnaires to solicit and quantify subjective perceptions of an individual's cognitive strengths and weaknesses, as well as

objective screening tools to quickly detect robust cognitive deficits associated with psychiatric disorders.

Surprisingly few studies have compared subjectively reported cognitive impairment to objectively quantified performance deficits in MDD or ADHD. The results to date have suggested that the two approaches may be assessing somewhat different constructs. One investigation of the relationship between objective and subjective measures of cognition in the elderly, for example, noted that people with MDD report more cognitive complaints compared to Healthy Controls (HC) without exhibiting a significant difference on objective cognitive measures (Fischer et al., 2008; O'Connor et al., 1990). Others, however, have demonstrated that MDD patients with subjective cognitive complaints performed worse on objective cognitive tests than MDD patients without subjective complaints (Antikainen et al., 2001; Chamelian and Feinstein, 2006).

Two published studies have directly examined associations between objective cognitive screening tools and subjective evaluations of cognition in adults diagnosed with MDD (Lahr et al., 2007; Svendsen et al., 2012). One study on 15 patients assessed before and after partial remission of symptoms of depression showed relatively weak and circumscribed correlations between subjective and objective measures, in which the former was much more severe on the first assessment and showed more robust improvement with treatment than the latter (Lahr et al., 2007). The objective tools utilized in this older report consisted of a brief ad hoc collection of neuropsychological instruments, whereas a more recent investigation (Svendsen et al., 2012) utilized a Danish translation of the Screen for Cognitive Impairment in Psychiatry (Purdon, 2005a). In a small sample of 15 patients with unipolar depression, objective deficits were apparent on the SCIP total score, and subjective deficits were apparent on the Massachucetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)(Fava et al., 2009) total score, but the SCIP was not strongly correlated with the CPFQ (Svendsen et al., 2012).

Potential explanations offered for the discrepancy between objective and subjective deficits in cognitive skills by the authors of the first study included a negatively

biased self-perception resulting in an over-statement of subjective deficits. Moreover, a potential amelioration of subjective limitations under the highly structured demands of most objective tests, or perhaps a lack of insight into one's own cognitive skills associated with MDD (Lahr et al., 2007). A negative bias was also offered as a potential explanation for the discrepancy observed in the second study, which also duplicated the more robust association between symptom measures of depression and severity of subjective deficits (Miskowiak and Carvalho, 2014; Ott et al., 2016; Svendsen et al., 2012). Regardless of the explanation, there is consensus that subjective and objective measurements are sensitive to different cognitive constructs and both types of measurement should be included in the clinical assessment of patients with MDD.

There is, as yet, no similar body of evidence to support an application of objective and subjective cognitive screening tools to the clinical assessment of patients suffering from ADHD, despite preliminary results suggesting a discrepancy between the two that is very similar to the discrepancy observed in MDD. In ADHD, the majority of studies investigating the relation between objective and subjective cognition have focused only on executive functions. The associations between subjective executive functioning scales and neuropsychological testing were found to be weak and mostly non-significant (Barkley and Fischer, 2011; Barkley and Murphy, 2011; Biederman et al., 2008). Moreover, in one of the very few studies to examine subjective and objective measures of attention and memory in addition to executive skills the ADHD sample again endorsed much more cognitive impairment on subjective tools than was evident on objective tests (Fuermaier et al., 2015).

The authors of the latter study suggested that the discrepancy may relate to a difference in the ecological validity of the two types of measures, with objective tests providing circumscribed demands for optimal performance, and subjective tests assessing more general or typical difficulties in day-to-day applications of cognitive skills. They also suggest that the discrepancy may relate to poor metacogntive skills, referring to diminished insight among individuals with ADHD regarding their own cognitive skills. In a previous consideration of the robust endorsement of cognitive

deficits by individual with ADHD, these authors also raised the possibility that individuals with ADHD may be prone to over-reporting to obtain secondary gain (Fuermaier et al., 2014). Also, the ADHD sample in the direct examination of subjective and objective deficits included a sizeable number of patients suffering from mood disorders and, therefore, the discrepancy may to some extent be related to a similar negative cognitive bias as that observed in MDD.

Another limitation in previous experiments investigating the association between objective and subjective cognition was the inconsistency in the instruments used to measure subjective cognition. Some studies included a combination of several questionnaires each assessing a specific cognitive function (i.e., Questionnaire for Experiences of Attention Deficits, Memory Self-Efficacy Questionnaire). This allowed for a comprehensive measure of each function (Fuermaier et al., 2015; Lahr et al., 2007), but was associated with several disadvantages as those studies generally included only a small number of cognitive processes, did not provide a global cognitive score and required more time to perform; hence the results were less easily transposable to a clinical setting. The validity of the questionnaires chosen to measure subjective cognition was also limited in some studies.

Specifically, the total score from the CPFQ includes several items relating to physical functioning which may have undermined the power to detect an association between objective and subjective cognitive impairment (Svendsen et al., 2012), another had never been validated in the studied population (Fischer et al., 2008) and some of the questionnaires consisted of a few isolated questions for which parametric features had not been evaluated (Chamelian and Feinstein, 2006; O'Connor et al., 1990). Therefore, it is increasingly important to replicate previous findings by using validated instruments that cover a wider range of cognitive functions, but that are also easy and quick to use, and thus, could possibly be integrated in clinical settings.

The main goal of the current study was to explore further the association between a screening tool for the objective evaluation of cognition and a brief self-assessment of cognition in a clinical population with a principal diagnosis of MDD, and ADHD relative to healthy controls (HC) using validated and clinically applicable tools. First,

we compared the performance of the three groups on objective and subjective measures of cognition. Then, we evaluated the association between objective and subjective measures of cognitive functioning in the three groups of participants.

2. Material and Methods

2.1. Participants

Three groups of participants took part in the current study: 40 individuals with MDD (17 males; mean age 51 ± 11 years; range 20-73 years), 36 individuals with ADHD (21 males; mean age 43 ± 12 years; range 22-65 years) and 35 HC (16 males; mean age 30 ± 8 years; range 22-52 years). Participants from the MDD and the ADHD groups were invited to participate to this study when attending a routine clinical visit in a mood and anxiety disorder program affiliated with the Institut Universitaire de Santé Mentale de Montréal (IUSMM). HC participants were recruited among students and employees of the IUSMM during the validation of a french translation of the objective assessment tool (submitted).

All participants from the MDD and ADHD groups had received a clinical diagnosis based on DSM-IV-TR criteria (American Psychiatric Association, 2013). In an attempt to approximate a naturalistic clinical population, potential participants were not excluded on the basis of illness severity, comorbidities, or medication status, meaning that there was a high variability in these features within each clinical group. Control participants were screened for any history of psychiatric disorder. Inclusion criteria for all participants included a working knowledge of French and the absence of neurological illness, or other conditions, which could be expected to affect cognitive function. Informed consent was obtained from participants. Healthy controls received monetary compensation for their participation. The local Institutional Review Board (IRB) of the IUSMM approved the study.

Detailed demographic data and clinical characteristic for all participants are reported in Table 1 and 2. There was a difference between the groups in term of age ($F(2, 109) = 37.7$, $p \leq .001$), as both clinical groups were older than HC (all $p \leq .001$), and

participants with MDD were older than those with ADHD ($p < .05$). The three groups also differed slightly on years of education ($F(2, 110) = 4.8$, $p \leq .05$), with a higher level of education for HC than for participants with ADHD ($p < .05$), but no difference between the clinical groups ($p = 1.0$), or between the MDD and the HC groups ($p = .09$). Groups were well matched in term of sex (χ^2 (2) = 2.0, $p = .35$), laterality (χ^2 (2) = 4.67, $p = .10$) and ethnicity (χ^2 (6) = 7.34, $p = .29$), but showed differences regarding the marital status (χ^2 (6) = 23.8, $p \leq .001$, V de Cramér = .33).

2.2. Procedure

For this study, participants took part in one experimental session at the IUSMM. First, they encountered a clinician with expertise in mood disorders and adult attention deficit disorder (S.V.Tourjman), who reviewed the medical file, confirmed the current diagnosis of MDD or ADHD, and evaluated the severity of the pathology using the clinical Global impression Severity Scale (CGI-S). The French version of the *CGI-S* (Guy and 19767) is a well-established rating tool in psychiatric populations that allows the quantification of the severity of the condition at a specific moment in time (Busner and Targum, 2007) and is correlated with many standardized evaluation instruments in psychiatry (Bandelow et al., 2006; Leucht et al., 2005; Zaider et al., 2003). In the MDD group, the clinical severity of the depressive symptoms was also rated on the 17-item version of the *Hamilton Depression Rating Scale* (Hamilton, 1960, 1966, 1967, 1980)(HAM-D). Both clinical groups completed the *Adult ADHD Self-Report Scale* (ASRS)(Kessler et al., 2005a). Participants were then asked to perform an objective assessment of cognitive functions, and to complete different questionnaires, detailed below. Broadly, these questionnaires included a brief review of demographic data, self-administered subjective measures of cognition, and rating scales about functioning in daily life.

2.3. Objective Cognitive Functions

Objective cognition was measured with a recently translated and validated French version of the *Screen for Cognitive Impairment in Psychiatry* (SCIP; Tourjman et al., submitted). This questionnaire, originally developed in English(Purdon, 2005a), was specifically designed to detect cognitive deficits in individuals with psychiatric disorders. It requires about fifteen minutes to complete and it consists of five subscales corresponding to a verbal learning test with immediate (VLT-I) and delayed (VLT-D) recall, a working memory test (WMT), a verbal fluency test (VFT), and a processing speed test (PST). The verbal learning test consisted of a list of ten words with instructions for immediate list repetition.

The immediate recall scores is the total number of words recalled over three trials (VLT-I). The delayed recall score is the total number of words recalled after a delay of five minutes without repetition of the list (VLT-D). The WMT entails presentation of a sequence of three consonants, followed by a given number. Participants count backwards from the given number for a specific period of time (0, 3, 9, or 18 seconds; two trials at each delay), and then to repeat the three consonants that had been presented. The VFT required the participant, within 30 seconds, to produce as many words as possible beginning with a given letter. Two trials are given with different letters. Each time the participant is instructed to follow three rules: (1) they are not to use words that are numbers, such as for the letter "T" saying thirty-one and thirty-two, (2) they cannot use any words that are commonly capitalized, such as the name of a place, a friend, or a city, and (3) they should not provide one word and repeatedly change the ending, such as dance,dancer, and dancing. Finally, for the PST, participants were asked to write the corresponding Morse code equivalent of a series of letters as fast as possible during one minute. Details concerning procedure and scoring are described in Purdon (Purdon, 2005a).

2.4. Subjective Cognitive Functions

The subjective perception of cognitive functioning was self-assessed with the *Échelle d'auto-évaluation cognitive* (EDEC). This self-report questionnaire, representing an integrated measure of the subjective global cognitive functioning, was recently validated and demonstrated strong reliability with a Cronbach's α coefficient of .95 in MDD, .92 in ADHD and .85 in HC (Tourjman et al., submitted). Each of its 16 items queried difficulties performing various tasks related to different cognitive functions, including memory (i.e. *Do you have memory difficulties, such as forgetting conversations that happened a few days ago?*), executive functioning (i.e. *Do you have difficulty to keep your documents and mail organized?*), verbal fluency (i.e. *Do you have difficulty to find the right word during conversations?*), visuo-spatial processing (i.e. *Do you have difficulty to follow directions on a map?*) and attention (i.e. *Do you have difficulty to cook or work and talk at the same time?*). Cognitive complaints were rated on an 11-point scale from 0 or "*No difficulty*" to 10 or "*Extreme difficulty*", with higher scores on the EDEC suggesting more severe perceived cognitive difficulties. Scores on each of the 16 items were summed in a global score, ranging from 0 to 160. This global score was then divided by the total number of items to reduce the range of the scores to 0 to 10, and this score was utilized in all analyses.

2.5. Level of functioning

Two different scales were used to assess the level of functioning of the participants; the *Global Assessment of Functioning* (GAF) and the *Sheehan Disability Scale* (SDS). The GAF is a numerical scale ranging from 1 to 100 which was part of the DSM-IV-TR (APA, 2000), and used by clinicians to assess social, occupational and psychological functioning, as well as severity of clinical symptoms. The SDS was developed to measure functional disturbances in three specific areas:work/education, social life and home/family life (Sheehan et al., 1996). Summation of the scores on

the three first items of the SDS was used in the current study, providing an overall impairment score ranging from 0 (unimpaired) to 30 (impaired).

2.6. Statistical Analysis

Differences in performance between the three groups on the SCIP and the EDEC were investigated using one-way ANOVAs. Effect size estimates were calculated using Cohen's d (Cohen, 1988). Since groups initially differed with respect to their mean age and their number of years of education, ANCOVAs were conducted to compare the SCIP and EDEC scores between the groups, while controlling for age and educational level. Correlations were performed on the scores from the different questionnaires, to determine whether there was an association between the objective and subjective measures of cognition, the severity of the psychopathology, and the level of functioning in daily life. Those correlations were first generated for the complete sample of participants. Partial correlations controlling for age and educational level of the participants were also performed. Then, they were repeated separately in each group of participants. Pearson coefficients were used when data where normally distributed, while Spearman correlations were computed in other cases. Statistical significance level was established at $p < .05$ (two-tailed).

3. Results

Since all group differences and correlations persisted after controlling for the age and the educational level of the participants, results from ANCOVAs and partial correlations were reported as Supplementary Material.

3.1. Objective Cognitive Functions

A main effect of group was obtained when comparing global performance on the SCIP between MDD, ADHD and HC ($F(2, 110) = 22.8$, $p \leq .001$, Cohen's $d = 1.3$; Fig. 1A). Scores on the SCIP were higher in HC than in MDD ($p \leq .001$) and ADHD

($p \leq .001$), and performance did not differ between clinical groups ($p = .48$). When looking separately at each subtest of the SCIP, groups differed on the VLT-I ($F(2, 110) = 6.9$, $p < .05$, Cohen's $d = .7$) with better scores in HC than in MDD ($p \leq .001$), as well as on the WMT ($F(2, 110) = 14.1$, $p \leq .001$, Cohen's $d = 1.0$) and the PST ($F(2, 110) = 55.2$, $p \leq .001$, Cohen's $d = 2.0$) for which HC had higher scores than both MDD ($p \leq .001$) and ADHD ($p \leq .001$). There was no difference between the three groups of participants for the VFT ($F(2, 110) = 2.0$, $p = .14$), or the VLT-D ($F(2, 110) = 2.1$, $p = .13$) subtests of the SCIP.

A negative correlation was observed between the scores on the SCIP and the CGI ($r = -.57$, $p \leq .001$), as the individuals with with the most severe condition manifested the poorest performance on the SCIP. When looking at results separately for each group, there was a negative correlation between performance on the SCIP and CGI in MDD ($r = -.31$, $p < .05$; Fig. 2A) and in ADHD ($r = -.50$, $p < .05$; Fig. 2B), but not in HC ($r = -.07$, $p = .68$; Fig. 2C), indicating that the objective measures of cognition varied according to the severity of the psychopathology in both clinical groups. In the MDD group, the SCIP was also correlated with the HAM-D scores ($rho = -.36$, $p < .05$).

3.2. Subjective Cognitive Function

A strong main effect of group was also observed for the EDEC ($F(2, 110) = 38.0$, $p \leq .001$, Cohen's $d = 1.68$; Fig. 1B). Lower scores were reported in HC than in MDD ($p \leq .001$) and in ADHD ($p \leq .001$), while no difference was observed between MDD and ADHD ($p = .14$), suggesting a higher level of cognitive complaints in MDD and ADHD than in HC based on the EDEC inventory.

There was a positive and strong association between the scores on the EDEC and the CGI scale ($r = .76$, $p \leq .001$), indicating that people with the most severe symptomatology reported the greatest cognitive difficulties. Positive correlations were observed in MDD ($r = .70$, $p \leq .001$; Fig. 2A) and in ADHD ($r = .44$, $p < .05$; Fig. 2B), but not in HC ($r = .26$, $p = .13$; Fig. 2C). A positive relation was also

observed in the MDD group between the scores on the EDEC and those on the HAM-D rating scale ($r = .68$, $p \leq .001$).

3.3. Comparison between objective and subjective measures of cognition

Overall, a moderate negative association was observed between the total scores on the SCIP and the EDEC ($r = -.53$, $p \leq .001$). Similar negative correlations were observed for each sub-scale of the SCIP except the VFT (VLT-I: $r = -.38$, $p \leq .001$; WMT: $r = -.51$, $p \leq .001$; VFT: $r = -.16$, $p = .09$; VLT-D: : $r = -.30$, $p < .05$; PST: $r = -.53$, $p \leq .001$). When analysing the relation between objective and subjective measures of cognition separately in each group of subjects, moderate negative correlations between the composite scores on the SCIP and those on the EDEC were obtained in MDD ($r = -.39$, $p < .05$; Fig. 3A) and in ADHD ($r = -.34$, $p < .05$; Fig. 3B), but this negative association was not significant in HC ($r = -.31$, $p = .07$; Fig. 3C). The individual sub-scales of the SCIP that significantly correlated with the EDEC were the WMT in MDD and ADHD, and the VMT in ADHD (all $p < .05$). Detailed correlations are reported in Table 3.

3.4. Cognition and Functioning in daily life

A main effect of group was observed for both the GAF ($F(2, 110) = 28.8$, $p \leq .001$, Cohen's $d = 1.5$) and the SDS ($F(2, 110) = 49.1$, $p \leq .001$, Cohen's $d = 1.9$), with better functioning in HC than in MDD and ADHD, and similar functioning level in both clinical groups (Fig. 4A). Combining across all three groups, the SCIP total score was related to the level of functioning quanitified by either the GAF ($r = .51$, $p \leq .001$) or the SDS ($r = -.51$, $p \leq .001$) scales (Fig. 4B). Within each group, however, only the association between total SCIP and GAF was significant and only within the ADHD group (MDD GAF: $r = .25$, $p = .12$; SDS : $r = -.29$, $p = .07$); ADHD GAF : $r = .40$, $p < .05$; SDS : $r = -.29$, $p = .09$; HC GAF: $r = .07$, $p = .67$; SDS : $r = -.01$, $p = .94$).

Analysis revealed strong associations between the scores on the EDEC and the level of functioning rated on the GAF ($r = -.68$, $p \leq .001$) and the SDS ($r = .88$, $p \leq .001$)

inventories (Fig. 4C). Similar associations were observed separately in MDD (GAF: $r = -.67$, $p \leq .001$; SDS : $r = .80$, $p \leq .001$) and ADHD (GAF : $r = -.27$, $p = 12$; SDS : $r = .79$, $p \leq .001$), but to a lesser extent in HC (GAF : $r = .08$, $p = .63$; SDS : $r = .43$, $p < .05$).

4. Discussion

The main objective of the current report was to investigate the relationship between objective and subjective cognition in a clinical population with a principal diagnosis of MDD, or ADHD and HC using clinically relevant screening tools. First, patients with MDD and ADHD performed worse than HC on objective measures, and they reported more cognitive difficulties in their daily life. Second, a moderate correlation between objective and subjective measures of cognition was observed in individuals with MDD and ADHD. Finally, we demonstrated that general adaptive functioning within each clinical group was better predicted by subjective cognition than by objective cognitive performance.

A comparison of objective cognitive performance in individuals with MDD, ADHD and HC demonstrated superior global scores on the SCIP in HC relative to either clinical group, while performance was similar for MDD and ADHD. Moreover, an association was observed between the scores on the SCIP and the severity of the psychopathology in MDD and ADHD, with the most seriously ill individuals showing the worst cognitive performance. These results were consistent with the majority of previous findings which reported moderate cognitive deficits associated with MDD (Beblo et al., 1999; Christensen et al., 1997; Den Hartog et al., 2003; Fossati et al., 2002; Porter et al., 2003; Svendsen et al., 2012; Veiel, 1997)(Austin et al., 1996) and ADHD (Barkley, 1997; Marchetta et al., 2008; Tucha et al., 2009; Tucha et al., 2005; Walker et al., 2000), while only a minority of studies did not observe impairments in cognitive performance (Fischer et al., 2008; Nigg et al., 2005).

When looking at the specific cognitive functions that were impaired in the clinical groups, MDD was associated with deficits in working memory, processing speed and verbal learning with immediate recall. This is consistent with prior reports of working memory, immediate recall, and processing speed deficits reported with more conventional neuropsychological instruments applied to this population (Austin et al., 1992; Beblo et al., 1999; Den Hartog et al., 2003; Fossati et al., 2002; Lahr et al., 2007). Similarly, significant differences between ADHD and HC were observed on the SCIP working memory and the processing speed subtests, but not on the verbal fluency subtest, very similar to the objective results reported from a broader assessment of subjective and objective deficits (Fuermaier et al., 2015), and consistent with previous examinations of objective deficits in ADHD (In de Braek et al., 2011; Marchetta et al., 2008; Rapport et al., 2001; Walker et al., 2000). Overall, the SCIP provided an accurate measure of the specific cognitive deficits that were previously identified in MDD and ADHD on more comprehensive neuropsychological batteries, confirming it to be a reliable instrument that could be integrated both in clinical and research settings, and extending previous investigations that have supported the construct validity of the English, Spanish of the SCIP (Pino et al., 2008; Purdon, 2005a).

The further objective of this study was to explore and compare subjective cognitive deficits in individuals with MDD, ADHD and HC. Patients with MDD and ADHD did not differ in their endorsement of deficits on the EDEC, but both groups reported significantly more cognitive difficulties than HC. These differences remained when controlling for age and education. Also, scores on the EDEC were positively correlated with the severity of the symptomatology in clinical groups, especially in MDD, as individuals with the most severe symptomatology also reported greater cognitive difficulties. Several studies have reported robust subjective cognitive deficits associated with MDD that are associated with symptom severity (Fischer et al., 2008; Svendsen et al., 2012).

A significant reduction in subjective cognitive complaints was also observed following therapy with antidepressants in patients suffering from MDD, while the

same treatment had little effect on objective measures of cognitive performance (Antikainen et al., 2001; Lahr et al., 2007). These results are consistent with prior suggestions of a negative cognitive biase associated with endorsement of more severe subjective cognitive deficits in MDD. This interpretation is supported by the observation that individuals who have suffered from traumatic brain injury do not exhibit differences in subjective cognitive complaints after controling for the contribution of depressive symptoms (Chamelian and Feinstein, 2006). Less research has been done on subjective cognition in patients with ADHD, but subjective complaints have been reported in relation to executive functions (Moore et al., 1997), attention (Fuermaier et al., 2015) and memory (Fuermaier et al., 2015), which were also seen in the EDEC scale. Therefore, findings from the EDEC were in line with the results of previous studies, and demonstrated that individuals with MDD and ADHD tended to report more cognitive difficulties than HC, and that the more severe were their depressive symptoms, the greater were their subjective complaints.

Our findings demonstrated a moderate negative correlation between scores on the SCIP and the EDEC, which indicated that individuals with MDD or ADHD presenting some difficulties on the objective neuropsychological tests also tended to perceive themselves as having the most cognitive problems. Recently, two studies have measured the association between the objective and subjective measures of cognition in patients with MDD (Lahr et al., 2007; Svendsen et al., 2012), and one of them also used the SCIP as the objective measure of cognition (Svendsen et al., 2012). Both studies reported only a weak trend toward an association between objective and subjective measures of cognition. The results of the current investigation suggest a potential domain-specificity to the association, with subjective ratings associated with objective performance on a test of working memory in MDD, and subjective ratings associated with objective performance on tests of working memory and processing speed in ADHD. In each case the domain-specific associations with sufficient to contribute to an association between the SCIP total score and the EDEC.

Interestingly, many studies in adults with medical conditions frequently associated with depressive symptoms, such as multiple sclerosis (Julian et al., 2007; Kinsinger et al., 2010), traumatic brain injuries (Drag et al., 2012; French et al., 2014), Lyme Borreliosis (Barr et al., 1999) or human immunodeficiency virus (HIV) infections (Moore et al., 1997; Woods et al., 2007), observed that subjective measures of cognition were more correlated with the score on a general depression scale than with the objective evaluation of cognition. In ADHD, litterature is sparse and most of it was limited to executive functions, suggesting a non significant to modest association between objective and subjective mesures of executive functioning (Barkley and Murphy, 2011; Biederman et al., 2008). The one study to extend the analysis of beyond objective measurement of executive functions also reported relative weak associations with subjective measures (Fuermaier et al., 2015; Lahr et al., 2007). Therefore, findings from the current study suggest an association in the same direction, but found that association to be somewhat stronger than what had previously been found between objective and objective cognition in MDD and ADHD.

Possible explanations for the significant correlations between objective and subjective measures of cognition in the present study, while most of the previous studies did not may be attributed to several factors. This study included the largest number of participants to date and evaluated a broader range of cognitive functions using different instruments. As mentioned, a great proportion of the previously used questionnaires either focused on a small number of cognitive process (Lahr et al., 2007), did not exclusively measure cognition (Svendsen et al., 2012) or have never been validated (Chamelian and Feinstein, 2006; O'Connor et al., 1990). In a recent study, performance on the EDEC was directly compared to that of another frequently used measure of subjective cognition, the PDQ-D-5 (Tourjman et al., in preparation). It was interesting to note that although the EDEC and the PDQ-5 were highly correlated; the correlation between the SCIP and the PDQ-D-5 was weak compared to the one between the SCIP and the EDEC. The fact that the EDEC was developed specifically to cover all major cognitive domains, including memory, executive

functions, attention, langage and visuo-spatial processing, could possibly explain why the results on the EDEC were closer to those on the SCIP. These characteristics would therefore make the EDEC a more integrated and complete measure of cognition compared to some other instruments.

Although we found an association between subjective and objective measures of cognition, the size of this correlation remained moderate. These findings thus raised the question of how to explain the discrepency between performance on neuropsychological evaluations and cognitive complaints reported by patients themselves. Three main hypotheses have been put foward to answer this interrogation. First, several studies have questioned the ecological validity of neuropsychological testing, because results from such evaluations were not always consistent with the capacities observed in natural settings Barkley, 1991; (Acker, 1990; Barkley and Murphy, 2011; Fuermaier et al., 2014; Koerts et al., 2011; Sbordone and Long, 1996). While neuropsychological tests evaluate how a person can perform on a circumscribed task in a highly structured environement under constant monitoring and isolated from external distractors, subjective assessments would reflect performance in daily life environment (Fuermaier et al., 2015; Lahr et al., 2007; Toplak et al., 2013).

In the latter environment, most of the tasks are unstructured and complex, often involving several cognitive processes simultaneously, and would be initiated without any supervision. Further, the completion of these tasks is influenced by multiple external factors such as physical distractors or interaction with other individuals (Fuermaier et al., 2015; Lahr et al., 2007; Toplak et al., 2013). Therefore, neuropsychological tests represent the measure of optimal performance, while self-evaluations would correspond to typical performance (Toplak et al., 2013). In MDD, it was also suggested that negative cognitions associated with depression could lead to a tendency to perceive themselves as having more deficits than they actually have (van den Bosch et al., 1993). This was supported by some studies showing that patients with MDD tended to overestimate their deficiencies as they reported more difficulties than observed in neuropsychological tests (Lahr et al., 2007; van den

Bosch et al., 1993), and that this negative bias were reduced folllowing pharmacological treatment (Antikainen et al., 2001; Lahr et al., 2007). Finally, as patients with MDD and ADHD exhibit certain cognitive difficulties, including in executive processing, it was proposed that the moderate association between objective and subjective measures of cognition may be due to a disorder of metacognition (Fuermaier et al., 2015). In this context, the difference between the scores on neuropsychological tests and self-reported evaluations would result from a difficulty in evaluating one's own performance and abilities (Fuermaier et al., 2015; Miskowiak et al., 2012; van den Bosch et al., 1993).

One way to assess the ecological validity of both measures of cognition was to examine their association with the key areas in general functioning of daily life (Barkley and Murphy, 2011). Therefore, we correlated objective and subjective cognitive performance of the participants with scores on the GAF and the SDS, two scales frequently used to assess general functioning in psychiatric populations. Results from these analyses showed that the association between the adaptive functioning and the scores on the EDEC was much stronger than with the scores on the SCIP. These results support previous litterature in ADHD which observed that self-reported measures of executive functioning were better predictors of the level of functioning than neuropsychological tests of executive functions (Barkley and Fischer, 2011; Barkley and Murphy, 2011), and confirmed the importance of self-evaluation.

It is important to note that the absence of significant correlation in HC between the objective and subjective measures of cognition, the severity of the symptoms and the level of functioning was not suprising. This can most probably be explained by the very low variability observed in the HC on the different questionnaires, since most were developed specifically for psychiatric populations. For example, the scale on the EDEC varied from 0 to 10, and the scores of the HC participants were all confinedto a range between 0 and 2.69 with a mean of .71 and a standard deviation of .65. On the other hand, scores ranged from .19 to 8.06 in MDD (3.74 ± 2.57) and from 1.13 to 9.44 in ADHD (4.66 ± 2.15). Furthermore, because the HC were free of

psychiatric conditions, the level of severity of disease was null and the level of functioning unimpairedfor most. For this reason, these results matched expectations, and did not cast doubt on the validity of the SCIP and the EDEC to assess cognitive processes in clinical populations.

4.1. Limitations

There are some limitations that need to be addressed concerning this study. First, we decided to include all participants with MDD or ADHD regardless of their commorbidities or medication status. This aspect significantly increases the external validity by performing the analysis on a sample of participants that was quite representative of the clinical population, but it may have introduced some bias in the comparison of the groups. In fact, as in previously studied populations with ADHD (Biederman et al., 1996; Biederman et al., 1993), it led to the inclusion of a great proportion of patients in the ADHD group that also had a commorbidity of MDD. Consequently, we compared our results with those obtained if those participants would instead have been classified in the MDD group, and results remained unchanged.

Concerning the effect of medication on objective and subjective cognition, it remains unclear (Balanza-Martinez et al., 2010), but it seems that it cannot account for most of the cognitive impairment found in psychiatric disorders (Millan et al., 2012). Age and education differed significantly between the groups. Since these two variables are known to influence cognition, we performed all our analyses by controling for these two factors. Therefore, we demonstrated that all the differences and associations found in the current study persisted taking into account the effect of age and education. Finally, we chose to use the SCIP, an abbreviated tool for the evaluation of general cognitive functioning, as an objective measure of cognition. This measure was therefore less exhaustive than a complete neuropsychological battery, but was chosen because it was an easily and quickly administered instrument that may be integrated in clinical settings. The fact that results based on the SCIP

were consistent with previous litterature on the subject reinforces the validity of our data.

4.2. Conclusion

This study demonstrates that, although cognitive deficits were not always apparent, patients with MDD and ADHD performed worse than HC on neuropsychological tests and reported more cognitive difficulties in their daily life. When examining the relationship between objective performance and subjective cognitive complaints, a moderate correlation was observed between both measures in individuals with MDD and ADHD, which represented a slightly stronger association than that observed in most previous studies but remained far from a perfect association.

While future research will be necessary to determine the specific factors influencing both of these measures, the principal recomendation emerging from this study is that neuropsychological testing and self-reported scales of cognition are not interchangeable but rather give information about different constructs. In addition, the value of self-evaluation is confirmed by the observation that it is more strongly related to function than objective cognitive performance. Thus the evaluation of cognitive functioning should ideally include both objective and subjective measures of cognition. Both the SCIP and the EDEC were demonstrated to be reliable measures that could easily be integrated as part of clinical or research evaluations. Finally, the value of self-evaluation is confirmed by the observation that it is more strongly related to function than objective cognitive performance.

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Table 1.
Demographic and clinical characteristics for the MDD, the ADHD and the HC groups

	MDD (n = 40)	ADHD (n = 36)	HC (n = 35)
Age (years) *	51.23 ± 11.43	43.14 ± 12.33	29.89 ± 7.48
Sex, *N* (%)			
Male	17 (42.5%)	21 (58.3%)	16 (45.7%)
Female	23 (57.5%)	15 (41.7%)	19 (54.3%)
Ethnicity, *N* (%)			
Caucasian	32 (80%)	33 (91.7%)	30 (85.7%)
Asian	0 (0%)	1 (2.8%)	0 (0%)
Black	5 (12.5%)	0 (0%)	2 (5.7%)
Other	3 (9.4%)	2 (5.6%)	3 (8.6%)
Marital Status, *N* (%) *			
Single	13 (32.5%)	15 (41.7%)	29 (82.9%)
Married	10 (25%)	4 (11.1%)	3 (8.6%)
Law partner	7 (17.5%)	8 (22.2%)	1 (2.9%)
Divorced	10 (25%)	9 (25%)	2 (5.7%)
Years of education *	15 ± 3.65	14.19 ± 4.89	17 ± 2.79
Laterality, *N* (%)			
Right-handed	39 (97.5%)	31 (86.1%)	29 (82.9%)
Left-handed	1 (2.5%)	5 (13.9%)	6 (17.1%)

* $p \leq .05$

Table 2.
Clinical features for the clinical groups of participants

MDD	
Clinical Specifiers, *N* (%)	
With psychotic features	1 (2.5%)
In remission	10 (25%)
Commorbidities, N (%)	
Anxiety Disorder	3 (7.5%)
Personnality Disorder	8 (20%)
ADHD	
Clinical Specifier, N (%)	
Combined Presentation	29 (80.6%)
Predominantly inattention presentation	6 (16.7%)
Predominantly hyperactive/ impulsive presentation	0 (0%)
Commorbidities, N (%)	
Anxiety Disorder	10 (27.8%)
Bipolar Disorder	2 (5,6%)
Depressive Disorder	
Major Depression Disorder (MDD)	5 (13.9%)
MDD in remission	8 (22.2%)
Cyclothymia	1 (2.8%)
Gilles de la Tourette's Disorder	2 (5.6%)
Substance-induced Psychosis in remission	1 (2.8%)
Personnality Disorder	9 (25%)

Table 3.
Substance use for the clinical groups of participants

MDD	MDD	ADHD
Actual Substance Use		
Tobacco Use, N (%)	14 (35%)	15 (41.7%)
Number of cigarette per day, M, ST	14 ± 8.4 (1 – 25)	17.6 ± 6.9 (10 – 30)
Alcool Use, N (%)	12 (30%)	18 (50%)
Number of drinks per week, M, ST	3.1 ± 3.1 (1 -12)	3.6 ± 3.9 (.5 – 15)
Cannabis Use, N (%)	1 (2.5%)	3 (8.3%)
Number of uses per day, M, ST		1 ± .9 (.5 – 2)
Other drugs Use, N (%)	0 (0%)	0 (0%)

Table 4.
Correlations between subjective cognition scores on the EDEC and objective cognition measured by the SCIP in participants with MDD, ADHD and in HC.

Cognitive Function (SCIP)	MDD	ADHD	HC
Global Cognition	r = -.39, $p \leq .05$*	r = -.34, $p \leq .05$ *	r = -.31, p = .07
VLT-I	r = -.30, p = .06	r = -.28, p = .10	r = -.22, p = .20
WMT	r = -.36, $p \leq .05$ *	r = -.34, $p \leq .05$ *	r = -.23, p = .18
VFT	r = -.21, p = .20	r = .04, p = .81	r = -.07, p = .70
VLT-D	r = -.22, p = .18	r = -.29, p = .09	r = -.30, p = .08
PST	r = -.20, p = .21	r = -.38, $p \leq .05$ *	r = -.19, p = .26

* $p \leq .05$

Figure 1.

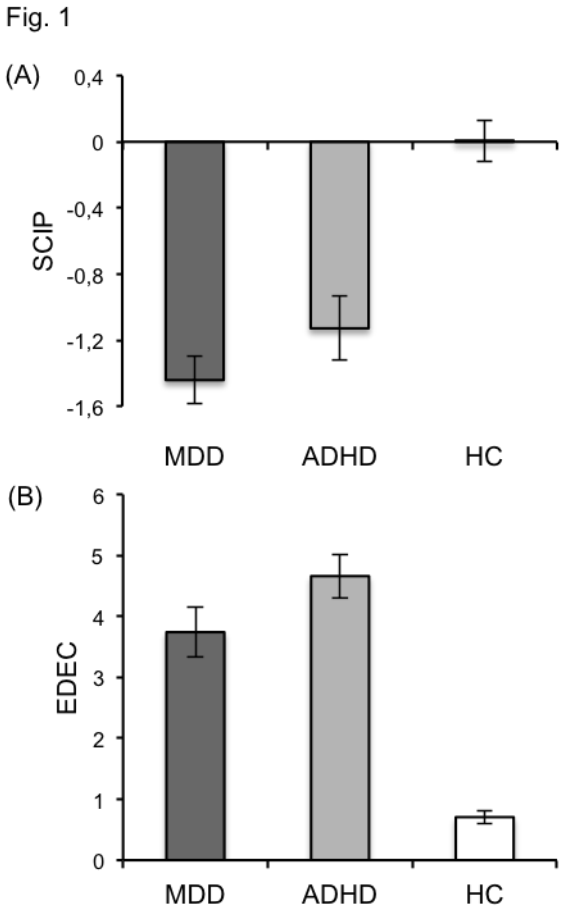
Fig. 1
(A)
0,4
0
-0,4
-0,8
-1,2
-1,6
SCIP
MDD
ADHD
HC
(B)
6
5
4
3
2
1
0
EDEC
MDD
ADHD
HC

Figure 2.

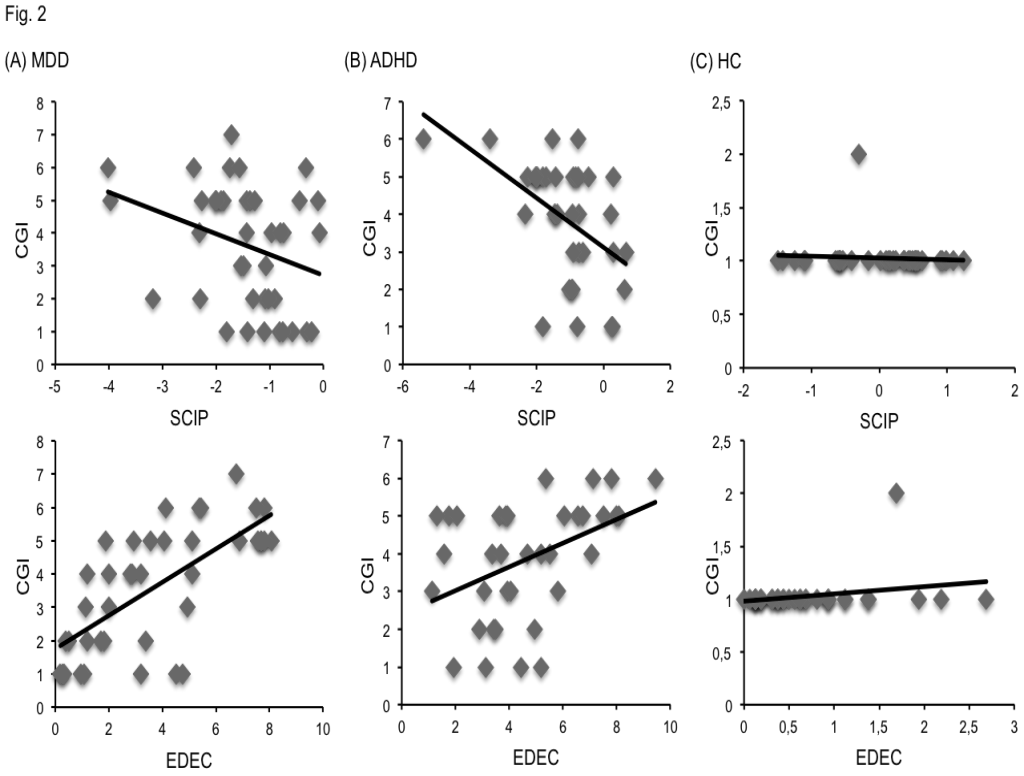

Figure 3.

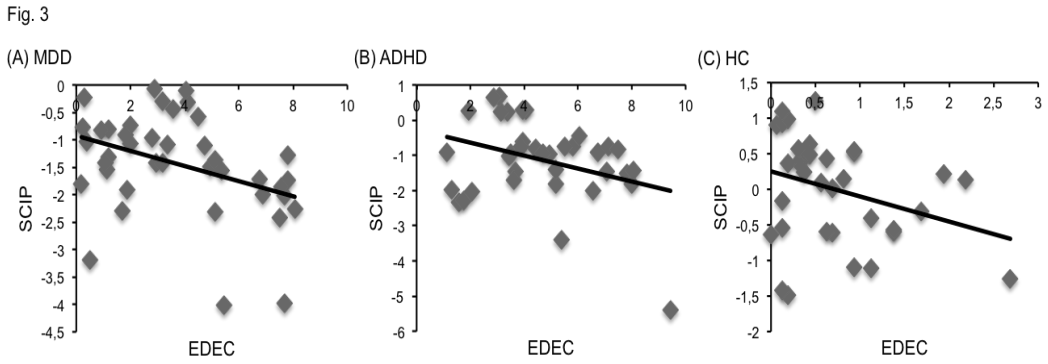

Figure 4.

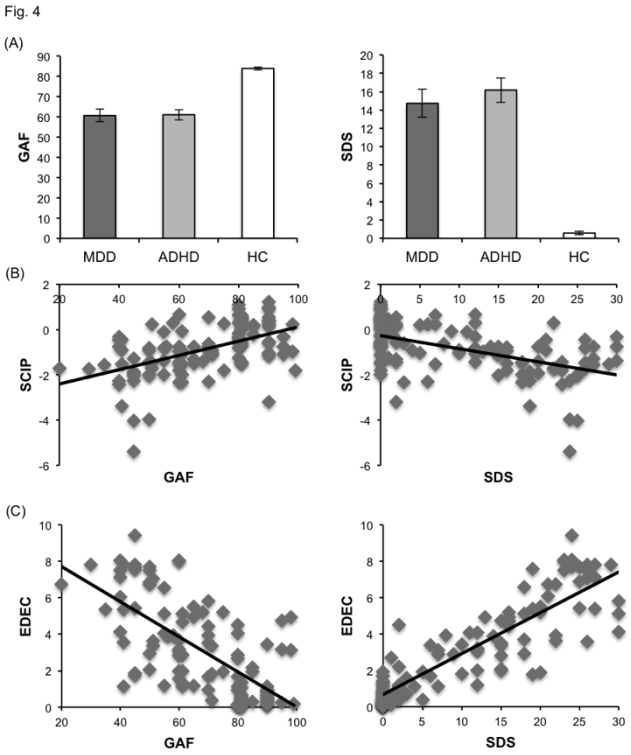
Fig. 4
(A)
GAF
MDD
ADHD
HC
SDS
MDD
ADHD
HC
(B)
SCIP
GAF
SCIP
SDS
(C)
EDEC
GAF
EDEC
SDS

Chapter 4.3: Article 3- Major depression and the Screen for Cognitive Impairment in Psychiatry

SUBMITTED TO THE JOURNAL OF AFFECTIVE DISORDERS

Major depression and the Screen for cognitive impairment in psychiatry

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ABSTRACT

Background: The prevalence and role of cognitive deficits in major depression has been increasingly recognized. Cognitive deficits are present both during acute episodes and between episodes. The impact of these deficits on function is intuitively evident but has been the focus of remarkably little research. The purpose of this study was to evaluate the feasibility of screening for the cognitive deficits of major depression in the clinical setting with an abbreviated cognitive battery, the Screen for Cognitive Impairment in Psychiatry (SCIP). Ancillary objectives are to describe the relationship of these deficits to other clinical parameters such as illness severity, subjective cognition and function.

Methods: Patients (n = 40) with major depression (DSM-IV-TR criteria) were invited to participate in the study following a routine clinical evaluation and were further compared to student controls (n = 74). Participants completed questionnaires and the SCIP was administered prior to the clinical evaluation.

Results: MDD patients showed significant cognitive impairments on all SCIP domains compared to healthy controls. The SCIP is correlated with self-evaluation of cognitive deficits and illness severity. Self-evaluation of cognitive deficits were more strongly correlated with SCIP cognitive performance than were clinical global impressions in analyses that combined MDD patients and healthy controls; on further analysis, this was the case only for MDD patients and not healthy controls. Cognitive impairment was correlated with functional impairment as indicated by employment status, days unproductive and days lost.

Conclusions: This study highlights the prevalence of cognitive deficits in individuals with major depression and suggests that the SCIP can be fruitfully added to the clinical tools for their evaluation. Furthermore, this study shows correlations between the cognitive deficits of depression and functional impairments confirming the importance of the evaluation and treatment of this symptomatic dimension.

Limitations: The sample size of this study is small and does not permit the detection of weaker correlations.

Key Words: cognition, depression, cognitive testing, function, clinical trial, cognitive deficit, SCIP

INTRODUCTION

The presence of cognitive deficits in major depression (MDD) is increasingly recognized as playing a determining role in the presentation and evolution of depression. Thus a significant number of patients with clinical depression complain of cognitive deficits in the acute phase and between cognitive episodes (Conradi et al., 2011). Further, these symptoms are among the most persistent and impairing in this population (Gonda et al., 2015). Despite this, the measurement of cognitive deficits in depression in the clinical setting remains the exception. This may be a result of the difficulty in obtaining neuropsychological evaluations due to high costs and a dearth of professionals. Yet, it is evident that a clear appreciation of a patient's cognitive deficits is essential for the elaboration of a personalized treatment plan.

In populations other than depression (e.g., elderly, schizophrenia), brief neuropsychological batteries have been developed (Cholet et al., 2014; Randolph et al., 1998). Despite their appellation, and indeed their brevity compared to standard neuropsychological testing, these tools remain impracticable in clinical settings, as they require 25-35 minutes to administer or access to computer technology. In order to address the need for a short objective evaluation of cognitive deficits in psychiatry, Purdon (Purdon, 2005a) developed the Screen for Cognitive Impairment in Psychiatry (SCIP). Administration of the SCIP requires 15 minutes, a pencil, paper, and a stop-watch. The SCIP has been validated in a variety of languages and has been shown to detect cognitive deficits in a sample with bipolar disorder (Cuesta et al., 2011; Gomez-Benito et al., 2013; Guilera et al., 2009; Ott et al., 2016; Pino et al., 2008; Purdon, 2005a; Rojo et al., 2010; Svendsen et al., 2012). Nevertheless, the possibility of integrating the SCIP in a routine clinical setting remains largely untested.

Our group proceeded to elaborate a protocol for the validation of a French version of the SCIP (Tourjman et al., 2016a) which included its testing in a variety of clinical populations. In this article we report the results of the use of the SCIP in a population of patients with major depression. The purpose of this study was to demonstrate the feasibility of using the SCIP in a routine clinical setting among individuals suffering

from major depression and to further compare their performance to that of healthy controls. Additional secondary objectives were to explore associations between the cognitive deficits of major depression as evaluated by the SCIP and clinical parameters such as severity of illness and functioning.

METHODS

Participants

This study was approved by the Institutional Review Board (IRB) of the Institut en Santé Mentale de Montréal (IUSMM) following established guidelines. All participants provided written informed consent after study procedures were explained. The work described was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Forty consecutive individuals consulting for follow up in a mood disorder clinic were invited to participate in the study.

The mood disorder clinic is part of the Mood and anxiety disorder programme of the IUSMM. Access to this programme requires the failure of a minimum of two treatments, usually trials of at least two antidepressants, but potentially a trial of antidepressant and a psychotherapy indicated in major depression. As much as possible, inclusion and exclusion criteria were limited so as to allow the closest possible approximation to the typical clinical population. Neurological disorders associated with cognitive deficits and individuals with known mental retardation were excluded. Inclusion criteria were limited to being followed by a psychiatrist, having a diagnosis of unipolar major depression, and being able to give informed consent. There were no exclusion criteria, although patients who had participated in the attention deficit disorder segment of the study could not participate despite having a comorbid major depressive disorder.

A description of the MDD sample can be found in Table 1. The sample (N = 40) consisted of a majority of women (n = 24) of whom half were menopausal (n = 12) and a minority of men (n = 16). A third of the sample was single, and a quarter

separated or divorced; the balance being in a relationship. Nearly half the sample were employed, 10% were unemployed or retired and 42.5% were on leave due to disability. Educational level spanned a range from high school graduates (32.5%), to college level and above (42.5%). Half of the sample had never smoked, with another 17.5% had stopped smoking. Only 32.5% were current smokers. None of the sample described use of illicit substances, while 60% used alcohol socially. Select comparative analyses included the healthy student controls (n = 74) who had participated in the validation phase of a French version of the SCIP. The characteristics of this sample can be found elsewhere (Tourjman et al., 2016a).

General Protocol

Participants were invited to participate in the study following a routine clinical evaluation. The study questionnaires and the SCIP were administered prior to the clinical evaluation. Instruments included a questionnaire developed in order to capture patient's experience of the SCIP, the Sheehan disability questionnaire (Sheehan et al., 1988) and the Echelle d'auto-évaluation cognitive (Beauchamp et al. submitted), a questionnaire of perceived cognitive deficits and of the impact of the deficits on functioning. Start and finish times for the administration of the SCIP were captured on a separate sheet and are as follows: M = 14.55 min, SD = 1.853. Much more variable was the perceived time of completion: M = 21.83, SD = 12.945. The treating psychiatrist (VT) completed a full DSM-IV-TR diagnosis (DSM-IV-TR 2000 4th ed., text rev.) and assigned a clinical global impression score (Berk et al., 2008) while blinded to the results of the questionnaires or the SCIP. A similar protocol was applied previously for the health controls (Tourjman et al., 2016a).

Statistical Analysis

Preliminary analyses employed one-way analysis of variance (ANOVA), Pearson product-by-moment correlations to respectively assess categorical relations (sex, menopause, race/ethnicity, civil status, occupation status, educational

attainment, health behaviors) and continuous associations (age, years of schooling) vis-à-vis separate domains of SCIP cognitive functioning. Tukey's post-hoc analysis was used for significant group differences. One-way ANOVAs were used to assess group differences in overall SCIP performance (SCIP sum score) according to MDD patients and controls. Pearson correlations were used to assess correlations among independent and dependent variables and are reported for descriptive purposes and the identification of the most significant measure of clinical impression and subjective appraisals vis-à-vis SCIP scores.

Main analyses employed sequential regressions to assess global SCIP indices among our MDD patients and healthy controls using as an outcome a SCIP global index that summed all five SCIP domains. Model 1 included group, sex, and age as covariates while Models 2 entered clinical impressions and subjective appraisals in turn for four different psychological measures. Specifically, Model 2A entered the CIinical Global Impression (CGI), Model 2B entered the Sheehan Disability Scale (SDS), Model 2C entered the Echelle d'auto-évaluation cognitive (EDEC) perceived cognitive deficits, and Model 2D entered the EDEC perceived functional impacts. In this manner, results reflect effects that are over and above those attributable to group, sex, and age. In confirmatory analyses, these regressions were re-run in analyses split by group in order to assess whether associations were manifest in either MDD or controls or both.

Beyond statistical significance, we focused on effect magnitude changes from Model 1 with covariates entered in comparison to Models 2A and 2B using R statistics to guide interpretation. Effect sizes and 95% confidence intervals (CI) are reported where appropriate with significance strictly set at $\alpha = .05$. Preliminary descriptive analyses of skew and kurtosis revealed that study variables were normally distributed. Statistical analysis was run using the Statistical Package for the Social Sciences© Version 22 for Macintosh and Prism 5© for Macintosh.

Results

Sample Descriptive for MDD Patients

No group differences were found as a function of race/ethnicity or alcohol consumption. A sex difference was found for the SCIP Verbal Learning Delayed score ($F_{[1,38]} = 4.54$, $p = .040$) whereby women scored higher than men. Menopause status among women was related to SCIP Verbal Learning Delayed ($F_{[2,37]} = 5.23$, $p = .010$): menopausal women scored higher than men ($p = .012$, CI: .48, 4.44). Civil status was significantly related to SCIP Verbal Learning Immediate ($F_{[2,37]} = 7.13$, $p = .002$): separated/divorced individuals had lower scores than single individuals ($p = .002$, CI: -9.57, -2.04) and married/common-law individuals ($p = .042$, CI: -7.25, -.12).

Occupational status was significantly related to SCIP Verbal Fluency scores ($F_{[2,37]} = 3.5$, $p = .041$) and SCIP Visuomotor Tracking score ($F_{[2,37]} = 9.03$, $p = .001$): individuals on sick-leave had lower verbal fluency scores than those who were employed ($p = .032$, CI: -8.04, -.31), while those who were employed had higher visuomotor tracking scores than those who were unemployed/retired ($p = .011$, CI: .78, 7.06) or on sick-leave ($p = .002$, CI: 1.0, 4.8). Smoking status was related to SCIP Working Memory ($F_{[2,37]} = 3.77$, $p = .032$) and SCIP Verbal Fluency ($F_{[2,37]} = 4.1$, $p = .025$): non-smokers scored lower on working memory than ex-smokers ($p = .034$, CI: .26, 7.6) who in turn scored higher on verbal fluency than smokers ($p = .019$, CI: -11.6, -.90). Illicit drug history was related to SCIP visuomotor tracking ($F_{[1,38]} = 4.6$, $p = .039$): ex-users scored higher than those with no history of use.

Using Pearson correlations, we found that age was negatively associated with SCIP Verbal Learning Immediate ($r = -.362$, $p = .022$) and SCIP Visuomotor Tracking ($r = -.534$, $p < .001$), but the correlation with years of schooling did not attain statistical significance.

Preliminary Analysis: Variable Associations

Preliminary analysis used Pearson's correlations to assess associations among actual time (M = 14.55, SD = 1.853) and perceived time (M = 21.83, SD = 12.945) for SCIP completion and cognitive performance. Only actual time of SCIP completion showed a negative correlation with the SCIP Global Index (r = -.347, p = .028): this was driven by SCIP verbal fluency (r = -.426, p = .006) and trending for SCIP verbal learning: immediate (r = -.291, p = .069).

Table 2 reports the descriptive statistics and correlation matrix of study variables used for exploratory purposes. Importantly, all psychometrics were strongly correlated with each other. In endeavoring to identify the single most significant clinical and subjective factors that would not be redundant, we decided to retain scores from the Clinical Global Impression Scale (CGI-S) and Sheehan Disability Scale (SDS) as well as the EDEC sub-scales that focused on perceived cognitive deficits and functional impacts.

Based on preliminary findings above that centered on a SCIP global index, we wanted to assess clinical and functional characteristics while adjusting for group, sex, and age in our main analyses that were in turn correlated to some of the aforementioned sample characteristics (e.g., age is positively correlated with marital status). Given the restrictions of sample size, we did not include health behaviors that were moreover of weaker statistical magnitude than sex and age when contrasted to the SCIP global index.

Preliminary Analysis: Cognitive Domains of Depressed Patients Compared to Healthy Controls

Figure 1 illustrates SCIP group differences according to MDD patients from a separate study of healthy controls in which the French version of the SCIP has been validated (Tourjman et al., 2016a). One-way ANOVAs revealed that MDD patients performed significantly worse than healthy controls for all SCIP domains: SCIP Verbal Learning – Immediate ($F_{[1,110]}$ = 22.37, p < .001), SCIP Working Memory

($F_{[1,110]} = 27.45$, $p < .001$), SCIP Verbal Fluency ($F_{[1,110]} = 16.34$, $p < .001$), SCIP Verbal Learning Delayed ($F_{[1,110]} = 11.04$, $p = .001$), and SCIP Visuomotor Tracking ($F_{[1,110]} = 172.78$, $p < .001$). All of these comparisons pass Bonferroni correction.

Main Analysis: Sequential Regressions Assessing Clinical Impression and Perceived Deficits

Four sequential regressions were used to predict global SCIP indices that had as a base model group (Control vs. MDD), sex (men vs. women), and age entered as covariates in Model 1. This was followed sequentially by CGI-S in Model 2A, the SDS in Model 2B, the EDEC perceived cognitive deficits in Model 2C, and the EDEC perceived functional impacts in Model 2D. In this manner, we were able to delineate the separate associations of interest while accounting for covariates. This was followed by confirmatory analyses that were split between MDD and controls.

All statistical parameters are reported in Table 3. Model 1 with covariates was significant ($F_{[3,108]} = 29.721$, $p < .001$). For the entire sample, the SCIP global index was significantly lower among the MDD patients compared to the controls, lower among men, and lower among older adults. Significance was attained beyond these covariates when entering global clinical impressions in Model 2A ($F_{[4,107]} = 26.0$, $p < .001$), when entering global disability (SDS) in Model 2B ($F_{[4,107]} = 25.39$, $p < .001$), when entering perceived cognitive deficits in Model 2C ($F_{[4,107]} = 27.08$, $p < .001$), and when entering perceived impacts of functional impairment in Model 2D ($F_{[4,107]} = 26.7$, $p < .001$). In each case, poorer clinical impressions and perceived cognitive deficits were associated with poorer SCIP performance; however, this was marginally strongest for the EDEC perceived sub-scales.

In confirmatory re-analyses split according to MDD or control groups (rather than as covariates) the aforementioned associations were only statistically significant for the MDD group. This confirms that clinical and functional associations are strictly manifest among MDD patients but not controls.

Discussion

The objective of this study was to demonstrate the feasibility of evaluating the cognitive deficits of major depression within the clinical context. The administration of the SCIP was mastered after a brief training session. Time of administration was relatively brief at 14.5 minutes and could easily be added to a routine clinical evaluation. Patients indicated that they considered the test to be a useful addition to the clinical evaluation and several requested retesting in order to assess their evolution over the course of time. The SCIP has 3 alternate versions making this a practicable option.

Ancillary and unexpected findings given the heterogeneity of the sample, comorbidities, and the variability in treatment were the robust correlations with clinical dimensions and indicators of cognitive functioning. Thus poorer performance on the working memory task of the SCIP correlated with higher clinical global impression confirming that illness severity influences cognitive function. Similarly, poorer performance on the working memory task, as well as on the verbal fluency task, were also correlated with worse functioning in the work-study domain of the Sheehan Disability Scale. Both days unproductive, and lost days were significantly correlated to deficits on the verbal fluency task and the visuomotor task. The correlation with the visuomotor task was particularly robust. Furthermore, cognitive deficit was also strongly correlated with the total score on the World Health Organization Disability Assessment Schedule 2.0. This study thus adds credence to the view that the cognitive deficits seen in depression are associated with decreased functioning.

Patients' perception of their cognitive deficits correlated with deficits in the working memory task. Discordance between subjective perception of cognitive deficit and objective measures of cognitive deficit have been reported ((Mahableshwarkar et al., 2015; Ott et al., 2016; Potvin et al., 2016a). Nevertheless, there is clearly some degree of correspondence between subjective perception and objective performance.

Particularly striking is Figure 1 showing marked impairments in all cognitive domains among MDD patients compared to healthy student controls. This speaks to marked cognitive disability in the context of depression that the SCIP is clearly detecting over and above the effects of covariates. Our main analysis further reveals that cognitive performance correlates with both clinical impressions and patients' subjective evaluations of their cognitive deficits and their impacts on their functional impairments. In terms of statistical magnitude, SCIP cognitive impairments were more strongly correlated with subjective evaluations of cognitive deficits than were clinical global impressions. Similarly, clinical global impressions were comparable to perceived impact of functional impairments. Perhaps most important is that these associations were only significant among MDD patients and not controls in split analyses. This confirmatory analysis strongly suggests that the SCIP is capturing cognitive impairments that are clearly distinguishable among individuals suffering from psychopathology. Future research is needed to further identify which specific SCIP domains differ between distinct psychiatric disorders.

Limitations

The sample size of this study is small and does not permit the detection of weaker correlations. Further studies with larger populations may permit greater sensitivity to detect subtler influences on cognition. The naturalistic nature of the population which is a strength of this study constitutes an additional limitation in that numerous confounding factors such as comorbidity, medication status, and illness phase were not excluded. Thus some patients were in remission. Polypharmacy was a rule with patients taking an average of three agents. Some patients had psychiatric or physical comorbidities. The sample size was insufficient to control for these factors. It is nonetheless remarkable that despite these confounding factors the association of cognitive deficits with functional impairment was statistically significant. While our main analyses did adjust for sex and age, it would have been more appropriate to have a matched control group. In summary, our findings will

need to be replicated in a larger sample that exerts greater control of intervening factors that the current study was not powered strongly enough to do.

Conclusions

This study highlights the prevalence of cognitive deficits in individuals with major depression. The results suggest that the SCIP can be fruitfully added to the clinical tools for the evaluation of the cognitive deficits found in major depression. Its brevity, simplicity, and availability in 3 versions are strong arguments for its place as part of a complete assessment of major depression. The French version used in this population has been validated in a control population, and shown to be acceptable and even appreciated by patients. Most importantly, this study shows clear correlations between the cognitive deficits of depression and functional impairments specifically among MDD patients in contrast to healthy controls, confirming the importance of the evaluation and treatment of this symptomatic dimension.

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Figure and Tables and Associated Captions

Figure 1. Estimated means (standard deviation) for scores on the Screen for Cognitive Assessment in Psychiatry (SCIP) as a function of Major Depressive Disorder (MDD) patients ($N = 40$) and healthy controls ($N = 74$). This Figure shows how the SCIP scores differ between the groups as assessed with one-way ANOVAs showing that the MDD group perform significantly lower than controls (***$p < .001$) for all SCIP cognitive domains.

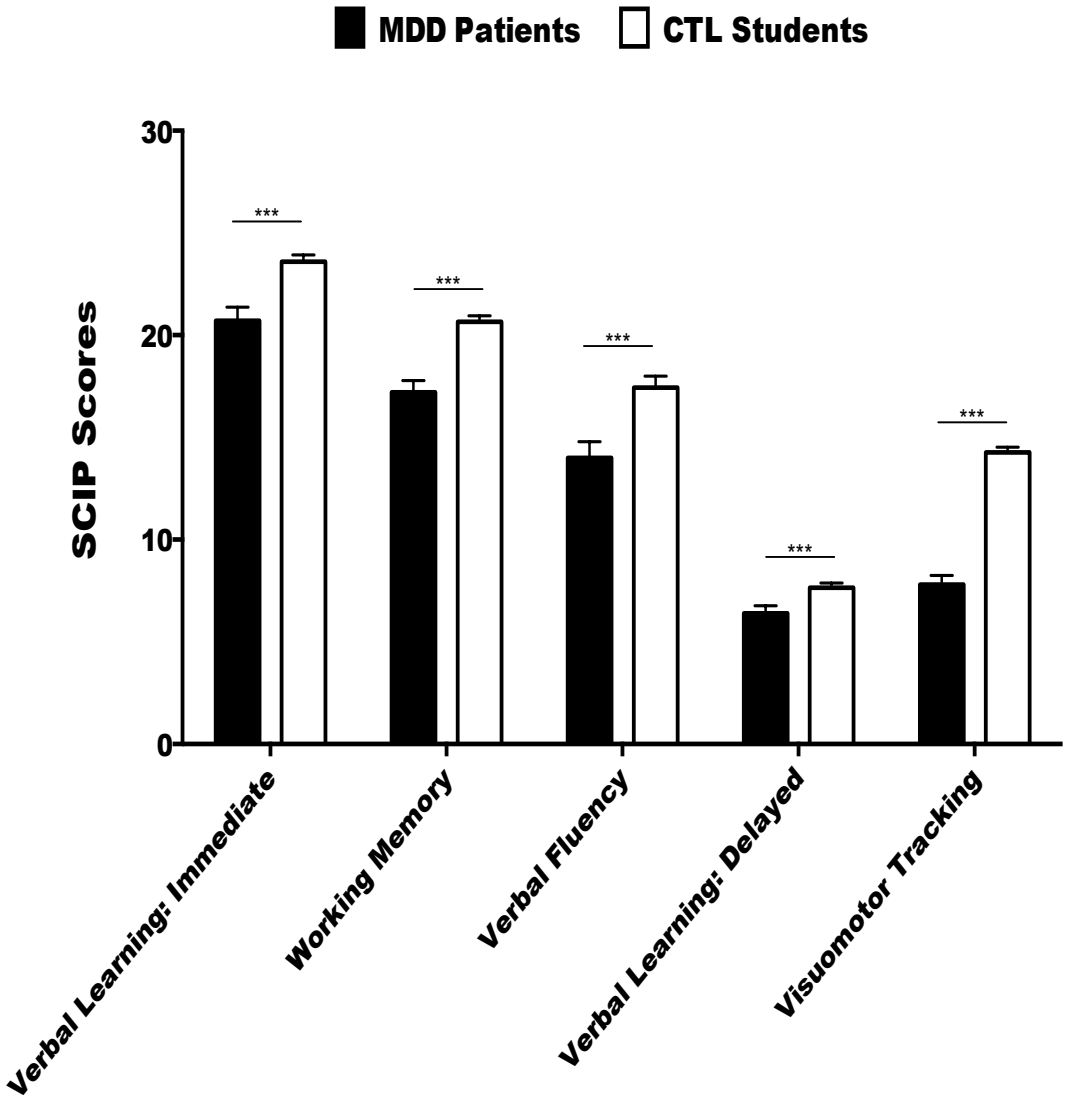

Table 1. Sample characteristics for patients with major depressive disorder.

Information	
N	40
Demographics	
Sex, % women	60
Age, M (SD)	50.8 (1.8)
Menopause status	
Menopausal women, %	30.0
Non-menopausal women, %	30.0
Race/ethnicity, % White	80
Civil status	
Single, %	32.5
Married or common-law, %	42.5
Divorced or separated, %	25
Occupation status	
Employed, %	47.5
Unemployed or retired, %	10
Sick-leave, %	42.5
Educational background	
Years of schooling, M (SD)	15.0 (.60)
Secondary-level, %	32.5
Pre-College (CEGEP), %	22.5
College, %	42.5
Health behaviors	
Smoking	
Non-Smokers, %	50.0
Ex-Smokers, %	17.5
Smokers, %	32.5
Illicit drugs	
Non-Users, %	90.0
Ex-Users, %	10.0
Alcohol	
Ex-Consumers, %	10.0
Non-Consumers, %	60.0
Characteristics	
Handedness	
Right handed, %	95.0

Table 2. Descriptive statistics and correlation matrix of study variables among patients with major depressive disorder.

		Correlations												
Variable	M (SD)	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. HDRS	12.7 (9.9)	–												
2. CGI	3.6 (1.8)	.781***	–											
3. GAF	61.0 (19.2)	-.798***	-.945***	–										
4. Global SDS	14.8 (9.4)	.798***	.832***	-.801***	–									
5. Global WHO–DAS	76.1 (24.1)	.671***	.514***	-.549***	.741***	–								
6. EDEC: Perceived Cognitive Deficits	58.7 (40.1)	.670***	.650***	-.636***	.848***	.68**	–							
7. EDEC: Perceived Functional Impacts	51.8 (41.9)	.667***	.647***	-.608***	.799***	.66**	.95**	–						
8. PDQ–D5	9.1 (5.2)	.808***	.718***	-.729***	.843***	.73**	.888***	.87**	–					
9. SCIP–VLTi	20.7 (4.2)	-.197	-.216	.222	-.201	.039	-.303†	-.260	-.204	–				
10. SCIP–WMT	17.2 (3.7)	-.291†	-.334*	.199	-.392*	.036	-.346*	-.327*	-.298†	.335*	–			
11. SCIP–VFT	14.0 (5.0)	-.219	-.183	.142	-.266	-.061	-.252	-.198	-.179	.309†	.312*	–		
12. SCIP–VLTd	6.4 (2.3)	-.079	-.183	.141	-.131	.155	-.208	-.145	-.047	.69**	.337*	.242	–	
13. SCIP–VMT	7.8 (2.8)	-.223	-.163	.153	-.232	-.02	-.194	-.195	-.129	.335*	.168	.42**	.199	–
14. SCIP–Global Index	66.1 (12.4)	-.305†	-.316*	.252	-.368*	.024	-.388*	-.335*	-.267†	.77**	.63**	.74**	.662***	.591***

Note: *** p < 0.001; ** p < 0.01; * p < 0.05; † p < 0.10
Abbreviations: *CGI* = Clinical Global Impression; *EDEC* = Échelle d'autoévaluation cognitive (self-evaluation of cognition scale), *GAF* = Global Assessment of Functioning Scale; *HDRS* = Hamilton Depression Rating Scale; *PDQ-D5* = Perceived Deficits Questionnaire for depression-5 item; *SCIP* = Screen for Cognitive Impairment in Psychiatry (*VLi*: Verbal learning immediate, *WMT*: working memory task, *VMT*: verbal memory task, *VLTd*: Verbal learning task delayed, *VMT*: Visuomotor tracking task); *SDS* = Sheehan Disability Scale; *WHO-DAS* = World Health Organization Disability Assessment Schedule 2.0.

Table 3. Sequential regression of SCIP global indices for depressed patients (n = 40) and healthy student controls (n = 74). Model 1 contained all covariates, while three separate Model 2s were entered thereafter to assess associations that were over and above these covariates. Confirmatory analysis that split these analyses separately between MDD and CTLs (rather than as a covariate) revealed that significance was attained strictly among the MDD patients.

Predictors	R^2	ΔR^2	*B*	*S. E.*	*T*	*P*	95% CI
Model 1.	.452	–	–	–	–	–	–
Group (0 = CTL; 1 = MDD)	–	–	-13.70	3.377	-4.056	.001	-20.39, -7.01
Sex (0 = ♂; 1 = ♀)	–	–	5.54	.116	2.746	.007	1.54, 9.54
Age (Continuous)	–	–	-.233	.116	-2.007	.047	-.474, -.003
Model 2A.	.493	.041	–	–	–	–	–
Clinical impression (*CGIS*)	–	–	-2.451	.837	-.293	.004	-4.11, -.792
Model 2B.	.487	.035	–	–	–	–	–
Global Disability (*SDS*)	–	–	-.453	.168	-2.691	.008	-.787, -.119
Model 2B.	.503	.051	–	–	–	–	–
Perceived Cognitive Deficits (*EDEC*)	–	–	-.123	.037	-3.308	.001	-.197, -.049
Model 2C.	.500	.047	–	–	–	–	–
Perceived Functional Impacts (*EDEC*)	–	–	-.114	. 036	-3.179	.002	-.186, -.043

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Chapter 4.4: Article 4- Attention deficit disorder and the Screen for Cognitive Impairment in Psychiatry

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ABSTRACT

Background: Cognitive deficits constitute a core dimension of attention deficit disorder (ADHD). This study aimed to evaluate the feasibility of screening for cognitive impairments in ADHD within the clinical setting with an abbreviated cognitive battery, the Screen for Cognitive Impairment in Psychiatry (SCIP).

Methods: Patients with ADHD completed questionnaires and the SCIP. DSM-IV-TR diagnoses and clinical global impression score were assigned while blinded to test results.

Results: ADHD patients (n = 36) showed significant cognitive impairments compared to controls (n = 74) that were comparable to those in patients with resistant depressive disorder (n = 40). Clinical and perceived indices of function and disability were associated with cognition.

Conclusions: This study shows that it is possible to evaluate cognition in ADHD with a brief instrument. Importantly, the cognitive deficits of ADHD were correlated to functional impairments confirming the importance of a global evaluation of cognition in attention deficit disorder.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a complex disorder with pleotropic presentations. It affects individuals across the lifespan. The disorder is associated with significant impairments in functioning (Goodman, 2007). Individuals with ADHD have lower levels of educational and professional achievement (Kupper et al., 2012). They also have greater levels of antisocial behavior, driving impairment, and addictive behaviors (Shaw et al., 2012). A recent review of the literature regarding the economic burden imposed by ADHD estimated the annual costs to the US economy of 143-266 billion USD (Doshi et al., 2012).

ADHD has been defined in large part by the presence of cognitive deficits, as well as hyperactivity and impulsivity (Bush, 2010). Several domains of cognitive dysfunction have been identified in ADHD (Castellanos et al., 2006): executive motor inhibition, planning, vigilance, set shifting, verbal and spatial working memory. Adults with ADHD show deficits in attention, behavioral inhibition and memory similar to those found in children (Seidman et al., 2004). Moreover, there is evidence to suggest that the cognitive deficits of ADHD are not limited to executive dysfunction(Vaidya and Stollstorff, 2008) and that the executive dysfunction may in part be explained by other more primary deficits(Castellanos et al., 2006; Kupper et al., 2012).

The clinical diagnosis of ADHD is established through the identification of symptoms of inattention, hyperactivity and impulsivity that continue throughout the lifespan (Haavik et al., 2010). Behavioral rating scales, most often self-rated, are often used for screening and for following the evolution of symptomatology over time (Coogan et al., 2012; Murphy and Adler, 2004). Although some propose that neuropsychological testing is essential to the diagnosis of ADHD (Gallagher and Blader, 2001), the pleotropic nature of the cognitive profiles of affected individuals limits the utility of this approach. As a result, neuropsychological evaluation is principally used to determine the specific cognitive profile of an individual in order to personalize global treatment plans (Koziol and Stevens, 2012; Lange et al., 2014).

The objective measurement of the cognitive deficits of ADHD in the clinical setting remains limited. This may be a result of several factors, one of which is the difficulty of obtaining neuropsychological evaluations due to high costs and a dearth of professionals. Another factor may be the complexity of interpreting the highly variable relationship between cognitive deficits manifested by individuals with ADHD and the symptom profile which justifies the clinical diagnosis of ADHD. Yet, it is clear that a greater appreciation of a patient's cognitive deficits is essential for the elaboration of a personalized treatment plan. Brief neuropsychological batteries have been developed for clinical populations such as the elderly and patients with schizophrenia (Cholet et al., 2014; Randolph et al., 1998). Despite their brevity compared to standard neuropsychological testing, these tools remain impracticable in clinical settings, as they require 25-35 minutes to administer or access to computer technology.

In order to address the need for a short objective evaluation of cognitive deficits in psychiatry, Scot Purdon developed the Screen for Cognitive Impairment in Psychiatry (SCIP)(Purdon, 2005j). Administration of the SCIP requires 15 minutes, a pencil, paper, and a stop-watch. The SCIP has been validated in a variety of languages and has been shown to detect cognitive deficits in patients with schizophrenia, bipolar disorder and major depressive disorder (Cuesta et al., 2011; Gomez-Benito et al., 2013; Guilera et al., 2009; Jensen et al., 2015; Ott et al., 2016; Pino et al., 2008; Purdon, 2005j; Rojo et al., 2010; Svendsen et al., 2012). This study is the first to report the use of the SCIP in a population with attention deficit hyperactivity disorder.

Our group proceeded to elaborate a protocol for the validation of a French version of the SCIP (Tourjman et al., 2016e) which included testing of this instrument in a variety of clinical populations. First we validated the French version of the SCIP in a healthy population required to have a college education in order to approximate Purdon's original validation of the English version. Subsequently, we proceeded to test the instrument in clinical populations within a clinic setting. In this article we report the results of the use of the SCIP in a population of patients with attention

deficit disorder. The purpose of this study was to demonstrate the feasibility of using the SCIP in a routine clinical setting among individuals suffering from attention deficit disorder.

METHODS

Participants

This study was approved by the Institutional Review Board (IRB) of the Institut en Santé Mentale de Montréal (IUSMM) following established guidelines. All participants provided written informed consent after study procedures were explained. The work described was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Thirty-six consecutive individuals consulting for follow up in a mood disorder clinic were invited to participate in the study.

The mood disorder clinic is part of the Mood and anxiety disorder programme of the IUSMM. Patients with suspected or complex ADHD are referred for diagnostic clarification and treatment. As much as possible, inclusion and exclusion criteria were kept to a minimum so as to allow the closest possible approximation to the typical clinical population. Inclusion criteria were limited to being followed by a psychiatrist in the programme, having a diagnosis of ADHD, and being able to give informed consent. There were no exclusion criteria other than being unable to comprehend French and having another diagnosis as the primary focus of treatment.

We compared the results of patients with ADHD to those of healthy controls and Major Depressive Disorder participants included in the same study. Healthy controls were included in the validation phase of this study and were required to have a college education in order to approximate Purdon's original validation sample (Purdon, 2005j). Patients with MDD were followed in the same clinic as the patients with ADHD and were invited to participate in the study and were subject to the same procedures as the patients with ADHD. Detailed analysis of healthy control subjects (Tourjman et al., 2016e) and patients with MDD(Tourjman et al., 2016i) is presented in separate articles.

General Protocol

Participants were invited to participate in the study following a routine clinical evaluation. The study questionnaires and the SCIP were administered prior to a clinical evaluation. Questionnaires included a self-report developed in order to capture patients' experience of the SCIP, the Sheehan disability questionnaire (Sheehan et al., 1988) and the Echelle d'auto-évaluation cognitive (EDEC) (Charbonneau et al., 2016), a questionnaire of perceived cognitive deficits and of the impact of these deficits on functioning. The EDEC items question specific cognitive impairments in daily life and then request the subject to indicate the impact of this impairment on function. Higher scores on each of these instruments indicate greater impairments. Start and finish times for the administration of the SCIP were captured on a separate sheet and are as follows: M = 12.50 minutes, SD = 2.93. Slightly more variable was the subjects' perceived time of completion: M = 17.92 minutes, SD = 6.02. The treating psychiatrist completed a full DSM-IV-TR diagnosis (DSM-IV-TR 2000 4th ed., text rev.) and assigned a clinical global impression score (CGI-S) (Berk et al., 2008) while blinded to the results of the questionnaires or the SCIP. Higher score on the CGI-S corresponds to greater clinical severity. The multiaxial DSM-IV-TR diagnosis included a global assessment of functioning (GAF), a measure which combines an assessment of severity of clinical symptoms and functioning. Lower scores on the GAF indicate greater severity, and or greater impairment of function.

Statistical Analysis

Preliminary analyses of the data obtained from patients with ADHD employed one-way analysis of variance (ANOVA), Pearson product-by-moment correlations to respectively assess categorical relations (sex, menopause, race/ethnicity, civil status, occupation status, educational attainment, health behaviors) and continuous associations (age, years of schooling) vis-à-vis separate domains of SCIP cognitive functioning. Tukey's post-hoc analysis was used for significant group differences. In order to compare the performance of the different groups (ADHD, MDD, healthy controls) on the SCIP subscales one-way ANOVAs

were used to assess group differences in overall SCIP performance (SCIP sum score) as a function of ADHD patients as well as the MDD patients and healthy controls.

Main analyses employed sequential regressions to assess global SCIP indices among patients with ADHD and the healthy control participants from the validation phase of the study and patients with MDD using as an outcome a SCIP global index that summed all five SCIP domains. Healthy controls and patients with MDD were included in order to increase the power of the analysis and in order to account for the contribution of clinical factors. Model 1 included group, age, and years of schooling as covariates. Model 2 entered clinical impressions and subjective appraisals in turn for five different psychological measures. Specifically, Model 2A entered the global assessment of function scale (GAF), Model 2B entered the clinical impressions of disability (CGI-S), Model 2C entered the Sheehan Disability Scale (SDS), Model 2D entered the Echelle d'auto-évaluation cognitive (EDEC) perceived cognitive deficits, and Model 2E entered the EDEC perceived functional impacts. In this manner, results reflect effects that are over and above those attributable to group, age, and years of schooling.

Beyond statistical significance, we focused on effect magnitude changes from Model 1 with covariates entered in comparison to Models 2A and 2B using R statistics to guide interpretation. Effect sizes and 95% confidence intervals (CI) are reported where appropriate with significance strictly set at $\alpha = .05$. Preliminary descriptive analyses of skew and kurtosis revealed that study variables were normally distributed. Statistical analysis was run using the Statistical Package for the Social Sciences© Version 22 for Macintosh and Prism 5© for Macintosh.

Results

Sample Descriptives

A description of the sample can be found in **Table 1**. With regards to SCIP performance, no group differences were found as a function of sex, race/ethnicity, handedness, alcohol consumption, cigarette smoking, drug use, work status, or civil status. Non-menopausal women scored higher than menopausal women on SCIP Visuomotor Tracking ($F_{[1,14]} = 4.79$, $p = .046$).

Using Pearson correlations, we found that age was negatively associated with SCIP Visuomotor Tracking (r = -.44, p = .007). Years of schooling was positively associated with SCIP Working Memory (r = .43, p = .008), SCIP Verbal Fluency (r = .56, p < .001), SCIP Verbal Leaning Delayed (r = .34, p = .043), and the SCIP Global Index (r = .55, p = .001). For this reason, years of schooling will be used as a covariate in our main analyses as well as age that is inherently associated with menopause.

Preliminary Analysis: Cognitive Performance and Control Comparisons

Figure 1 illustrates SCIP group differences according to MDD patients (n = 40), healthy controls (n = 74), and ADHD patients (n = 36). In a preceding analysis our group reported that MDD patients performed significantly worse than healthy controls on all SCIP domains (Tourjman et al., 2016i). In the current study, this was also the case for ADHD patients who scored lower than controls for all SCIP domains (ps < .002). Specifically, Tukey post-hoc analyses revealed that the ADHD patients scored lower on SCIP Verbal Fluency (p = .037, 95%CI: .0964, 3.881), SCIP Working Memory (p < .001, 95%CI: 1.98, 5.285), SCIP Verbal Fluency (p = .016, 95%CI: .466, 5.646), SCIP Verbal Learning Delayed (p = .019, 95% CI: .176, 2.42), and SCIP Visuomotor Tracking (p < .001, 2.98, 5.427). When comparing patient groups, the only significant finding revealed that despite impairment on this task, ADHD patients scored significantly better than MDD patients on SCIP Visuomotor Tracking (p = .001, -3.594, -.804).

Preliminary Analysis: Variable Associations

Preliminary analysis used Pearson's correlations to assess associations among actual time (M = 12.50, SD = 2.93) and perceived time (M = 17.92, SD = 6.02) for SCIP completion and cognitive performance. Interestingly, actual time and perceived time to complete the SCIP were not correlated. Only perceived time of SCIP completion showed a negative correlation with the SCIP Global Index (r = -.44, p = .007). Specifically, perceived time was negatively associated with SCIP Working

Memory (r = -.38, p = .021), SCIP Verbal Fluency (r = -.34 p = .045), and SCIP Visuomotor Tracking (r = -.38, p = .024).

Preliminary analyses comparing the passage of time between ADHD and MDD patients revealed no difference in perceived time (p = .22), but MDD patients spent significantly longer than ADHD completing the SCIP ($F_{[1,72]}$ = 13.31, p < .001).

Table 2 reports the descriptive statistics and correlation matrix of study variables used for exploratory purposes. Importantly, all psychometrics were strongly correlated with each other.

Main Analysis: Sequential Regressions

Five sequential regressions were used to predict global SCIP indices that had as a base model group (Control vs. ADHD), age (continuous), and years of schooling (continuous) entered as covariates in Model 1. This was followed sequentially by GAF in Model 2A, the CGIS in Model 2B, the SDS in Model 2C, the EDEC perceived cognitive deficits in Model 2D, and the EDEC perceived functional impacts in Model 2E. In this manner, we were able to delineate the separate associations of interest while accounting for covariates. This was followed by confirmatory analyses that were split between ADHD and controls.

All statistical parameters are reported in **Table 3**. Model 1 with covariates was significant ($F_{[3,106]}$ = 21.97, p < .001). For the entire sample, the SCIP global index was significantly negatively associated with age and negatively associated with years of school, while only trending towards poorer performance among ADHD patients compared to controls. Significance was attained beyond these covariates only when entering global clinical impressions (CGI-S) in Model 2A ($F_{[4,105]}$ = 18.76, p < .001) and when entering the EDEC perceived cognitive deficits in Model 2D ($F_{[4,105]}$ = 17.92, p < .001). In both cases among ADHD and HC, SCIP Global Indices were significantly lower (indicating decreased cognitive deficit) as these clinical impressions and perceived cognitive deficits were higher (indicating increased clinical severity and increased perception of cognitive deficit).

Discussion

Cognitive performance was significantly impaired in ADHD. Patients with ADHD performed worse than controls on all domains. They were as impaired as patients with major depression with the exception of the visuomotor tracking task, a measure of executive function, where they performed somewhat better than the major depression group. The performance on the SCIP was strongly correlated with clinical global impression suggesting that cognitive performance is an important determinant of clinical severity in ADHD.

Patients' perception of their cognitive deficits correlated with deficits in the working memory task, with perception of worse functioning being associated with worse performance on the working memory task, although this relationship was only marginally significant. In major depression (Mahbleshwarkar et al 2015, Potvin et al. submitted, Ott et al. 2016) as well as schizophrenia (Gould et al., 2013; Medalia and Lim, 2004) discordance between subjective perception of cognitive deficit and objective measures of cognitive deficit has been reported. Despite a moderate correlation, a discordance of subjective and objective cognitive function similar to that seen in major depression is noted in our ADHD sample. Nevertheless, there was an intriguing difference between the ADHD and MDD groups. In particular, the perception of time to complete the SCIP was correlated to cognitive performance in ADHD, while the actual time to complete the test was correlated to cognitive performance in MDD. This suggests differences in the perception of the passage of time which may be unique to ADHD(Suarez et al., 2013; Wilson et al., 2013) and may explain some of the symptomatology known to be characteristic of ADHD.

The objective of this study was to demonstrate the feasibility of evaluating the cognitive deficits of ADHD with a brief neuropsychological battery within a clinical context. The administration of the SCIP was mastered after a brief training session. Time of administration was relatively short at 12 minutes and was easily added to a routine clinical evaluation. Patients indicated that they considered the test to be a useful addition to the clinical evaluation and testing led to a re-evaluation of

treatment in several cases. The SCIP has 3 alternate versions making it possible to follow an individual's evolution with changes in treatment.

In this sample years of schooling and age affected performance on the SCIP and this underlines the importance of understanding performance on cognitive tests in the context of the individual's distinctive characteristics.

Limitations

The sample size of this study is small and does not permit the detection of weaker correlations. Even though we controlled for it, the patient population included in the study were not matched for age. Treatment status and response was not controlled. This naturalistic aspect reinforces the sensitivity and importance of testing suggesting important deficits despite treatment. Nevertheless, these results cannot be considered definitive and require future longitudinal approaches. Further studies with larger populations may permit greater sensitivity to detect subtler influences on cognition.

Conclusions

This study highlights the prevalence of cognitive deficits in a clinical sample of individuals with ADHD. Cognition was related to function and this despite numerous potential confounding factors, including active treatment. A tool enabling the objective evaluation of cognitive function has the potential to inform clinical decisions. This study suggests that a brief cognitive test such as the SCIP can be such a tool. Most importantly, the demonstration of the scale of objective cognitive deficits in a clinical sample of adults with ADHD and the correlation of these with clinical status and with functioning reinforces the importance of integrating objective as well as subjective evaluations of cognition to the assessment of attention deficit disorder.

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Figures and Tables and Associated Captions

Figure 1. Estimated means (standard deviation) for scores on the Screen for Cognitive Assessment in Psychiatry (SCIP) as a function of Major Depressive Disorder (MDD) patients (*n* = 40), a control (CTL) group (*n* = 74), and Attention Deficit Hyperactivity Disorder (ADHD) patients (*n* = 36). This Figure shows how the SCIP scores differ significantly (***p < .001, **p < .01) between the CTL group for both MDD and ADHD patients as assessed with one-way ANOVAs for all cognitive domains. ADHD patients scored significantly higher on SCIP Visuomotor Tracking than did MDD patients.

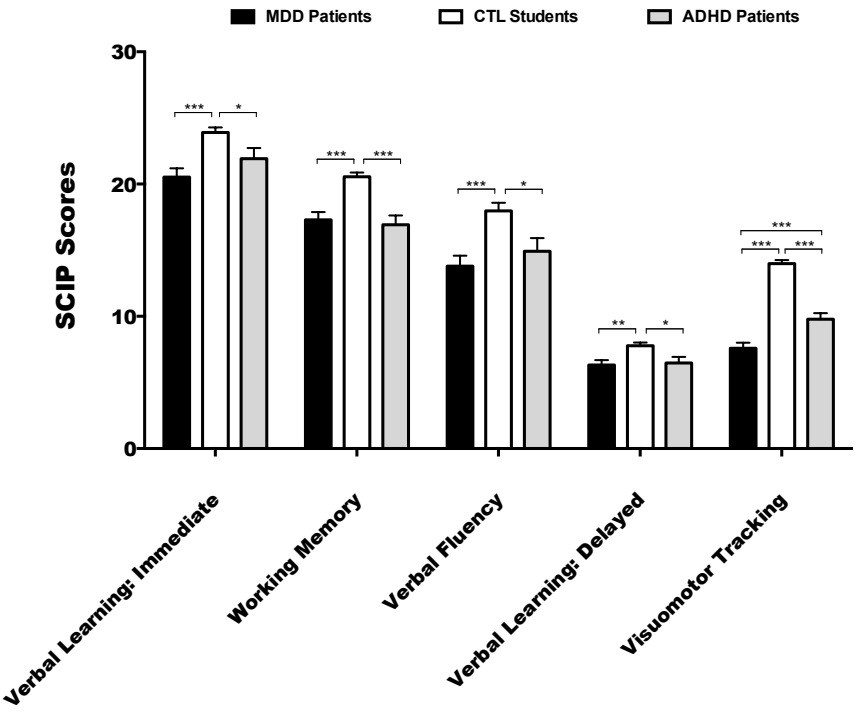

Table 1. Sample characteristics

Information	
N	36
Demographics	
Sex, % women	38.9
Age, M (SD)	39.59 (11.98)
Menopause status	
Menopaused women, %	30.0
Non-menopaused women, %	70.0
Race/ethnicity, % White	86.1
Civil status	
Single, %	41.7
Married or common-law, %	33.3
Divorced or separated, %	25
Occupation status	
Employed, %	58.3
Student, %	8.3
Unemployed or retired, %	5.6
Sick-leave, %	27.8
Educational background	
Years of schooling, M (SD)	14.19 (4.89)
Secondary-level, %	47.2
Pre-College (CEGEP), %	16.7
College, %	35.9
Health behaviors	
Smoking	
Non-Smokers, %	30.6
Ex-Smokers, %	27.8
Smokers, %	41.7
Illicit drugs	
Users, %	50.0
Non-Users, %	55.6
Ex-Users, %	36.1
Alcohol	
Consumers, %	50.0
Ex-Consumers, %	13.9
Non-Consumers, %	36.1
Characteristics	
Handedness	
Right handed, %	77.8

Table 2. Descriptive statistics and correlation matrix of study variables

		Correlations									
Variable	**M (SD)**	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
1. CGI	3.9 (1.5)	–									
2. GAF	61.0 (15.4)	-.82***	–								
3. Global SDS	15.8 (7.8)	.50***	-.41*	–							
4. EDEC: Perceived Cognitive Deficits	74.4 (34.4)	.45**	-.27	.70***	–						
5. EDEC: Perceived Functional Impacts	63.8 (63.8)	.46**	-.25	.74***	.93***	–					
6. SCIP–VLTi	21.9 (4.9)	-.23	.15	-.19	-.27	-.16	–				
7. SCIP–WMT	16.9 (4.2)	-.51**	.43**	-.22	-.34*	-.33*	.54***	–			
8. SCIP–VFT	14.9 (6.0)	-.45**	.39*	-.05	.038	.012	.21	.54***	–		
9. SCIP–VLTd	6.5 (2.7)	-.22	.12	-.21	-.28	-.218	.78***	.51***	.22	–	
10. SCIP–VMT	9.8 (2.8)	-.56***	.48**	-.47**	-.39*	-.42**	.42**	.69***	.47**	.41*	–
11. SCIP–Global Index	70.0 (15.6)	-.52***	.42*	-.26	-.28†	-.25	.75***	.86***	.72***	.71***	.75***

Note: *** p < 0.001; ** p < 0.01; * p < 0.05; † p < 0.10

Abbreviations: ***CGI*** = Clinical Global Impression; ***EDEC*** = Échelle d'autoévaluation cognitive (self-evaluation of cognition scale), ***GAF*** = Global Assessment of Functioning Scale; ***SCIP*** = Screen for Cognitive Impairment in Psychiatry (***VLi***: Verbal learning immediate, ***WMT***: working memory task, ***VMT***: verbal memory task, ***VLTd***: Verbal learning task delayed, ***VMT***: Visuomotor tracking task); ***SDS*** = Sheehan Disability Scale.

Table 3. Sequential regression prediction SCIP Global Indices for ADHD patients ($N = 36$) and healthy CTLs ($N = 74$). Model 1 contained all covariates, while five separate Model 2s were entered thereafter to assess associations that were over and above these covariates. While adjusting for covariates, only Clinical Global Impressions (CGI-S) in Model 2B and Perceived Cognitive Deficits (EDEC) in Model 2D predicted SCIP performance.

Predictors	R^2	ΔR^2	*B*	*S. E.*	*t*	*p*/Δ*p*	95% CI
Model 1.	.38	–	–	–	–	–	–
Group (0 = CTL; 1 = ADHD)	–	–	-5.50	3.02	-1.82	.071	-11.47, .48
Age (Continuous)	–	–	-.36	.12	-3.00	.004	-.61, -.12
Years of Schooling	–	–	1.46	.31	1.25	.001	-.083, .37
Model 2A.	.39	.01	–	–	–	–	–
Global Assessment of Function (*GAF*)	–	–	.14	.11	1.25	.214	-.083, .37
Model 2B.	.42	.03	–	–	–	–	–
Clinical Global Impression (*CGI-S*)			-3.00	1.21	-2.45	.016	-5.34, -.56
Model 2C.	.39	.01	–	–	–	–	–
Global Disability (*SDS*)	–	–	-.24	.23	-1.03	.305	-.71, .22
Model 2D.	.41	.02	–	–	–	–	–
Perceived Cognitive Deficits (*EDEC*)	–	–	-.09	.05	-1.98	.049	-.18, -.00
Model 2E.	.40	.02	–	–	–	–	–
Perceived Functional Impacts (*EDEC*)	–	–	-.07	.04	-1.64	.104	-.15, -.01

Chapter 4.5: Article 5 - Antipsychotics' effects on blood levels of cytokines in schizophrenia : a meta-analysis

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Keywords : Schizophrenia Antipsychotic drugs Cytokines Inflammation

Objectives : Evidence-based medicine suggests that schizophrenia is associated with an inflammatory syndrome, but the extent to which this syndrome is normalized by antipsychotic treatment has yet to be determined. Methods : A systematic quantitative review of the effects of antipsychotics on peripheral cytokine levels in schizophrenia was performed, using follow-up studies providing in vivo cytokine assessments before and after treatment. Results : We retrieved 23 studies (total of 762 subjects) which showed that antipsychotic treatment significantly increases plasma levels of soluble interleukin-2 receptor and reduces the plasma levels of interleukin-1β and interferon-γ. Conclusions : These results show that antipsychotics produce anti-inflammatory effects in schizophrenia.

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1. Introduction

The incidence rates of schizophrenia are on the order of 12 to 15 per 100,000 person-years (McGrath et al., 2008). This mental disorder is associated with poor outcome, and significant and persistent impairment (Newman et al., 2012). Schizophrenia is a heterogeneous disorder and its etiology remains incompletely elucidated. Among possible causes, immunological factors have been increasingly implicated in its pathogenesis and course (Benros et al., 2012). The inflammatory system may trigger or modulate the course of schizophrenia through complex mechanisms influencing neuroplasticity and neurotransmission (Benros et al., 2012). Alterations in cytokine levels in schizophrenia have been repeatedly described (Miller et al., 2011; Potvin et al., 2008). The effect of antipsychotics on cytokine levels remains, as yet, incompletely explored. A few groups have recently published reviews which concluded that antipsychotics have anti-inflammatory effects in schizophrenia that may be related to antipsychotic response, and in some cases, pro-inflammatory effects that may be related to important side effects, such as weight gain (Drzyzga et al., 2006) ; Tourjman et al., 2012). In order to further clarify the extent of these effects, we conducted a meta-analysis of antipsychotic-induced cytokine changes in schizophrenia.

2. Methods

2.1. Selection procedures

2.1.1. Search strategies A systematic search was performed in the electronic databases PubMed and EMBASE using the keywords “antipsychotic” and “inflammation” or “cytokine” or “interleukin” or “inflammatory markers” or “IFN” or “TGF” or “TNF”. This search identified studies before January 1st, 2013. Additionally, studies were identified by cross-referencing.

2.1.2. Selection criteria Studies were included if they met the following criteria : (a) had involved subjects with DSM/ICD schizophrenia-spectrum disorder ; (b) had employed a pre–post design which involved the administration of antipsychotics

(typical, atypical, mixed); and (c) had measured in vivo the level of at least one cytokine before and after the treatment Schizophrenia Research 151 (2013) 43–47 in plasma or serum. When several articles dealt with the same population, we selected the article with the largest sample. Studies were excluded if : 1) the study design was cross-sectional ; 2) the sample of patients comprised patients with DSM Axis-I disorders other than schizophrenia-spectrum disorders ; 3) cytokine levels were measured using cerebrospinal fluid ; and 4) cytokine levels were measured using supernatants of leucocytes stimulated in vitro, which vary widely in the conditions of in vitro incubation. We excluded from the metaanalysis outcome measures reported in less than 2 studies. 2.1.3. Recorded variables The variables for each article included in the meta-analysis were : sample sizes, year of publication, gender (proportion of females), participants' mean age, follow-up length, duration of illness, antipsychotic type, and type of cytokine assessed. To achieve a high standard of reporting, we have adopted ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA) guidelines (Moher et al., 2009).

2.2. Statistical analysis Data were entered into an electronic database and analyzed with a quantitative meta-analytical approach using Comprehensive MetaAnalysis software version 2 (Biostat, Inc., Englewood, NJ, USA). CMA software employs the same computational algorithms used by the Cochrane collaborators to weight studies by the inverse variance method (Borenstein et al., 2009). The primary effect size measure was the difference in plasmatic cytokines after antipsychotic treatment (followup vs baseline). The effect size was estimated by calculating Hedges' unbiased g, with negative values reflecting decreased levels of plasmatic cytokines at follow-up as compared to baseline. Hedges' g is obtained with the difference between the means of the baseline and follow-up groups, divided by the SD and weighted for sample size, in order to correct for bias from small sample sizes (Hedges and Olkin, 1985). To determine whether categorical factors modified the cytokine changes, subgroup analyses were performed (Paulson and Bazemore, 2010). The influence of continuous moderator variables was tested using meta-regression analyses. To limit risk of false positive (type I) errors arising from multiple

comparisons we adjusted pb0.05 by dividing α with the number of meta-regressions. Heterogeneity among study point estimates was assessed with the Q statistics (Paulson and Bazemore, 2010) with magnitude of heterogeneity being evaluated with the I^2 index (Higgins and Thompson, 2002; Higgins et al., 2003). As the database was characterized by high heterogeneity, we employed random effect models which are more conservative than fixed-effect models, and appear to better address heterogeneity between studies and study populations (Cooper et al., 2009). The possibility of publication bias in the present study was examined by applying the regression intercept of Egger (Egger et al., 1997). In case of publication bias, we adopted the 'trim and fill' method, which aims to both identify and correct for funnel, plot asymmetry arising from publication bias (Duval and Tweedie, 2000). To assess the robustness of the results, we performed sensitivity analyses by sequentially removing each study and rerunning the analysis.

3. Results

3.1. Database This literature search uncovered 71 potential articles. After initial assessment, 48 articles were excluded for the following reasons : in vitro studies, add-on treatment with drugs other than antipsychotics supposed to affect the immune system, incomplete data or non-parametric statistics, and the measure of other immune markers. The final database included 23 studies for a total of 762 subjects (mean age ± SD: 35 ± 6.8 years; mean % of female: 45; n = 21 studies) (Akiyama, 1999; Baptista et al., 2007; Crespo-Facorro et al., 2008; Hinze-Selch et al., 1998; Hinze-Selch et al., 2000; Hori et al., 2007; Igue et al., 2011; Kim et al., 2001; Kim et al., 2000; Kim et al., 2004; Kim et al., 2009; Lin et al., 2011; Maes et al., 2000; Maes et al., 2002; Maes et al., 1995a; Maes et al., 1997; Monteleone et al., 1997; Muller et al., 1997; Pae et al., 2006; Pollmacher et al., 1996; Sarandol et al., 2007; Sirota et al., 2005; Song et al., 2009; Zhang et al., 2009). The follow-up assessment of the cytokine levels was performed on average after 8 weeks. The PRISMA flow chart for inclusion in the meta-analysis and the details of the retrieved studies are described in Supplementary Fig. 1 and Supplementary Table 1.

3.2. Heterogeneity The overall database was characterized for moderate level of between-studies heterogeneity (Q = 47.679, I2 = 53.9%, p b 0.001) which justified the use of random effect models in the analysis.

3.3. Publication bias The visual inspection of funnel plot did not reveal any clear asymmetry, and Egger's regression test (p= 0.65) indicated no publication bias. 3.4. Antipsychotic effects on cytokine levels

3.4.1. Antipsychotic effects on specific cytokines Antipsychotic treatment increased the plasmatic levels of IL-12 and sIL-2R and reduced the plasmatic levels of IL-1β and IFN-γ (Fig. 1A, B). No effects were observed on IL-2, IL-4, IL-6, IL-10, IL-1RA, sIL-6R, TGF-β1 and TNF-α (Fig. 1A, B). In the case of cytokines measured in less than 2 studies, preliminary evidence suggests that antipsychotic treatment increased the plasmatic levels of soluble TNF receptors (sTNF-R) and reduced plasmatic levels of IL-13. No clear evidence of antipsychotic effect on IL-8 has been reported.

3.5. Sensitivity analysis Sensitivity analysis confirmed that the results were robust as no study affected the meta-analytic estimate by more than 6%. 3.6. Moderators Meta-regression analysis revealed that treatment duration had no effect on the meta-analytical estimates (β = −0.005 ; CI95% : −0.028 to 0.016; p = 0.595). There was a significant effect for publication year on meta-analytical estimates (β = −0.018 ; CI95%: −0.033 to −0.004; p = 0.012), with older studies estimating larger effect sizes than the most recent ones. Publication year was able to explain a very little part of the observed heterogeneity (Q = 6.32; p = 0.012). Gender and age revealed no significant effect (β = −0.001 ; CI95% : −0.005 to 0.003; p = 0.604; β = 0.001; CI95% : −0.011 to 0.013; p = 0.876; respectively ; n = 21 studies).

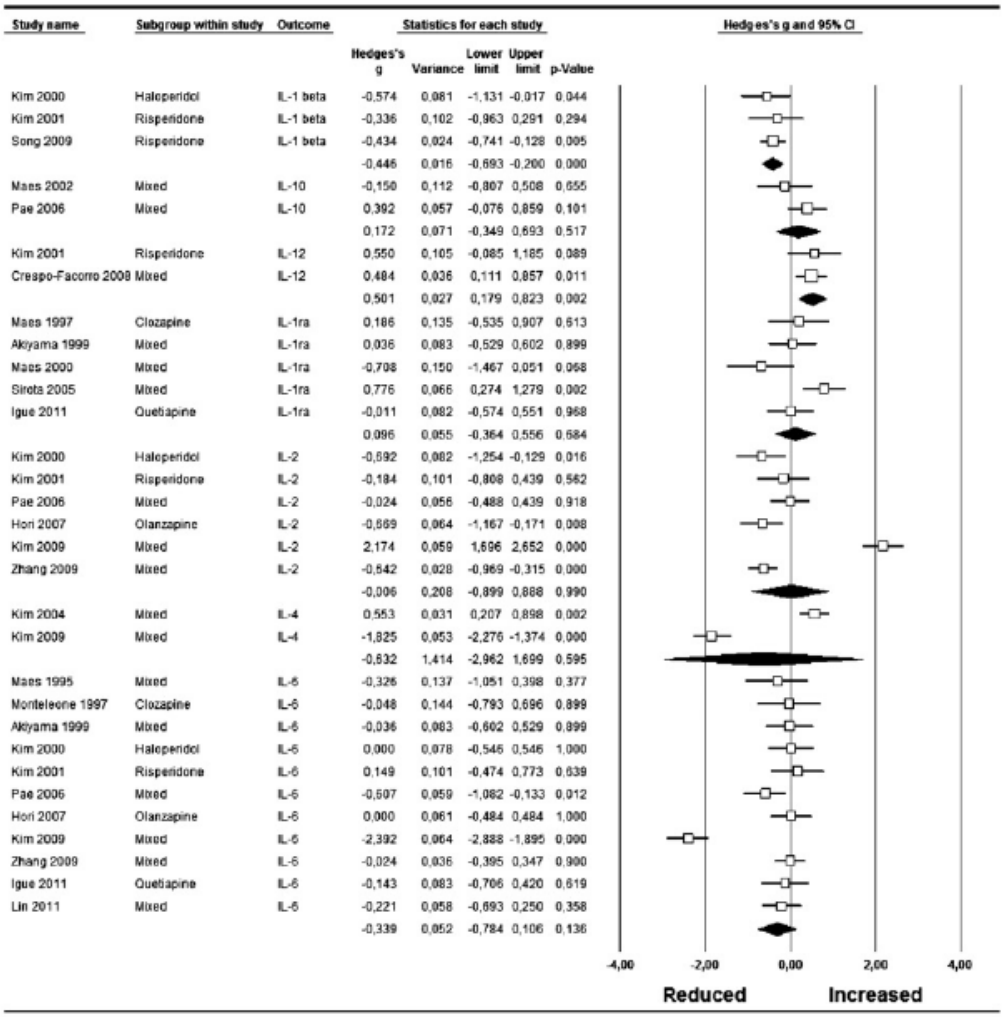
4. Discussion

This meta-analysis confirms that antipsychotic treatment increases peripheral sIL-2R levels in schizophrenia, as previously observed by others (Drzyzga et al., 2006; Miller et al., 2011). Despite significant heterogeneity across studies, the data

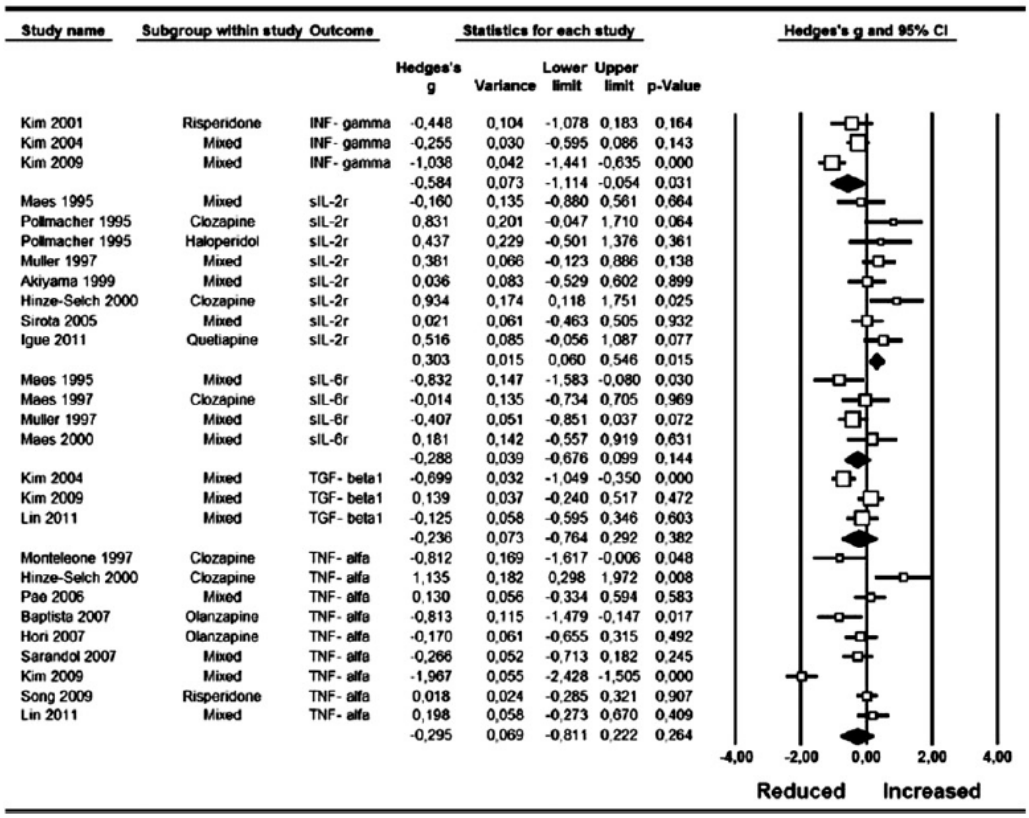
cumulated here also demonstrates in a quantitative manner that antipsychotic treatment leads to decreases in IL-1β and IFN-γ levels in schizophrenia-spectrum disorders, and possibly to increases in IL-12. Although treatment with clozapine seems to be associated with increased IL-6 levels (Maes et al., 1997), this pro-inflammatory cytokine is generally unaffected by antipsychotic treatment. Also unchanged are IL-2, IL-4, IL-10, IL-1RA, sIL-6R, TGF-β1 and TNF-α. Most of the observations are consistent with an anti-inflammatory effect. Activated T-cells shed sIL-2R, and the presence of this receptor competes with its membrane counterpart, thus attenuating the activity of IL-2. Hence, the presence of sIL-2R is a reliable indicator of 44 Fig. 1. A, B. Meta-analysis of the effects of antipsychotics on human cytokines. Negative values of Hedge's g reflect decreased levels of plasmatic cytokines following antipsychotic treatment, while positive results reflect the reverse. 43–47 45 inflammatory disease (Zhang et al., 2009). IFN-γ and IL-1β are pro-inflammatory cytokines and a decrease in their levels would contribute to an attenuation of inflammation (Bast, 2011; Drzyzga et al., 2006). The decrease in these cytokines observed is thus consistent with an anti-inflammatory effect of antipsychotics. Although preliminary, the increase in the soluble receptors of TNF-α seen with clozapine may suggest an anti-inflammatory effect of this agent (Hinze-Selch et al., 2000), since these soluble receptors attenuate the pro-inflammatory activity of TNF-α (Bradley, 2008). These results are in keeping with those showing an increase in sIL-2R by antipsychotics, and deserve further investigation (Igue et al., 2011). Treatment with some antipsychotic agents, such as clozapine and olanzapine, may lead to opposing effects on inflammation possibly through their propensity to generate metabolic syndrome with its consequent effect on the inflammatory system and its response to stress (Hinze-Selch et al., 2000; Zhang et al., 2005). However, there were not enough studies on clozapine and olanzapine to substantiate this assumption. The statistically significant increase in the pro-inflammatory cytokine IL-12 (Vignali and Kuchroo, 2012) subsequent to treatment with risperidone contrasts with the general conception of antipsychotics as having an antiinflammatory effect. Subsequent studies are necessary to confirm these results ; however, they have been attributed by both (Crespo-Facorro et al., 2008) and (Kim

et al., 2001) to the short (≤6 weeks) duration of treatment. This meta-analysis highlights limitations in the understanding of the complex relationship of inflammation and antipsychotic treatment. The challenge of controlling for confounding factors such as phase and duration of illness, medical comorbidities, substance use and psychosocial stress may have hampered the accrual of reliable data. In the case of some cytokines, very little research is available. However, we found no effect of treatment duration, gender and age on outcome, but a very small association emerged with year of publication. Although unexpected, this latter finding may simply be explained by the fact that most studies on sIL-2R (which is increased by antipsychotics) were performed before 2000, whereas most studies on IL-1β and IFN-γ (which are decreased by antipsychotics) were performed after 2000 (see Fig. 1A, B). Overall, the general thrust of data summarized here confirms that antipsychotic treatment corrects, at least in part, the inflammatory state that has been documented previously in schizophrenia (Potvin et al., 2008). The mechanisms through which antipsychotics affect cytokines and their soluble receptors remain unknown. However, a putative role of neurotransmitter receptors that are the targets of antipsychotics on neurons, and are also expressed in several immune cells (Pacheco et al., 2010), should deserve further investigation.

A


Study name
Subgroup within study
Outcome
Statistics for each study
Hedges's g and 95% CI
Hedges's g
Variance
Lower limit
Upper limit
p-Value
Kim 2000 Haloperidol IL-1 beta -0,574 0,081 -1,131 -0,017 0,044
Kim 2001 Risperidone IL-1 beta -0,336 0,102 -0,963 0,291 0,294
Song 2009 Risperidone IL-1 beta -0,434 0,024 -0,741 -0,128 0,005
-0,446 0,016 -0,693 -0,200 0,000
Maes 2002 Mixed IL-10 -0,150 0,112 -0,807 0,508 0,655
Pae 2006 Mixed IL-10 0,392 0,057 -0,076 0,859 0,101
0,172 0,071 -0,349 0,693 0,517
Kim 2001 Risperidone IL-12 0,550 0,105 -0,085 1,185 0,089
Crespo-Facorro 2008 Mixed IL-12 0,484 0,036 0,111 0,857 0,011
0,501 0,027 0,179 0,823 0,002
Maes 1997 Clozapine IL-1ra 0,186 0,135 -0,535 0,907 0,613
Akiyama 1999 Mixed IL-1ra 0,036 0,083 -0,529 0,602 0,899
Maes 2000 Mixed IL-1ra -0,708 0,150 -1,467 0,051 0,068
Sirota 2005 Mixed IL-1ra 0,776 0,066 0,274 1,279 0,002
Igue 2011 Quetiapine IL-1ra -0,011 0,082 -0,574 0,551 0,968
0,096 0,055 -0,364 0,556 0,684
Kim 2000 Haloperidol IL-2 -0,692 0,082 -1,254 -0,129 0,016
Kim 2001 Risperidone IL-2 -0,184 0,101 -0,808 0,439 0,562
Pae 2006 Mixed IL-2 -0,024 0,056 -0,488 0,439 0,918
Hori 2007 Olanzapine IL-2 -0,869 0,064 -1,167 -0,171 0,008
Kim 2009 Mixed IL-2 2,174 0,059 1,696 2,652 0,000
Zhang 2009 Mixed IL-2 -0,642 0,028 -0,969 -0,315 0,000
-0,006 0,208 -0,899 0,888 0,990
Kim 2004 Mixed IL-4 0,553 0,031 0,207 0,898 0,002
Kim 2009 Mixed IL-4 -1,825 0,053 -2,276 -1,374 0,000
-0,632 1,414 -2,962 1,699 0,595
Maes 1995 Mixed IL-6 -0,326 0,137 -1,051 0,398 0,377
Monteleone 1997 Clozapine IL-6 -0,048 0,144 -0,793 0,696 0,899
Akiyama 1999 Mixed IL-6 -0,036 0,083 -0,602 0,529 0,899
Kim 2000 Haloperidol IL-6 0,000 0,078 -0,545 0,545 1,000
Kim 2001 Risperidone IL-6 0,149 0,101 -0,474 0,773 0,639
Pae 2006 Mixed IL-6 -0,597 0,059 -1,082 -0,133 0,012
Hori 2007 Olanzapine IL-6 0,000 0,061 -0,484 0,484 1,000
Kim 2009 Mixed IL-6 -2,392 0,064 -2,888 -1,895 0,000
Zhang 2009 Mixed IL-6 -0,024 0,036 -0,395 0,347 0,900
Igue 2011 Quetiapine IL-6 -0,143 0,083 -0,706 0,420 0,619
Lin 2011 Mixed IL-6 -0,221 0,058 -0,693 0,250 0,358
-0,339 0,052 -0,784 0,106 0,136
-4,00
-2,00
0,00
2,00
4,00
Reduced
Increased

B



Study name	Subgroup within study	Outcome	Hedges's g	Variance	Lower limit	Upper limit	p-Value
Kim 2001	Risperidone	INF- gamma	-0,448	0,104	-1,078	0,183	0,164
Kim 2004	Mixed	INF- gamma	-0,255	0,030	-0,595	0,086	0,143
Kim 2009	Mixed	INF- gamma	-1,038	0,042	-1,441	-0,635	0,000
			-0,584	0,073	-1,114	-0,054	0,031
Maes 1995	Mixed	sIL-2r	-0,160	0,135	-0,880	0,561	0,664
Pollmacher 1995	Clozapine	sIL-2r	0,831	0,201	-0,047	1,710	0,064
Pollmacher 1995	Haloperidol	sIL-2r	0,437	0,229	-0,501	1,376	0,361
Muller 1997	Mixed	sIL-2r	0,381	0,066	-0,123	0,886	0,138
Akiyama 1999	Mixed	sIL-2r	0,036	0,083	-0,529	0,602	0,899
Hinze-Selch 2000	Clozapine	sIL-2r	0,934	0,174	0,118	1,751	0,025
Sirota 2005	Mixed	sIL-2r	0,021	0,061	-0,463	0,505	0,932
Igue 2011	Quetiapine	sIL-2r	0,516	0,085	-0,056	1,087	0,077
			0,303	0,015	0,060	0,546	0,015
Maes 1995	Mixed	sIL-6r	-0,832	0,147	-1,583	-0,080	0,030
Maes 1997	Clozapine	sIL-6r	-0,014	0,135	-0,734	0,705	0,969
Muller 1997	Mixed	sIL-6r	-0,407	0,051	-0,851	0,037	0,072
Maes 2000	Mixed	sIL-6r	0,181	0,142	-0,557	0,919	0,631
			-0,288	0,039	-0,676	0,099	0,144
Kim 2004	Mixed	TGF- beta1	-0,699	0,032	-1,049	-0,350	0,000
Kim 2009	Mixed	TGF- beta1	0,139	0,037	-0,240	0,517	0,472
Lin 2011	Mixed	TGF- beta1	-0,125	0,058	-0,595	0,346	0,603
			-0,236	0,073	-0,764	0,292	0,382
Monteleone 1997	Clozapine	TNF- alfa	-0,812	0,169	-1,617	-0,006	0,048
Hinze-Selch 2000	Clozapine	TNF- alfa	1,135	0,182	0,298	1,972	0,008
Pae 2006	Mixed	TNF- alfa	0,130	0,056	-0,334	0,594	0,583
Baptista 2007	Olanzapine	TNF- alfa	-0,813	0,115	-1,479	-0,147	0,017
Hori 2007	Olanzapine	TNF- alfa	-0,170	0,061	-0,655	0,315	0,492
Sarandol 2007	Mixed	TNF- alfa	-0,266	0,052	-0,713	0,182	0,245
Kim 2009	Mixed	TNF- alfa	-1,967	0,055	-2,428	-1,505	0,000
Song 2009	Risperidone	TNF- alfa	0,018	0,024	-0,285	0,321	0,907
Lin 2011	Mixed	TNF- alfa	0,198	0,058	-0,273	0,670	0,409
			-0,295	0,069	-0,811	0,222	0,264

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.10.011.

Supplementary Table: Characteristics of studies included in the meta-analysis

Study	Subjects	% females	Age (years)	Diagnostic criteria	Diagnosis	Phase / state of illness	Length of illness (months)	Drug at baseline	Follow-up (weeks)	Anti-psychotic	Cytokines checked
Akiyama 1999	26	58	34	DSM-IV	Schizophrenia	NS; NS	63.8	no	8	Mixed	IL-1rRA, IL-6, sIL2R-α
Baptista 2007	18	33	NS	DSM-IV	Schizophrenia	Chronic; in-patients	NS	yes	14	Olan-zapine	TNF-α
Crespo-Facorro 2008	56	38	27	DSM-IV	Schizophrenia-spectrum	First-episode; in-patients	10.9	no	6	Mixed	IL-12
Hinze-Selch 2000	12	50	39	DSM-III-R	Schizophrenic disorder	NS; in-patients	NS	yes	6	Clozapine	sIL-2R, TNF-α
Hori 2007	32	44	35	DSM-IV	Schizophrenia	NS; in- / out-patients	42.0	yes	8	Olan-zapine	IL-2, IL-6, TNF-α
Igue 2011	24	NS	NS	DSM-IV	Schizophrenia-spectrum & SUD	NS; out-patients	90.9	yes	12	Quetia-pine	IL-1RA, IL-6, sIL-2R
Kim 2009	53	55	34	DSM-IV	Schizophrenia	NS; in-patients	74.9	no	6	Mixed	IL-2, IL-4, IL-6, IFN-γ, TGF-β1, TNF-α
Kim 2004	66	61	33	DSM-IV	Schizophrenia	NS; in-patients	54.2	no	8	Mixed	IL-4, IFN-γ, TGF-β1
Kim 2001	19	42	28	DSM-IV	Schizophrenia	NS; in-patients	30.0	no	4	Ris-peridone	IL-1β, IL-12, IL-2, IL-6, IFN-γ
Kim 2000	25	0	30	DSM-IV	Schizophrenia	NS; in-patients	40.0	no	8	Halo-peridol	IL-1β, IL-2, IL-6
Lin 2011	34	53	35	DSM-IV	Schizophrenia	NS; acute	102.8	no	4	Mixed	IL-6, TGF-β1, TNF-α
Maes 2002	17	53	49	DSM-IV	Schizophrenia	Treat-ment-resistant; NS	NS	no	17	Mixed	IL-10
Maes 2000	17	53	49	DSM-IV	Schizophrenia	Treat-ment-resistant; NS	NS	no	17	Mixed	IL-1RA, sIL-6R
Maes 1997	14	35	38	DSM-III-R	Schizophrenia	NS; NS	NS	no	2	Clozapine	IL-1RA, sIL-6R
Maes 1995	14	76	28	DSM-III-R	Schizophrenia	NS; NS	NS	no	9	Mixed	IL-6, sIL-2R, sIL-6r
Monte-leone 1997	13	59	25	DSM-IV	Schizophrenia	NS; NS	90.0	NS	10	Clozapine	IL-6, TNF-α
Muller 1997	39	44	31	DSM-III-R	Schizophrenia	NS; in-patients	54.5	no	11	Mixed	sIL-6R, sIL-2R
Pae 2006	35	40	38	DSM-IV	Schizophrenia	NS; in-patients	72.0	no	8	Mixed	IL-10, IL-2, IL-6, TNF-α
Poll-macher 1995	18	28	32	DSM-III-R	Schizophrenic disorder	NS; NS	NS	NS	6	Clozapine halo-peridol	sIL-2R
Sarandol 2007	40	55	35	DSM-IV	Schizophrenia	NS; NS	NS	no	6	Mixed	TNF-α
Sirota 2005	32	NS	40	DSM-IV	Schizophrenia	NS; NS	71.2	no	8	Mixed	IL-1RA, sIL-2Rα
Song 2009	83	48	27	DSM-IV	Schizophrenia	First-episode; NS	7.0	no	4	Ris-peridone	IL-1β, TNF-α
Zhang 2009	75	23	44	DSM-III-R	Schizophrenia	Chronic; in-patients	246.0	no	12	Mixed	IL-2, IL-6

NS= not specified; SUD= comorbid substance use disorders

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General Discussion

This thesis contributes to the body of literature regarding cognition and inflammation in psychiatry. We propose that these dimensions are transdiagnostic and are highly likely to be inter-related. We approached this question from several directions. In a parallel fashion; we explored both the expression of inflammation in schizophrenia and in particular the effect of antipsychotic treatment on inflammatory markers, and adapted tools to measure cognition in clinical practice. During this process, we also examined the application of these tools in clinical practice and generated information on cognitive function in several clinical populations: depression, attention deficit disorder, and bipolar disorder. The investigation of the applicability of measuring cognitive function in the clinical context in bipolar disorder is ongoing, although a poster of preliminary results has already been presented at the congress of the International Society of Bipolar Disorders (Abdel-Malek et al., 2015). Finally, we initiaited a study which attempts to explore the relationship between cognition and inflammation in major depression. The initial recruitment target for this study was 20 subjects but has been increased to 60. The study of the relationship of cognition and inflammatory markers in major depression is ongoing. Preliminary results on the first 38 subjects have been presented at the international forum of mood and anxiety disorders 2016 (Tourjman et al., 2016k; Tourjman et al., 2016m; Tourjman et al., 2016n). In this thesis we present the results of the first phases of this endeavor.

Cognition in psychiatry

Cognition can be considered to be a primary dimension of human functioning. As described in chapters 1 to 3 of this thesis, deficits of cognitive capacity are found in many if not most psychiatric disorders (Alves et al., 2014; Etkin et al., 2013; Martino et al., 2015; Schaefer et al., 2013). Furthermore, these deficits contribute to the impairment in functioning associated with major psychiatric psychopathologies such as major depression (Evans et al., 2014; Lam et al., 2014), bipolar disorder (Baune and Malhi, 2015) and schizophrenia (Green, 2016). As a result, cognition has been

increasingly the focus of research seeking to clarify the specific deficits associated with psychiatric disorders, the pathophysiology contributing to changes in cognitive capacity, and the clinical implications of our growing knowledge base in this area.

In parallel, we identified a need for a paper and pencil test to objectively evaluate cognition which was adapted to psychiatric populations with more subtle cognitive impairment. As a first step, we validated a French version of a brief neuropsychological battery (Tourjman et al., 2016h), the Screen for Cognitive Impairment in Psychiatry (SCIP), which has been used to measure cognition in various psychiatric disorders (Castano Ramirez et al., 2015; Guilera et al., 2009; Pino et al., 2008; Rojo et al., 2010) (Cuesta et al., 2011; Gomez-Benito et al., 2013). Our validation showed that the French version generated similar results and had similar properties to the original English version. This test can be administered in a 15 minute time frame.

Following the validation of the French version of the SCIP (SCIP-F), we proceeded to evaluate the applicability of integrating the SCIP as part of a routine clinical evaluation in depression (Tourjman et al., submitted) and attention deficit disorder with or without hyperactivity (ADHD) (Tourjman et al., submitted). The SCIP was able to detect deficits in both clinical populations and was well accepted by the patient population. Reassuringly, the deficits detected in working memory and executive function found in depression and ADHD were in line with those described as typical in the literature. Both studies showed significant correlations between functioning and objectively measured cognition.

Intriguingly, we found a discrepancy between objectively evaluated cognition, and subjective or self-evaluation of cognition. While a discordance of these two types of evaluation of cognition has been recognized as characteristic of schizophrenia (Homayoun et al., 2011), it has only recently been documented that a similar discordance exists in major depression (Ott et al., 2016). Thus, our publication confirming the presence of this discordance has added to this nascent realization (Potvin et al., 2016b).

In this work, we used a scale we developed in 2007, the *Echelle d'évaluation cognitive (EDEC)*. The EDEC was statistically significantly related both to the clinical global impression and to the Sheehan Disability Scale in the study of cognition in major depression. The visuomotor task, a measure of executive function, was also correlated to these measures. The sample size was insufficient to determine through path analysis to what extent these measures are directly correlated to each other rather than indirectly through the relationship with symptom intensity.

This work demonstrates the usefulness of a brief neuropsychological battery as a screening tool, although it is clear that technological advances will provide automated means of evaluating cognition which will likely be even more easily integrated into clinical practice. A freely available automated tool has recently been developed and validated, although population norms have not been established (http://thinc.progress.im) and is thus only applicable for research purposes. Like the SCIP, it contains tasks similar to those found in standard neuropsychological batteries. This tool has the shortcoming of not including verbal memory, a domain that has often been noted to be affected in psychiatric disorders. It thus does not replace the SCIP entirely.

Inflammation in psychiatry

A parallel line of investigation into the causes of psychiatric disorders has implicated inflammatory processes. Research identified infection as a possible cause of schizophrenia (Kirch, 1993), and bipolar disorders (Boyd et al., 1986). With time, a pro-inflammatory status was found to be more common in schizophrenia (Tanaka et al., 2016), bipolar disorder (Tanaka et al., 2016) and major depression (Li et al., 2011). The relationship between these disorders and inflammatory processes is complex (Leboyer et al., 2016). Inflammation has been advanced as a cause of psychiatric pathology (Kirch, 1993; Leboyer et al., 2012). In particular the similarity of the components of sickness behavior to the symptoms of depression (Kiecolt-Glaser et al., 2015; Maes et al., 2012) has led to the cytokine hypothesis of depression (Jeon and Kim, 2016) that proposes that at least some depressions are caused by increased inflammation. The relationship of inflammation to psychiatric

psychopathology has been bolstered by evidence suggesting the anti-inflammatory effect of antipsychotics (Haring et al., 2015), and antidepressants (Kubera et al., 2001b; Xia et al., 1996). Further support for the contribution of inflammation to psychopathology is provided by data showing the efficacy of celecoxib, an anti-inflammatory agent (cyclo-oxygenase 2 inhibitor) as an add-on treatment of schizophrenia (Akhondzadeh et al., 2007), depression (Faridhosseini et al., 2014), and more recently as an adjunctive treatment in acute mania (Arabzadeh et al., 2015).

In the light of numerous reports confirming a pro-inflammatory state in schizophrenia, we conducted a literature review of the effect of antipsychotic treatment on markers of inflammation in this disorder (Tourjman et al., 2012). This work was followed by a meta-analysis (Tourjman et al., 2013) which allowed quantification of the findings of the review. The final data-base included 23 studies. We identified an increase of soluble interleukin-2 receptor, as well as a decrease of interleukin-1beta and interferon-gamma following treatment indicating an anti-inflammatory effect of these agents. In particular, we attempted to examine the factors modulating this effect. Although not amenable to statistical analysis because of the heterogeneity of the data, the metabolic impact of clozapine seemed to counteract any anti-inflammatory effect. This suggests that the efficacy of this medication is independent of inflammation although this observation needs confirmation in studies where this is the primary objective.

Future directions: Relationship between cognition and inflammation in major depression

In step with this work we are conducting two studies whose principal objective is to examine the relationship of cognition in major depression and markers of inflammation at baseline and after treatment with two different antidepressant drugs. These studies have similar inclusion and exclusion criteria. Thirteen subjects have been recruited in the first study and 25 in the second. We have submitted three reports (accepted) presenting preliminary data from this study to the International Forum of Mood and Anxiety Disorders (december 2016). These investigations attempt to correct for shortcomings in studies in this area. For example, by ensuring that

subjects did not have inflammatory conditions which could influence measurement of markers of inflammation and by selecting for recent onset depression in order to identify the effects of major depression as opposed to the effects of chronicity. Initial analyses show that these criteria select for a subgroup of patients who have little cognitive impairment or inflammation. Only a subgroup of these individuals with recent onset depression showed cognitive deficits and these improved with treatment. In the subgroup with higher levels of CRP, this parameter declined over the first 8 weeks of treatment and increased over baseline by week 16. These results must be interpreted with caution but suggest that the factor of time, heretofore neglected in studies of inflammation could influence the observations of the effects of treatment on inflammatory markers.

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Conclusion

Psychiatric disorders are characterised by cognitive deficits and the presence of a pro-inflammatory state. Despite divergent findings the data do not show pathognomonic patterns which can be proposed to be unique to a particular psychiatric disorder. Rather, the data are more consistent with the hypothesis that both of these dimensions cut across diagnostic categories. Furthermore, research consistently identifies an association between the two dimensions suggesting that they may be related. Indeed, there are plausible mechanistic explanations which justify a causal relationship, with inflammation causing cognitive deficits. Equally consistently, however, inflammation is either modestly or at most moderately related to cognition and explains only part of the variance. Although this causal relationship may explain the association of these dimensions in psychiatric disorders in part, it is likely that other factors may influence the manifestation of both. It is important for future research to elucidate the complex interactions of psychosocial factors, stress, concurrent medical conditions, and biological predispositions with both inflammation and cognition. Increased understanding of these interactions has the potential to inform both psychosocial and pharmacologic therapeutic interventions.

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