Understanding Persistent Negative Symptoms in First Episode Psychosis: Implementing Neurocognitive and Neuroanatomical Approaches

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“You measure the size of the accomplishment by the obstacles you had to overcome to reach your goals.”

Grandma and Grandpa Hovington, thank you for your love.

Grand-papa Courchesne et Grand-maman Julie, merci pour votre amour.
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Contributions

Peer Reviewed Articles


Contributions of authors: Dr. Lepage, Dr. Bodnar and myself designed this analysis. I undertook all statistical analyses and wrote the first draft of the manuscript. Drs. Malla and Joober managed all patient recruitment and clinical assessments. I was trained to perform the neuropsychological assessments and negative symptom assessments. All authors contributed to revisions of the manuscript.


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In Preparation

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Abstract

**Background.** Negative symptoms (alogia, blunted affect, amotivation, reduced social drive) are a core feature of psychotic disorders. While a patient used to be considered remitted once positive symptoms had subsided, recent studies show that negative symptoms may remain present despite improvement of positive symptoms, and contribute greatly to poor outcome. In comparison to positive symptoms, negative symptoms do not respond well to treatment, thus becoming persistent in a large percentage of psychosis patients. Persistent negative symptoms (PNS) remain an unmet therapeutic need, in part, due to our lack of understanding of the cognitive and neural correlates of these symptoms. Furthermore, most studies ill investigate PNS in patients with enduring schizophrenia, which introduces confounding factors such as illness duration, sedentary lifestyle and long-term antipsychotic use. Hence, there is a need for a better understanding of these symptoms in patients with a first episode of psychosis.

**Purpose.** Our overall aim was to define and characterize the cognitive and neural correlates of persistent negative symptoms identified in patients with first episode psychosis.

**Methods.** All first episode psychosis patients were treated at the Prevention and Early Intervention Program for Psychosis (PEPP) at the Douglas Mental Health University Institute in Montreal. First, the heuristic value of various PNS definitions applied in the literature was explored. The relationship between PNS definitions and functional outcome was also explored. The most clinically relevant PNS definition was then applied to subsequent studies. Secondly, memory ability was examined in three memory domains including verbal, visual and working memory. Memory was compared at baseline in FEP patients with PNS and without PNS. In
addition, the trajectory of memory ability was assessed at a 12-month follow-up. Lastly, white matter microstructure was investigated in FEP patients identified as having PNS. A region of interest analysis was applied to assess fronto-temporo-limbic white matter tracts. Fractional anisotropy was measured in each tract and compared between PNS patients, non-PNS and healthy controls.

**Results.** Persistent negative symptoms were defined as having a score of 3 or greater in at least 1 global subscales of the Scale for the Assessment of Negative Symptoms (SANS). In addition, FEP patients were required to have minimal positive, depressive, and extrapyramidal symptoms. Patients whose negative symptoms at the above-mentioned level of severity persisted beyond month 3 of their first year of treatment in the PEPP program met the criteria for PNS. Applying this definition allowed us to determine the prevalence of PNS in FEP, which was found to be 27%. Further, patients with PNS had poorer functioning at month 12 than those without PNS. All FEP patients were administered neuropsychological tests with focus being placed on memory ability in those affected with PNS. Results suggested that in comparison to patients without PNS and healthy controls, patients affected by PNS had poorer verbal memory ability. In addition, follow up memory scores indicated that memory impairments in PNS were stable through the first year. Lastly, fractional anisotropy was shown to be lower in both patient groups compared to healthy controls. While the non-PNS demonstrated significantly lower FA values in the uncinate fasciculus compared to healthy controls, lower fornix FA was found in the PNS group compared to healthy controls.
**Conclusions and significance.**

Our studies highlight a 27% prevalence of PNS in first episode psychosis, supporting previous assumptions of a greater prevalence of PNS in comparison to deficit syndrome (with a prevalence estimated at 15%). Patients with PNS present with: poorer functional outcome, greater verbal memory deficits and impaired white matter integrity in the limbic system. Thus, applying the PNS definition in future studies may help further elucidate the impact of negative symptoms in FEP, by providing a more homogenous subgroup of patients who are more severely impaired than patients without PNS.
Résumé

Contexte. Les symptômes négatifs (réduction de langage parlé, émoussement de l’affect, amotivation, retrait social) sont au cœur des troubles psychotiques. Auparavant, les patients étaient considérés en rémission une fois leurs symptômes positifs dissipés. Des études récentes ont montré que les symptômes négatifs peuvent persister malgré une amélioration des symptômes positifs et ainsi, mener à un faible pronostic. Contrairement aux symptômes positifs, les symptômes négatifs sont peu influencés par le traitement pharmacologique et tendent à persister dans une proportion élevée de patients. Les symptômes négatifs persistants (SNP) sont encore peu ciblés par des nouveaux traitements, en partie, dû à notre connaissance limitée des corrélats neuronaux et cognitifs de ces symptômes. Par ailleurs, plusieurs études examinent de façon sous-optimale les symptômes négatifs en s’intéressant aux patients souffrant de schizophrénie depuis longtemps, ce qui entraîne des facteurs de nuisance, tels la durée de la maladie, les habitudes de vie sédentaires et la prise des antipsychotiques à long terme et les nombreuses hospitalisations. Par conséquent, il est pertinent de mieux comprendre les symptômes négatifs en début d’évolution chez les patients présentant un premier épisode psychotique.

Objectif. L’objectif global de notre étude est de définir et caractériser les corrélats neuronaux et cognitifs des symptômes négatifs persistants identifiés chez les patients présentant un premier épisode psychotique.

Méthode. Les patients présentant un premier épisode psychotique ont été traités au Programme d'évaluation, d'intervention et de prévention des psychoses, (PEPP) à l’institut universitaire de santé mentale Douglas à Montréal.
Tout d’abord, la valeur heuristique de plusieurs définitions des SNP employée dans la littérature a été investiguée. La relation entre les définitions des SNP et l’évolution fonctionnelle a également été explorée. La définition la plus cliniquement pertinente a été appliquée aux études subséquentes.

Ensuite, la capacité de la mémoire incluant la mémoire verbale, visuelle et de travail a été examiné pour son lien possible avec les symptômes négatifs. Spécifiquement la performance mnésiques des patients avec ou sans SNP a été comparée au niveau de base soit quelques semaines après le début du traitement. De plus, la trajectoire de la capacité de la mémoire a été évaluée après 12 mois de suivi.

Finalement, la microstructure de la matière blanche des patients présentant un premier épisode psychotique avec SNP a été examinée. Une approche par régions d’intérêt a été préconisée afin d’évaluer les faisceaux fronto-temporo-limbiques de la matière blanche. L’anisotropie fractionnelle (AF) a été mesurée pour chaque faisceau et comparée entre trois groupes de participants; les patients avec SNP, sans SNP et des sujets sains (libre de troubles psychiatriques).

**Résultats.** Un score de 3 ou plus sur au moins une des sous-échelles globales de l’échelle d’évaluation des symptômes négatifs (Scale for the Assessment of Negative Symptoms, SANS) représentait un des critères pour définir les symptômes négatifs persistants. De plus, les patients présentant un premier épisode psychotique devaient avoir peu de symptômes positifs, dépressifs ou extrapyramidaux. Finalement, les patients dont les symptômes négatifs persistaient au-delà de 3 mois dans leur première année de traitement dans le programme de PEPP, répondaient aux critères de sélection pour les SNP. En appliquant cette définition nous avons observé une
prévalence des SNP de 27% chez les premiers épisodes psychotiques. De plus, les patients avec SNP avaient un fonctionnement plus faible après 12 mois de suivi que ceux sans des SNP. Les tests neuropsychologiques administrés à tous les patients présentant un premier épisode psychotique ont mis l’accent sur la capacité de la mémoire. Les résultats suggèrent que les patients avec SNP, par rapport aux patients sans SNP et les sujets sains, avaient une capacité de mémoire verbale plus faible. De plus, le suivi des scores de mémoire ont indiqué que les troubles de la mémoire associés aux SNP étaient stables pendant la première année. Enfin, l’anisotropie fractionnelle s’est avérée plus faible dans les deux groupes de patients (avec et sans SNP), comparée aux sujets sains.

De plus, les patients sans SNP ont obtenu des valeurs de FA significativement plus faibles dans le faisceau unciné que les contrôles sains, alors que les patients avec SNP ont en plus obtenus des valeurs de FA plus faibles dans le fornix.

**Conclusions.** Nos études démontrent une prévalence des SNP de 27% chez les patients présentant un premier épisode psychotique, ce qui confirme des recherches antérieures. Les patients atteints des SNP sont caractérisés par un fonctionnement plus faible, une capacité de mémoire verbale plus faible et des valeurs de FA plus faibles dans les régions limbiques. Ainsi, l’application de la définition des SNP dans de futures études pourrait aider à élucider d’avantage l’impact des symptômes négatifs lors du premier épisode psychotique, en identifiant de façon précoce, un groupe plus homogène de patients qui présentent une issue clinique et fonctionnelle moins favorable.
Table of Contents

ACKNOWLEDGEMENTS ........................................................................................................................ II

CONTRIBUTIONS................................................................................................................................. V
  PEER REVIEWED ARTICLES .................................................................................................................. V
  IN PREPARATION ............................................................................................................................... V

OTHER PUBLICATIONS AND CONTRIBUTIONS ................................................................................... VI
  PEER REVIEWED ARTICLES ................................................................................................................ VI
  PUBLISHED ABSTRACTS .................................................................................................................. VI

ABSTRACT ........................................................................................................................................ VII

RÉSUMÉ ............................................................................................................................................... X

TABLE OF CONTENTS ......................................................................................................................... XIII

ABBREVIATIONS .............................................................................................................................. XVI

CHAPTER 1: GENERAL INTRODUCTION .............................................................................................. 18
  1.1 THE IMPORTANCE OF STUDYING PERSISTENT NEGATIVE SYMPTOMS ..................................... 19
  1.2 NEGATIVE SYMPTOMS IN PSYCHOSIS AND SCHIZOPHRENIA .............................................. 20
  1.3 PERSISTENT NEGATIVE SYMPTOMS .......................................................................................... 22
  1.4 METHOD OF IDENTIFYING PERSISTENT NEGATIVE SYMPTOMS IN THE LITERATURE ....... 24
  1.5 NEUROCOGNITIVE CORRELATES OF PERSISTENT NEGATIVE SYMPTOMS ....................... 25
    1.5.1 PNS ........................................................................................................................................... 25
    1.5.2 Deficit Syndrome ...................................................................................................................... 27
  1.6 PRELIMINARY EVIDENCE OF COGNITIVE CORRELATES OF PERSISTENT NEGATIVE SYMPTOMS IN FIRST EPISODE SCHIZOPHRENIA .................................................. 33
  1.7 NEURAL CORRELATES OF NEGATIVE SYMPTOMS ................................................................... 34
    1.7.1 Frontal Lobe Abnormalities ...................................................................................................... 34
    1.7.2 Temporal Lobe Abnormalities .................................................................................................. 43
    1.7.3 Preliminary Evidence in First Episode Schizophrenia .............................................................. 49
  1.8 RATIONAL AND OBJECTIVES OF THIS THESIS ...................................................................... 49
    1.8.1 Specific Objectives of This Thesis ........................................................................................... 50
    1.8.2 Objective #1 – Prevalence of Persistent Negative Symptoms in First Episode Psychosis.... 51
    1.8.3 Objective #2 – Exploring Memory Domains in First Episode Patients with Persistent Negative Symptoms .............................................................................................................. 51
    1.8.4 Objective #3 – White Matter Integrity in First Episode Patients with Persistent Negative Symptoms ................................................................. 52

CHAPTER 2: IDENTIFYING PERSISTENT NEGATIVE SYMPTOMS IN FIRST EPISODE PSYCHOSIS ......... 53
  2.1 ABSTRACT ...................................................................................................................................... 55
  2.2 INTRODUCTION ........................................................................................................................... 57
  2.3 METHODS .................................................................................................................................... 61
    2.3.1 Subjects ................................................................................................................................... 61
    2.3.2 Clinical Assessment .................................................................................................................. 62
CHAPTER 3: PERSISTENT NEGATIVE SYMPTOMS IN FIRST EPISODE PSYCHOSIS: RELATION TO MEMORY

2.3.3 Method for Identifying Persistent Negative Symptoms .............................................................. 64
2.3.4 Statistical analysis .................................................................................................................... 66
2.4 RESULTS ..................................................................................................................................... 67

2.4.1 Demographics and Symptoms ................................................................................................. 67
2.4.2 Prevalence and Associations with Functional Outcome ....................................................... 75
2.4.3 Supplementary Analysis of the PNS_1 group ........................................................................ 78

2.5 DISCUSSION .............................................................................................................................. 79

2.5.1 Main Findings .......................................................................................................................... 79
2.5.2 Can the Deficit Syndrome Criteria be applied in First Episode Psychosis? ......................... 80
2.5.3 Influence of Persisting Negative Symptoms on Functional Outcome .................................. 81
2.5.4 Secondary Negative Symptoms .............................................................................................. 83

2.5.5 Characterization of the PNS Cohort ....................................................................................... 83
2.5.6 Choosing a PNS Definition ..................................................................................................... 84

2.5.7 Limitations ................................................................................................................................ 85

CHAPTER 4: WHITE MATTER MICROSTRUCTURE IN FIRST EPISODE PSYCHOSIS PATIENTS WITH PERSISTENT NEGATIVE SYMPTOMS ................................................................. 112

PREFACE ........................................................................................................................................ 112
4.1 ABSTRACT ................................................................................................................................. 114
4.2 INTRODUCTION ......................................................................................................................... 116

4.3 METHODS ................................................................................................................................ 119

4.3.1 Subjects .................................................................................................................................. 119
4.3.2 Clinical Assessment ............................................................................................................... 120

4.3.3 Identifying Persistent Negative Symptoms ......................................................................... 120
4.3.4 Scanning Procedures ............................................................................................................. 121

4.3.5 Diffusion tensor imaging ...................................................................................................... 122
4.3.6 Region of Interest Analysis .................................................................................................. 123

4.3.7 Statistical Analysis ............................................................................................................... 123

4.4 RESULTS .................................................................................................................................. 124

4.5 DISCUSSION ............................................................................................................................. 131

4.6 LIMITATIONS ........................................................................................................................... 134

4.7 CONCLUSIONS ......................................................................................................................... 135

CHAPTER 5: CONCLUSIONS AND SIGNIFICANCE .......................................................................... 136

LIMITATIONS .................................................................................................................................. 140

CONTRIBUTIONS .......................................................................................................................... 141

FUTURE STUDIES AND CLOSING REMARKS: ........................................................................... 142
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHC</td>
<td>Amygdala-Hippocampal Complex</td>
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<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
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<td>CDSS</td>
<td>Calgary Depression Scale for Schizophrenia</td>
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<tr>
<td>CORS</td>
<td>Circumstances of Onset and Relapse Schedule</td>
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<tr>
<td>CPZ</td>
<td>Chlorpromazine Equivalents</td>
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<tr>
<td>DLPFC</td>
<td>Dorsolateral Prefrontal Cortex</td>
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<td>DS</td>
<td>Deficit Syndrome</td>
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<tr>
<td>DOI</td>
<td>Duration of Illness</td>
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<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
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<tr>
<td>DUI</td>
<td>Duration of Untreated Illness</td>
</tr>
<tr>
<td>DUP</td>
<td>Duration of Untreated Psychosis</td>
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<tr>
<td>ESRS</td>
<td>Extrapyramidal Symptoms Rating Scale</td>
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<tr>
<td>FA</td>
<td>Fractional Anisotropy</td>
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<td>FEP</td>
<td>First Episode Psychosis</td>
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<tr>
<td>FES</td>
<td>First Episode Schizophrenia</td>
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<tr>
<td>FMRIIB</td>
<td>Functional Magnetic Resonance Imaging of the Brain</td>
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<tr>
<td>IRAOS</td>
<td>Interview for the Retrospective Assessment of Schizophrenia</td>
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<tr>
<td>LM</td>
<td>Logical Memory of WMS-III</td>
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<tr>
<td>MATRICS</td>
<td>NIMH-Measurement and Treatment Research to Improve Cognition in Schizophrenia</td>
</tr>
<tr>
<td>NDS</td>
<td>Non-Deficit Syndrome</td>
</tr>
<tr>
<td>NIMH</td>
<td>National Institute of Mental Health</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
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<tr>
<td>PAS</td>
<td>The Premorbid Adjustment Scale</td>
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<tr>
<td>PDS</td>
<td>Proxy for the Deficit Syndrome</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>PEPP</td>
<td>Prevention and Early Intervention Program for Psychoses</td>
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<td>PNS</td>
<td>Persistent Negative Symptoms</td>
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SANS</td>
<td>Scale for the Assessment of Negative Symptoms</td>
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<tr>
<td>SAPS</td>
<td>Scale for the Assessment of Positive Symptoms</td>
</tr>
<tr>
<td>SDS</td>
<td>Schedule for the Deficit Syndrome</td>
</tr>
<tr>
<td>SES</td>
<td>Parental Socio-Economic Status</td>
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<tr>
<td>SLF</td>
<td>Superior Longitudinal Fasciculus</td>
</tr>
<tr>
<td>SOFAS</td>
<td>Social and Occupational Functioning Assessment Scale</td>
</tr>
<tr>
<td>UF</td>
<td>Uncinate Fasciculus</td>
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<tr>
<td>VBM</td>
<td>Voxel Based Morphometry</td>
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<tr>
<td>WAIS-III</td>
<td>Wechsler Adult Intelligence Scale – Third Edition</td>
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<tr>
<td>WCST</td>
<td>Wisconsin Card Sorting Test</td>
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<tr>
<td>WMS-III</td>
<td>Wechsler Memory Scale – Third Edition (WMS-III)</td>
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Chapter 1: General Introduction
1.1 The Importance of Studying Persistent Negative Symptoms

Research on the negative symptomatology of schizophrenia has burgeoned over the years and longitudinal studies have identified negative symptoms as a predictor of poor clinical outcome (Addington and Addington, 1991, McGurk et al., 2000a, Herbener and Harrow, 2004, Mancevski et al., 2007). Numerous studies have attempted to shed light on the etiology of negative symptoms from neurobiological (Potkin et al., 2002), functional (Ho et al., 1998a), neuropsychological (O'Leary et al., 2000) or structural perspectives (Sanfilipo et al., 2000, Wible et al., 2001, Zetzsche et al., 2008). Nonetheless, negative symptoms remain poorly understood. According to a recent consensus statement, the negative symptom construct includes blunted affect, anhedonia, alogia, asociality and avolition (Kirkpatrick et al., 2006). Further efforts have led to the delineation of several subtypes, including primary or idiopathic negative symptoms, secondary negative symptoms (caused by positive symptoms, depression, or extrapyramidal symptoms), deficit syndrome (combination of two or more primary negative symptoms that persist for more than 12 months in the context of relative clinical stability) (Kirkpatrick et al., 1989), and persistent negative symptoms (PNS) (primary or secondary negative symptoms evident more than 6 months after the first episode of psychosis). Though the concept of PNS has been present in the literature for several years (Castellon et al., 1994, Tandon et al., 2000, Mancevski et al., 2007), it has only recently been acknowledged in the form of an NIMH consensus statement, which described PNS as “[representing] an unmet therapeutic need” (Kirkpatrick et al., 2006). As such, it is imperative that greater attention be directed toward the identification and treatment of patients belonging to this subpopulation. One of the major obstacles in schizophrenia is inconsistency in findings, which has been the driving force of the contention behind the etiology of schizophrenia. Many factors may contribute to this
discordance, including illness chronicity, duration of illness, antipsychotic medications and symptom classification, such as negative symptoms. The negative symptomatology in psychotic disorders is often studied as one construct; however, research has begun to shed light on the degree of diversity within negative symptoms. Thus, it may be beneficial to be more specific when defining negative symptoms (i.e. primary, secondary, deficit syndrome (DS) or PNS). This thesis focuses on PNS in FEP and attempts to better delineate these symptoms as well as identify some neurocognitive and neural correlates.

1.2 Negative Symptoms in Psychosis and Schizophrenia

Negative symptoms are not specific to schizophrenia. They have been identified in other psychiatric and neurological disorders such as depression (Bottlender et al., 2003a), Parkinson’s Disease, (Pluck and Brown, 2002) Alzheimer’s disease (Reichman and Negron, 2001), eating disorders (Peterson et al., 2010) as well as the general population (Pfeifer et al., 2009). Nevertheless, its prevalence seems to be greatest in schizophrenia (Herbener and Harrow, 2001, Bottlender et al., 2003a, Bobes et al., 2010), with an estimated 25% of first-episode patients ultimately developing PNS (Alphs et al., 2007, Makinen et al., 2008b). Negative symptoms are hypothesized to contribute to poor functional outcome to a greater extent than positive symptoms (Remington et al., 2011). However, several challenges arise in terms of identifying and treating negative symptoms. First, the identification of negative symptoms has proven difficult. This is especially true during the prodromal phase and among first-episode patients, which is a corollary of the absence of insight, predominance of positive symptoms, and cognitive impairments (Selten et al., 2000). Accordingly, therapeutic intervention is often delayed considerably, with
attendant consequences for patients. Despite the difficulty to identify negative symptoms during the prodrome, some have suggested that negative symptoms appear before positive symptoms (Remington et al., 2011). Consequently some have proposed that the duration of untreated psychosis (DUP) definition should not only include the onset of positive symptoms, but should take into account the onset of negative symptoms given that they may have started earlier than positive symptoms (Compton et al., 2007, Murphy et al., 2008, Cuesta et al., 2012).

Secondly, several subtypes of negative symptoms have been recognized in an attempt to identify homogenous subgroups within schizophrenia. Thus, it may be beneficial to address each subtype and target them individually for treatment considering that each one may respond differently. For instance, primary negative symptoms, which are intrinsic to schizophrenia, are related to poor outcome and long-term disability (Fenton and McGlashan, 1994). These primary symptoms respond poorly to pharmacological interventions, while secondary negative symptoms have a better response (Murphy et al., 2006). Nonetheless, primary and secondary negative symptoms are not mutually exclusive, which is why it is necessary to better understand and demarcate negative symptom subtypes. As primary symptoms endure (for a minimum of 12 months), they are referred to as deficit symptoms (given the proper criteria is met), or what is now known as deficit syndrome (Kirkpatrick et al., 1989). These negative symptoms are associated with structural abnormalities, albeit deficits can also be observed in individuals who do not meet the criteria for DS (Buchanan et al., 1993). It is now generally accepted that abnormalities related to negative symptoms can be observed prior to the 12-month criterion of DS. This subtype is referred to as persistent negative symptoms. As illness duration increases, some patients may meet the criteria for Kraepelinian schizophrenia (Keefe et al., 1988) such that they are unable to
live an independent life or meet remission criteria for the past five years. This subtype overlaps with deficit syndrome, yet appears to have some distinct structural characteristics as well (Nakaya and Ohmori, 2006). Both PNS and DS will be reviewed in further detail below.

1.3 Persistent Negative Symptoms

In schizophrenia, negative symptoms typically oscillate throughout the course of the illness, becoming more prominent over time, usually due to the abatement of positive symptoms (Husted et al., 1995, Herbener and Harrow, 2001, Bottlender et al., 2003a). In first episode schizophrenia (FES), an estimated 25% of patients will have PNS, however little information exists regarding the prevalence of PNS in chronic schizophrenia. Recently, Buchanan proposed some criteria to help identify individuals with PNS, and contrasted them with the already well-established criteria for DS (Buchanan, 2007). Deficit schizophrenia, or deficit syndrome requires the presence of at least two of the following six negative symptoms: restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive. These symptoms must be present during a period of clinical stability for a minimum of 12 months. In contrast, primary or secondary negative symptoms that persist during a period of clinical stability for a minimum of six months are refereed to as persistent negative symptoms. Patients with a longer DUP, worse premorbid adjustment, and more severe flattened affect have been shown to be more susceptible to developing PNS (Edwards et al., 1999, Malla et al., 2004). Thus, it is plausible that PNS can be predicted early on, and perhaps be prevented.
Varying terminology has been used to describe “enduring negative symptoms” (Edwards et al., 1999) including “persistently high negative symptoms” (McGlashan et al., 1997), “prominent negative symptoms” (Foussias and Remington, 2010), “residual negative symptoms” (Alphs et al., 2007), “permanent negative symptoms” (Makinen et al., 2008b), “negative schizophrenia” (Ke et al., 2010) and “persisting negative symptoms” (Buchanan, 2007). The criteria used to identify patients with PNS have likewise been marked by divergency. Despite a recently proposed set of criteria (Buchanan, 2007), no consensus definition currently exists for PNS. Buchanan outlines distinctions between deficit syndrome and PNS. One of the major differences is the fact that deficit syndrome only includes enduring primary negative symptoms, whereas PNS may also include secondary negative symptoms. These secondary negative symptoms must have a minimal severity and must be resistant to treatment. Also, in contrast to DS, which is measured using the Schedule for the Deficit Syndrome (SDS), PNS does not have a validated measurement scale. Instead, any validated negative symptom rating scale can be used to measure the symptom severity, including the Scale for the Assessment of Negative Symptoms (SANS), Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Though Buchanan’s proposed criteria stipulate that an individual must have “at least moderate severity of negative symptoms,” this inexactitude may lead to differing interpretations. For instance, regarding the SANS, a score of moderate severity can be obtained by either a global SANS score or individual subscales of the SANS. These are two of the several interpretations that have been employed by several studies (Edwards et al., 1999, Bottlender et al., 2003a, Malla et al., 2004). Discordant interpretations of a validated negative symptoms scale can lead to contrasting PNS findings. Earlier studies preceding Buchanan’s criteria have applied similar conditions to identify PNS. Castellon et al. (Castellon et al., 1994) defined PNS as having
moderate severity on any one of three BPRS negative symptoms items that consistently persists for 52 weeks. Similarly, Bottlender et al. (Bottlender et al., 2003a) also required subjects to have non-fluctuating negative symptoms for a 1-year period, however the severity of symptoms were not required to be moderate (a SANS score of 2 or more). Unfortunately, these contrasting symptom severities can influence final results. This was described in an earlier study by Edwards et al. (Edwards et al., 1999).

In sum, studies must be consistent in their criteria for symptom severity and in the number of symptoms they set as their threshold. An overestimation or underestimation of individuals with PNS can be made if negative symptom severity thresholds are set either too low or too high, respectively. Thus, caution is warranted when applying a threshold for negative symptom in order not to be too liberal or conservative but that is clinically meaningful.

1.4 Method of Identifying Persistent Negative Symptoms in the Literature

One faces many obstacles when reviewing the literature on PNS, the first being that few studies label patients with negative symptoms that persist more than 6 months after FEP as having “PNS” (Sanfilipo et al., 2000, Wible et al., 2001, Zetzsche et al., 2008). Furthermore, many groups adopt their own unique criteria for identifying PNS and this results in ambiguous findings (Edwards et al., 1999, Bottlender et al., 2003a, Malla et al., 2004). Thus, in an attempt to standardize the studies reviewed in this thesis, inclusion and exclusion criteria were employed. Studies were included if: subjects were shown to have negative symptoms of mild or moderate severity, as measured using a validated negative symptom scale; and if subjects were assessed a
minimum of 6 months after first-episode psychosis. Mild symptoms were also included given that most studies have not adopted PNS criteria that include only moderate negative symptoms. Thus, in order to increase the number of studies to be reviewed in this thesis, cohorts with mild negative symptoms were also included. Studies were excluded if negative symptom scores and duration of illness were not specified, or if patients met criteria for “deficit syndrome” as indexed by the SDS. Longitudinal studies were also reviewed in order to obtain a better understanding of negative symptoms over time. For the purpose of the literature review of this thesis, studies were included even if information regarding the stability over time of negative symptoms was missing. This was done in order to have a better understanding of PNS that do not fully meet the proposed PNS criteria (Buchanan, 2007) and whether or not they still show some relations with neuroimaging and neurocognitive findings.

1.5 Neurocognitive Correlates of Persistent Negative Symptoms

1.5.1 PNS

Neuropsychological deficits are a well-documented pathologic dimension of schizophrenia, with some evidence showing a relationship between cognitive deficits and negative symptoms. For example, meta-analytical studies have suggested there is an association between impairments in memory, attention, executive function and severity of negative symptoms in schizophrenia (Aleman et al., 1999, Nieuwenstein et al., 2001, Harvey et al., 2006, Dibben et al., 2009), although the correlations have been modest. In addition, the relationship between cognitive deficits and severity of negative symptoms appears to be specific to schizophrenia. For instance,
a meta-analytical study by Bora et al. (Bora et al., 2009) examining the differences in cognitive functioning between patients suffering from schizophrenia, schizoaffective disorder and affective psychosis, revealed that patients with schizophrenia had significantly greater cognitive deficits relative to the other groups. Further, these differences were driven by several factors including younger age at onset of illness and severity of negative symptoms. Hence, this may suggest that it is better to examine these groups separately due to different etiologies and symptomatology that are specific to each diagnostic entity. Unfortunately, these correlations do not allow us to determine whether the relationship between cognitive deficits and negative symptoms is causal, or whether they share a common etiology.

The longitudinal relationship between negative symptoms and cognition has previously been evaluated in order to determine whether the associations documented at FES remain in the later stages of the illness. These findings have yielded somewhat consistent patterns. Schizophrenia patients with a mean DOI of about 10 years and with moderate scores on the global subscales of the SANS (2.7-3.5), received a neuropsychological test battery assessing attention, verbal and non-verbal memory, executive function and verbal fluency (O'Leary et al., 2000). Patients in this cohort met both the DOI and negative symptoms severity of the PNS criteria. They were shown to have cognitive deficits more strongly related to negative symptoms. In particular, SANS subdomain scores were inversely correlated with measures of verbal learning, verbal memory, nonverbal memory, and verbal fluency. In keeping with these findings, a longitudinal study (baseline and follow-up 6 months apart) by Hughes et al. (Hughes et al., 2003) evaluated patients with an average DOI of 13.9 years, and diagnosed as either schizophrenia or schizoaffective disorder (Hughes et al., 2003). With the objective of evaluating longitudinal changes of clinical
symptoms and cognition, results revealed that severity of negative symptoms predicted cognitive deficits in memory and verbal fluency. However, negative symptom improvements were not paralleled with improved neuropsychological performance, suggesting a lack of causal relationship between the negative symptomatology of schizophrenia and cognition. Bell and Mishara (Bell and Mishara, 2006) also argue that neurocognitive deficits and negative symptoms are not related, and therefore improvements in symptoms would be independent of any cognitive improvements. This argument was supported by their findings that failed to show a relationship between cognitive deficits and negative symptom severity in a group of schizophrenic patients (PANSS 18.3±5.8).

1.5.2 Deficit Syndrome

Neurocognitive impairments have also been documented in DS in comparison to healthy controls; whereas in comparison to NDS (individuals with significantly lower negative symptoms scores), results have been mixed (see Cohen et al. for review (Cohen et al., 2007)). For instance, in a large Chinese sample, a neuropsychological test battery was administered to a group of 30 DS, 93 NDS and 103 healthy controls (Wang et al., 2008). Compared to NDS patients, DS patients were found to have greater impairments on measures of executive functioning, including the Wisconsin Card Sorting Test (WCST) and the Trial Making Test. In terms of explicit memory, performance in both patient groups was comparable. The lack of significant difference in memory impairments between DS and NDS was further substantiated by Bryson et al. (Bryson et al., 2001) who compared 2 cognitive domains including executive function and memory. Deficit patients had significantly worse scores in executive functioning but failed to show any significant differences relative to NDS in terms of memory. Memory has
not been the only cognitive domain that has been similar in both DS and NDS. Using a larger neuropsychological test battery, results from a more recent study also failed to find a distinct neuropsychological marker central to the deficit syndrome (Cascella et al., 2008). In fact, only verbal fluency reached significance, with DS patients performing more poorly than NDS. Hence, it appears that cognitive deficits seen in DS may not necessarily be distinct from those in NDS. Interestingly, although NDS patients in this study had significantly lower negative symptom scores than DS on the SANS (6.2±3.5 vs 16.3±3.2, respectively), they had a much longer illness durations than patients with DS (19.1±10.5 vs 11.9±8.8 years, respectively). This suggests that unlike the suggested criteria of “moderate” negative symptoms, as outlined by Buchanan (Buchanan, 2007), individuals with persisting negative symptoms of mild severity have cognitive deficits similar to those seen in DS. Thus, as previously mentioned, NDS subgroups in schizophrenia warrant attention and should not be ignored.

Not all findings support a lack of difference in memory between DS and NDS. At odds with these particular findings, Galderisi et al. (Galderisi et al., 2002) only found a group difference for the focused/sustained attention domain, while executive function (measured by the WCST) was affected to a larger degree in NDS patients. In an attempt to shed light on these discordant findings, a recent study implemented a factor analytical approach in order to provide more sensitivity to the executive function domain (Polgar et al., 2010). Briefly, a factor analysis of the WCST revealed 2 factors and demonstrated that DS patients are indeed more impaired than both healthy controls and NDS in terms of “general executive function” factor (factor 1). On the other hand, differences between DS and NDS only approached statistical significance in terms of “non-perseverative errors” (factor 2). The authors suggested that DS patients might have more
difficulty identifying and later switching, a sorting rule, whereas NDS patients ineffectively shift responses in order to test different hypotheses. Hence, both patients groups may have executive function deficits but their deficits are distinct.

Taken together, these studies suggest that cognitive deficits are indeed a putative finding in PNS as well as both DS and NDS. Interestingly, memory deficits appear to be more prominent in PNS when compared to DS. The contribution of functional deficits to neuropsychological impairments and their association to negative symptoms remains poorly understood. See Table 1.1 for a summary of neurocognitive abnormalities in PNS and DS.
Table 1.1 Correlations of Cognitive Domains and Neuropsychological Tests with Persistent Negative Symptoms

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects (m/f)</th>
<th>Age (yrs)</th>
<th>DOI (yrs)</th>
<th>NS Scale</th>
<th>NS Score</th>
<th>Neuropsychological tests</th>
<th>Results</th>
<th>Findings specific to Negative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Leary et al. 2000</td>
<td>SCZ 134 (90/44); N/A</td>
<td>31.2 (9.6); N/A</td>
<td>10.5</td>
<td>SANS</td>
<td>10.5 (8.3)</td>
<td>WAIS-R, logical memory, word list learning, paired-associate learning, Rey-Osterrieth figure; Benton Visual Retention Test; CPT; Circle’s A; Trail’s B; Finger Tapping (right hand); WCST; verbal fluency; Stroop interference test</td>
<td>No significant correlations were found with PS and cognitive deficits</td>
<td></td>
</tr>
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<td></td>
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</tbody>
</table>
| Hughes et al. 2003 | SCZ 62 (39/23); HC 25 (15/10) | 37.7 (10.3); 34.9 (13.0) | 13.9      | PANSS    | N/A      | Executive function (WCST, FAS, Trails B, TOL, EGT); memory (WMS, HVLT); attention (Continuous Performance Test); psychomotor speed (Trails A, FTT) | Over a 6 month duration (no treatment), patients significantly improved on verbal memory, WCST, Trails A and B and CPT | Significant correlations between NS scores and logical memory tests (immediate and 1-hour recall); list learning (immediate and 1-hour recall), paired-associate learning; Circle’s A time and Trail’s B time  

(6 month longitudinal study)
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (yrs)</th>
<th>DOI (yrs)</th>
<th>NS Scale</th>
<th>NS Score</th>
<th>Neuropsychological tests</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCZ 267 (233/34); HC 0</td>
<td>43.1 (8.7)</td>
<td>Age of onset= 22.6 (7.5)</td>
<td>PANSS 18.3 (5.8)</td>
<td>WCST; CPT; BLERT; GORHAM’ S proverbs; Trails; WMS-R; HVLT; word fluency</td>
<td>commission errors. N/A</td>
<td></td>
</tr>
</tbody>
</table>

### Deficit Syndrome

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (yrs)</th>
<th>DOI (yrs)</th>
<th>NS Scale</th>
<th>NS Score</th>
<th>Neuropsychological tests</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS 33 (30/3); NDS 57 (53/4)</td>
<td>40.0 (9.1); 42.7 (7.6)</td>
<td>Age of first hospitalization: 24.6 (5.8); 24.9 (6.3)</td>
<td>PANSS SDS 25.7 (6.3); 13.8 (3.7)</td>
<td>WAIS; WCST; WMS-R; HVLT</td>
<td>DS performed significantly worse than NDS in WCST (categories complete)</td>
<td></td>
</tr>
<tr>
<td>SCZ 58 (43/15); DS 54 (41/13); HC 26 (18/8)</td>
<td>35.2 (7.3); 34.4 (7.7); matched within 3 years</td>
<td>13.6 (7.4); 12.8 (6.9)</td>
<td>SDS SANS Sum of global scores: 13.3 (3.1); 10.0 (3.2)</td>
<td>WAIS-R; WCST; Picture memory and Interference Test; Trails A &amp; B; Auditory Verbal Learning Test; Benton Judgment of Line Orientation GPT; TMT (A &amp; B); BTA; CPT; nWCST;</td>
<td>NDS patients performed more poorly on executive function tests compared to DS</td>
<td></td>
</tr>
<tr>
<td>DS 26 (20/6);</td>
<td>35.1 (12.2); 11.9 (8.8); 19.</td>
<td>SDS SANS SANS sum 16.3 (3.2); 6.2</td>
<td></td>
<td></td>
<td>DS patients performed significantly worse than HC on flexibility index</td>
<td></td>
</tr>
</tbody>
</table>

- No significant correlations were found between SANS scores and neurocognitive measures
<table>
<thead>
<tr>
<th>Study</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
<th>Group 9</th>
<th>Group 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DS 30</td>
<td>NDS 93</td>
<td>DS 154</td>
<td>NDS 128</td>
<td>NDS 30</td>
<td>NDS 128</td>
<td>DS 154</td>
<td>NDS 128</td>
<td>DS 30</td>
<td>NDS 128</td>
</tr>
<tr>
<td></td>
<td>(21/9)</td>
<td>(64/29)</td>
<td>(71/83)</td>
<td>(60/87)</td>
<td>(21/9)</td>
<td>(71/83)</td>
<td>(71/83)</td>
<td>(60/87)</td>
<td>(21/9)</td>
<td>(71/83)</td>
</tr>
<tr>
<td></td>
<td>42.6</td>
<td>42.7</td>
<td>38.8</td>
<td>35.9</td>
<td>41.5</td>
<td>36.2</td>
<td>42.6</td>
<td>35.9</td>
<td>41.5</td>
<td>(10.3)</td>
</tr>
<tr>
<td></td>
<td>(9.3)</td>
<td>(10.0)</td>
<td>(11.9)</td>
<td>(11.0)</td>
<td>(10.5)</td>
<td>(11.8)</td>
<td>(9.3)</td>
<td>(10.0)</td>
<td>(10.5)</td>
<td>(9.3)</td>
</tr>
<tr>
<td></td>
<td>17.2</td>
<td>17.0</td>
<td>N/A</td>
<td>N/A</td>
<td>SANS</td>
<td>SANS</td>
<td>SANS total</td>
<td>SANS total</td>
<td>SANS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(8.5)</td>
<td>(9.2)</td>
<td>N/A</td>
<td>N/A</td>
<td>(10.0)</td>
<td>(10.5)</td>
<td>53.7 (15.8)</td>
<td>53.7 (15.8)</td>
<td>35.8</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
<td>17.2 (8.5)</td>
<td>17.0 (9.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
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</tbody>
</table>

- DS performed significantly worse than NDS on Block Design tests; Trail B; WCST
- DS performed more poorly in general executive function than NDS
- Non-perseverative error type was more common in NDS compared to DS (low flexibility)

DOI= duration of illness; SCZ=schizophrenia; HC=healthy controls; DS=deficit syndrome; NDS=non-deficit syndrome; SANS=Scale for the assessment of negative symptoms; PANSS=Positive and Negative Symptom Scale; SDS=Schedule for the Deficit Syndrome; GPT=grooved pegboard test; TMT=Trail Making; BTA=Brief Test of Attention; CPT=Continuous Performance Test; WCST=Wisconsin Card Sorting Test; nWCST=Nelson Wisconsin Card Sorting Test; HVLT-R=Hopkins Verbal Learning Test-Revisited; BVMT-R=Brief Visuospatial Memory Test-Revised; WMS-R=Wechsler Memory Scales-Revised; WAIS-R=Wechsler Adult Intelligence Scale-Revised; FAS=Verbal Fluency Letters; TOL=Tower of London; BLERT=Bell-Lysaker Emotion Recognition Task; BTA= Brief Test of Attention; FTT=Finger Tapper Test; EGT=Executive-Golf Task.
1.6 Preliminary Evidence of Cognitive Correlates of Persistent Negative Symptoms in First Episode Schizophrenia

Generalized neuropsychological deficits have been documented as early as at a first episode. In a study by Heydebrand and colleagues (Heydebrand et al., 2004), in which 307 FES patients were evaluated at baseline (prior to being assigned to a double blind treatment), PANSS negative symptoms scores were modestly ($r=-0.29$) but significantly correlated ($p<0.001$) with memory and psychomotor speed ($r=-0.21$) and with executive function ($p<0.01$). Accordingly, a group of 94 clinically stabilized FES patients, the following neuropsychological domains were evaluated: language, memory, attention, motor function, executive function, visuospatial memory and premorbid IQ (Bilder et al., 2000). When compared to healthy controls, patients showed greater generalized neuropsychological deficits. Severity of negative symptoms (precise scores were not provided), as measured by the SANS, correlated with the following neuropsychological deficits; executive function significantly correlated with affective flattening and alogia and memory as well as attention correlated with alogia. Several lines of evidence support the notion of memory deficits being associated with negative symptoms during FES. In extension to the above findings, Milev et al. provided evidence for the ability of both negative symptoms and cognition to predict future outcome (Milev et al., 2005). In this longitudinal study, in which FEP patients were followed for 7 years, increasing negative symptom severity was associated with worsening cognitive deficits. This relationship was not observed for positive symptoms. Additionally, negative symptoms were the strongest predictor of psychosocial functioning at follow-up and shared variance in prediction with memory and attention. Thus, taken together, the aforementioned neurocognitive studies shed light on a relationship between cognitive deficits and the severity of negative symptoms. More
importantly, although results are variable, one consistent finding seems to be the relationship between negative symptoms and memory. This relationship warrants further study in a FEP sample to help elucidate its association without the influence of confounding factors due to illness chronicity.

1.7 Neural Correlates of Negative Symptoms

Neuroimaging studies on schizophrenia reveal progressive brain alterations in the dorsolateral prefrontal cortex (DLPFC), amygdala, lateral ventricles, nucleus accumbens and cingulate gyri [for review see (Shenton et al., 2001, Hulshoff Pol and Kahn, 2008, Puri, 2010)]. However, it remains unclear whether these changes are specific to PNS, or more generally to schizophrenia. For this thesis, structural abnormalities will be reviewed from a lobar approach with emphasis placed on the frontal and temporal lobes. For each of these lobes, structural anomalies will be compared to DS.

1.7.1 Frontal Lobe Abnormalities

1.7.1.1 PNS

While results regarding structural brain alterations in schizophrenia have been mixed, there appear to be some consistencies regarding white matter abnormalities and severity of negative symptoms (Sanfilipo et al., 2000, Wible et al., 2001, Ho et al., 2003, Zetzsche et al., 2008). DTI is a rather “new” imaging modality, having been first introduced in 1994 (Basser 1994). It allows for the visualization and characterization of white matter, thus enabling the investigation of white matter architecture and integrity. White matter fiber tracts can be affected by tissue properties including the density of the fibers, the thickness of the myelin
sheaths, the fiber diameter as well as the directionality (or coherence) of the fibers in each voxel (Kubicki M 2007). Irregularities in white matter have previously been documented in schizophrenia and have included disruptions in white matter integrity (Lim et al., 1999) as well as volumetric reductions (Sanfilipo et al., 2000). Given that white matter composes the infrastructure for neural connectivity, one would presume that a reduction in white matter would contribute to schizophrenia via cortical dysfunction (Kubicki et al., 2007). In a group of 53 male patients suffering from chronic schizophrenia (DOI: 14 years) and identified as having mild negative symptoms according to the sum of global SANS, reductions in prefrontal white matter in the schizophrenia group were shown to significantly correlate with the severity of negative symptoms (Sanfilipo et al., 2000). Further, no correlations were found between duration of illness or age at onset and prefrontal white matter deficits. Several ensuing studies have been able to replicate these findings. For instance, by employing regions of interest (ROI) Wible et al. also found a correlation between reduced right prefrontal white matter volumes and severity of negative symptoms (total SANS score of 11±4) in patients with schizophrenia (DOI: 30 years) (Wible et al., 2001). Preliminary evidence using fractional anisotropy (FA) (an indicator of white matter integrity) has revealed correlations between white matter microstructure and SANS global subscores. Frontal white matter FA was shown to correlate with both SANS global ratings of affective flattening and anhedonia. In extension to the above findings, Zetzsche et al. (Zetzsche et al., 2008), who also employed ROI, concluded that more severe negative symptoms (PANSS negative symptoms score of 38.4±10.1, which are of clinical significance), in schizophrenia patients with an illness duration of about 6.8 years, positively correlated with white matter volume reductions in the frontal lobe. Similarly to the previously mentioned studies, no differences were found when comparing frontal white matter volumes of healthy controls and schizophrenia patients, thereby further substantiating that this
finding may be specific to negative symptoms. While these studies are suggestive of an association between prefrontal white matter reductions and negative symptoms persisting up to 20 years, PNS were not specifically addressed in any of these studies, thereby making it difficult to make any conclusions.

Using voxel-based morphometric (VBM), a technique used to measure the density of brain tissue, studies have suggested that reductions in gray matter density may also be implicated in the pathophysiology of schizophrenia (Kuperberg et al., 2003, Schultz et al., 2010). Regionally selective thinning has been associated with the negative symptom construct of schizophrenia. For instance, to assess whether structural abnormalities were specific to each symptom dimension Koutsouleris et al. divided a group of 17 patients with schizophrenia into 3 groups according to PANSS symptom dimensions (negative, positive and disorganized factor) (Koutsouleris et al., 2008). Compared to healthy controls, all patient groups had greater gray matter density reductions in prefrontal, limbic, paralimbic, temporal and thalamic regions. Furthermore, the group with prominent negative symptoms had greater reductions in the orbital frontal, medial prefrontal and lateral prefrontal areas. The authors referred to these patients as having primary enduring negative symptoms or “deficit syndrome” given the fact that their symptoms matched the criteria outlined by Kirkpatrick (Kirkpatrick et al., 2001). However, given that: 1) the SDS was not employed to identify DS, 2) patients had an illness duration of greater than 2 years and 3) patients in the “negative group” had nearly clinically significant PANSS scores (PANSS total of 26.6), for the purpose of this thesis, these symptoms were classified as PNS.
1.7.1.2 Deficit Syndrome

Throughout the years, studies investigating deficit syndrome have yielded several unexpected findings, such as more pronounced structural abnormalities among non-deficit syndrome (NDS) patients relative to deficit patients. For instance, in an attempt to delineate the underlying structures involved in deficit syndrome, a manually based ROI study was conducted by Buchanan et al. (Buchanan et al., 1993). In comparison to healthy controls, NDS patients had decreased white matter volumes in both left and right prefrontal cortices. Prefrontal gray matter was also reduced in NDS, though this did not reach significance. With respect to DS patients, no significant differences in frontal volumes were found compared to healthy controls. More pronounced structural deficits in NDS patients have been replicated in other findings (Galderisi et al., 2008).

Using similar methodologies as the previously mentioned group (Buchanan et al., 1993), automated volume ROI analyses for gray matter were employed to investigate 35 patients (DOI: 14 years) with DS, 32 with NDS and 31 healthy comparisons (Galderisi et al., 2008). By applying the Talairach grid (Quarantelli et al., 2002), major structures including frontal, parietal, temporal and lateral ventricles were analyzed. Clinical characteristics were comparable between patient groups, with only negative symptom severity and social relationships reaching significant difference (worse in DS). Findings revealed a lack of significant difference between DS and NDS patients in lateral ventricular volume, DLPFC volume and the cingulate gyri. When compared to healthy controls, NDS patients had significantly larger lateral ventricles, smaller left and right dorsolateral prefrontal cortices as
well as a smaller left cingulate gyrus. Discordant findings have been documented in a group using VBM techniques (Cascella et al., 2010). Volumes of both white and gray matter were measured in a group of 19 DS and 31 NDS patients and compared to 90 healthy controls. As a whole, both patient groups had reduced gray matter volumes in areas including the left medial frontal gyrus and right inferior frontal gyrus. However, when either patient groups were compared to healthy controls, DS had reduced gray matter volume in the left medial frontal gyrus and NDS had reductions in the left medial frontal gyrus. Although the NDS group was older and had a longer duration of illness, when compared to DS the NDS group had less gray matter volume reductions in frontal regions including bilateral superior frontal gyrus, right medial frontal gyrus and the anterior cingulate.

The above results may suggest that there is a subgroup in addition to deficit syndrome that present with less severe negative symptoms persisting into the chronic stages of schizophrenia and are associated with structural deficits distinctive from individuals with deficit syndrome. Given the instability of secondary negative symptoms, which are included in PNS as well as NDS, this may partly account for some of the variability in findings. Nonetheless, patients with NDS do represent a subgroup with some morphological correlates. In order to better distinguish the difference between DS, NDS and PNS, future studies should compare the 3 groups and apply standardized methods of measurements for each, such as the SDS and standardized PNS criteria (including symptoms persisting a minimum of 6 months, and a moderate severity of negative symptoms). This would allow for a better understanding of structural differences between these groups and would provide a direct comparison of PNS and NDS. For a summary of the findings regarding the frontal lobe, see Table 1.2.
### Table 1.2. Frontal Lobe Abnormalities Associated with Persistent Negative Symptoms

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Age at scan yrs (SD)</th>
<th>DOI yrs (SD)</th>
<th>NS Score (SD)</th>
<th>Measuring Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanfilipo et al. 2000</td>
<td>SCZ 53; HC 29 (all males)</td>
<td>38.7 (5.5); 35.8 (8.7)</td>
<td>14.4±6.8</td>
<td>SANS</td>
<td>Sum of Global SANS 11.8 (3.4)</td>
<td>• SCZ group had greater reductions in bilateral prefrontal and temporal gray matter (superior temporal gyrus) but not white matter</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Automatic segmentation and manual tracing</td>
<td>• Total prefrontal (orbitofrontal regions) white matter inversely related with NS (r=0.49; p=0.002)</td>
</tr>
<tr>
<td></td>
<td>Wible et al. 2001</td>
<td>44 (N/A); 40 (N/A)</td>
<td>20 (N/A)</td>
<td>SANS</td>
<td>Total SANS score 11(4)</td>
<td>• No between group differences were found between groups for gray matter volume</td>
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<td></td>
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<td></td>
<td>Semi-automated segmentation</td>
<td>• SCZ group had significant white matter reductions compared to HC</td>
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<td></td>
<td>• Left frontal gray matter volume correlated with total SANS scores (r=-0.50; p=0.043 for absolute volume)</td>
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<td></td>
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<td></td>
<td>• When data from a previous study was combined with those of current study, right prefrontal white matter volume reductions correlated with more severe</td>
</tr>
<tr>
<td>Study</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Age at initial MRI</td>
<td>SANS</td>
<td>Sum of 4 global ratings</td>
<td>Automated segmentation</td>
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<tr>
<td>Ho et al. 2003 (3 yr longitudinal study)</td>
<td>SCZ 73 (53/20); HC 23 (15/8)</td>
<td>24.5 (4.7); 26.9 (5.3)</td>
<td>SANS</td>
<td>Sum of 4 global ratings 8.6 (2.83)</td>
<td>Automated segmentation</td>
<td>Patients had progressive decreases in frontal lobe white matter</td>
</tr>
<tr>
<td>Zetzsche et al. 2008</td>
<td>SCZ 50; HC 50</td>
<td>30.0 (8.4); 30.2 (8.8)</td>
<td>PANSS</td>
<td>N/A</td>
<td>Automated segmentation</td>
<td>No significant differences in white matter volume between SCZ patients and HC</td>
</tr>
<tr>
<td>Koutsouleris et al. 2008</td>
<td>SCZ 175 (130/45) (were divided according to the 3 factor subgroups of PANSS); HC 177</td>
<td>31.7 (10.2); 31.5 (9.2)</td>
<td>Age of disease onset = 27.4 (9.7)</td>
<td>PANSS 22.3 (9.8)</td>
<td>VBM</td>
<td>Large clusters of significant GMD reductions between SCZ and HC in lateral orbitofrontal regions, middle and superior frontal gyri as well as dorsomedial prefrontal cortex</td>
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</tbody>
</table>
reductions were found in PS group, reductions were more pronounced in NS subgroup.

Takahashi et al. 2009
SCZ 16 (8/8); HC 16 (9/7)
27.8 (6.8); 28.8 (4.1)
6.7 (3.6) PANSS 21.1 (9.3) Semi-automated
• No significant differences between HC and SCZ groups for delta α measurements for prefrontal or frontoparietal regions
• Correlation between negative symptom severity and prefrontal asymmetry coefficient ([R-L]/[R+L] of delta α values) (r=-0.56; p<0.05)

### Deficit Syndrome

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Age at scan yrs(SD)</th>
<th>DOI yrs (SD)</th>
<th>NS Scale</th>
<th>Measuring Method</th>
<th>DS vs HC</th>
<th>NDS vs HC</th>
<th>DS vs NDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchanan et al. 1993</td>
<td>DS17; NDS 24; HC 30</td>
<td>35.5 (6.6); 35.6 (6.0); 34.0 (8.1)</td>
<td>15.3 (6.5); 13.4 (6.0)</td>
<td>SDS Automated segmentation</td>
<td>Prefrontal total volume: DS=HC NDS&lt;HC</td>
<td>Left prefrontal white matter volume: NDS&lt;HC</td>
<td>Right prefrontal gray matter volume: NDS = HC</td>
<td>Total right prefrontal volume: DS&gt; NDS</td>
</tr>
<tr>
<td>Study</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Fractional Volumes of Right and Left Frontal Lobe: DS &lt; HC; NDS &lt; HC</td>
<td>GMV of DLPFC: DS = NDS</td>
<td>GMV in Right Inferior Frontal Gyrus: SCZ &lt; HC</td>
<td>GMV in Left Superior Frontal Gyrus</td>
<td>GMV in Right Medial Frontal Gyrus: DS &lt; NDS</td>
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<tr>
<td>Quarantelli et al. 2002</td>
<td>DS 14 (13/1); NDS 14 (13-1); HC 25 (19/6)</td>
<td>37.1 (8.4); 34.8 (8.4); 18-50</td>
<td>15.1 (8.7); 15.3 (6.6)</td>
<td>SDS SANS EBPRS Manual tracing and automated segmentation</td>
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<tr>
<td>Galderisi et al. 2008</td>
<td>DS 34 (25/9); NDS 32 (26/6); HC 31 (21/10)</td>
<td>35.8 (7.4); 34.2 (8.1); 34.4 (8.3)</td>
<td>14.0 (8.0); 14.1 (6.6)</td>
<td>SDS SANS EBPRS Manual tracing and automated segmentation</td>
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<tr>
<td>Cascella et al. 2010</td>
<td>DS 19 (16/3); NDS 31 (21/10); HC 90 (43/47)</td>
<td>35.1 (11.9); 44.4 (10.3); 46.3 (12.7)</td>
<td>11.8 (9.3); 19.7 (11.5)</td>
<td>SDS SANS VBM Manual tracing and automated segmentation</td>
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</table>

DOI= duration of illness; SCZ=schizophrenia; HC=healthy controls; DS=deficit syndrome; NDS=non-deficit syndrome; SANS=Scale for the assessment of negative symptoms; PANSS=Positive and Negative Symptom Scale; SDS=Schedule for the Deficit Syndrome; GMV=gray matter volume; GMD=gray matter density; NS=negative symptoms; DLPFC=dorsolateral prefrontal cortex; VBM=voxel-based morphometry.
1.7.2 Temporal Lobe Abnormalities

1.7.2.1 PNS

In addition to white matter volume reductions in the frontal lobe, structural abnormalities in the temporal lobe have been associated with PNS. A recent longitudinal study compared chronic schizophrenia patients (DOI: 16 years) and healthy controls over a three-year period (Yoshida et al., 2009). Manually delineated ROI included the superior temporal gyrus and amygdala-hippocampal complex (AHC). Cross-sectional findings at two time points (baseline and year 3) failed to reveal a significant progression of volume reductions in the ROI’s of the patient group. However, when compared to healthy controls, the patient group had smaller relative volumes of the superior temporal gyrus and AHC at both time points. Volumetric reductions in the left anterior AHC, a critical area for memory function, was associated with more prominent PNS in patients, as measured by the PANSS (mean score of 10.3±5.7). In extension to these findings, a cross-sectional MRI study comparing patients with chronic schizophrenia and healthy controls, found a positive correlation between volume asymmetry of the AHC and negative symptoms using a 3D shape representation technique (Shenton et al., 2002). The patient group was shown to have similar overall amygdala-hippocampal shape and volume as the controls; however, left/right amygdala-hippocampal asymmetry (volume and shape) was significantly greater in patients with chronic schizophrenia. In contrast, although volume reductions of the AHC were also found in a group of chronic schizophrenia patients with predominately negative symptoms, these reductions failed to show any relationship with either positive or negative symptoms (Anderson et al., 2002). Patients from this study had average illness durations of 16.69 years and mild total SANS scores of 11.3.
Several factors including divergent methodologies have been assumed to contribute to the variability of results in schizophrenia. Nonetheless, investigations of structural deficits in chronic schizophrenia employing VBM have also revealed associations between PNS and temporal structures (Koutsouleris et al., 2008, Meisenzahl et al., 2008). Separating the patient group according to the 3 dimensions of the PANSS allowed Koutsouleris and colleagues to investigate the extent each symptom domain has on the structural deficits of the brain (Koutsouleris et al., 2008). In addition to the deficits seen in frontal structures as described earlier, VBM analyses also revealed reductions in gray matter density in several cortical regions in patients of all three PANSS dimension groups. However, the negative symptom group demonstrated more substantial gray matter reductions than the other patient groups. Larger reductions of gray matter density in the limbic structures were specific to the group with predominantly negative symptom. In another group of patients with predominantly negative symptoms, VBM analyses revealed gray matter volume reductions in the anterior cingulate, left medial temporal lobe and left superior temporal gyrus (Sigmundsson et al., 2001). Multiple regression analyses failed to show a relationship between gray matter volume deficits in these structures and the severity of negative symptoms (Sigmundsson et al., 2001). In contrast, significant associations between positive symptom severity and both white and gray matter were found. Of note, although the authors stated that patients were required to “meet the criteria for the deficit syndrome of schizophrenia”, only the PANSS was administered and no further information regarding their deficit diagnosis was provided.
1.7.2.2  Deficit Syndrome

Gray matter volume deficits in the temporal lobe have also been found in patients with DS. When three groups, including DS, NDS and healthy controls were compared, large clusters of gray matter volume reductions in the temporal gyrus were observed in DS compared to healthy controls (Cascella et al., 2010). However, when NDS patients were compared to the control group, gray matter reductions were more specific to the inferior temporal gyrus and left middle temporal gyrus. Overall, the DS group had larger gray matter reductions in these regions. Other findings have not been in line with these results. Regardless of the fact that the DS group had significantly worse mean scores for the avolition-apathy subscale of the SANS, results of a study by Quarantelli et al. failed to show significant differences in temporal gray matter volumes between DS and NDS groups (Quarantelli et al., 2002). Although deficits in temporal volumes have been documented in DS compared to healthy controls, the lack of significant difference between DS and NDS in gray matter volumes of temporal structures has been replicated in other MRI studies (Buchanan et al., 1993, Galderisi et al., 2008). See Table 1.3 for a summary of findings for the temporal lobes.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Age at scan yrs (SD)</th>
<th>DOI yrs (SD)</th>
<th>NS Scale</th>
<th>NS Score (SD)</th>
<th>Measuring Method</th>
<th>Results</th>
<th>Findings Specific to Negative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmundsson et al. 2001</td>
<td>SCZ 27 (26/1); HC 27 (25/2)</td>
<td>34.9 (7.6); 32.2 (6.7)</td>
<td>13.9 (6.6)</td>
<td>PANSS</td>
<td>25 (5.9)</td>
<td>VBM</td>
<td>Left superior temporal gyrus GMV reduced in SCZ compared to HC</td>
<td>No significant correlations between GMV reductions and NS</td>
</tr>
<tr>
<td>Shenton et al. 2002</td>
<td>SCZ 15; HC 15 (all males)</td>
<td>37.6 (9.3); aged matched HC</td>
<td>15.7 (8.8)</td>
<td>SANS</td>
<td>N/A</td>
<td>Automated and manual segmentation</td>
<td>No differences between groups for total AHC volume</td>
<td>Volume and shape asymmetry of AHC correlated with negative symptoms to a greater extent than positive symptoms</td>
</tr>
<tr>
<td>Anderson et al. 2002</td>
<td>SCZ 16; HC 15 (all males)</td>
<td>42.5 (8.8); 41.6 (7.5)</td>
<td>19.7 (8.6)</td>
<td>SANS</td>
<td>SANS total score 11.3 (N/A)</td>
<td>Semi-automated segmentation</td>
<td>Smaller anterior AHC in SCZ compared to HC (no significance in posterior AHC)</td>
<td>No correlations were found between any findings and NS scores</td>
</tr>
<tr>
<td>Koutsouleris</td>
<td>SCZ 175</td>
<td>31.7 (10.2); Age of PANSS</td>
<td>22.3 (9.8)</td>
<td>VBM</td>
<td></td>
<td></td>
<td>GMV reductions in SCZ compared to HC</td>
<td>SCZ patients with</td>
</tr>
</tbody>
</table>
et al. 2008 (130/45); HC 177 (123/54)

31.5 (9.2) disease onset = 27.4 (9.7)

Yoshida et al. 2009 (3 year longitudinal study)

SCZ 16; HC 20

38.6 (6.7); 40.9 (8.1) 16.3 (8.5) SANS SANS total score 10.3 (5.7) Manual tracing

Ke et al. 2010

SCZ NS 16 (12/4); SCZ PS 16 (12/4); HC 16 (12/4)

24 (5.7); 24.6 (5.9); 24.6 (4.5) N/A PANSS 24.5 (5.7); 18 (5.2) Automated segmentation

Deficit Syndrome

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Age at scan yrs(SD)</th>
<th>DOI yrs (SD)</th>
<th>NS Scale</th>
<th>Measuring Method</th>
<th>DS vs HC</th>
<th>NDS vs HC</th>
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<tbody>
<tr>
<td>et al. 2008</td>
<td>(130/45); HC 177 (123/54)</td>
<td>31.5 (9.2)</td>
<td>disease onset = 27.4 (9.7)</td>
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<tr>
<td>Yoshida et al. 2009 (3 year longitudinal study)</td>
<td>SCZ 16; HC 20</td>
<td>38.6 (6.7); 40.9 (8.1) 16.3 (8.5) SANS SANS total score 10.3 (5.7) Manual tracing</td>
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<tr>
<td>Ke et al. 2010</td>
<td>SCZ NS 16 (12/4); SCZ PS 16 (12/4); HC 16 (12/4)</td>
<td>24 (5.7); 24.6 (5.9); 24.6 (4.5) N/A PANSS 24.5 (5.7); 18 (5.2) Automated segmentation</td>
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</table>

Greater reductions in inferior temporal structures and limbic structures

Correlation between NS score of PANSS and percent change of left anterior AHC ($r=-0.48; p=0.06$)

Ke et al. 2010

SCZ NS 16 (12/4); SCZ PS 16 (12/4); HC 16 (12/4)

24 (5.7); 24.6 (5.9); 24.6 (4.5) N/A PANSS 24.5 (5.7); 18 (5.2) Automated segmentation

Asymmetry of functional connectivity in temporal lobe: SCZ NS < HC

Asymmetry of functional connectivity in right temporal lobe: SCZ PS < HC

Reduced asymmetry of functional connectivity in temporal lobe was greater in the negative SCZ group

Negative group had significantly increased rightward asymmetry of functional connectivity
<table>
<thead>
<tr>
<th>Study</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Outcome 1</th>
<th>Outcome 2</th>
<th>Outcome 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchanan et al. 1993</td>
<td>DS17; NDS 24; HC 30</td>
<td>NDS 14 (13-1); HC 25 (19/6)</td>
<td>35.5 (6.6); 35.6 (6.0); 34.0 (8.1)</td>
<td>SDS Automated segmentation</td>
<td>Right and left AHC: DS &lt; HC; NDS &lt; HC</td>
<td>AHC: DS = NDS</td>
</tr>
<tr>
<td>Quarantelli et al. 2002</td>
<td>DS 14 (13/1); NDS 14 (13-1); HC 25 (19/6)</td>
<td>37.1 (8.4); 34.8 (8.4); range = 18-50</td>
<td>15.1 (8.7); 15.3 (6.6)</td>
<td>SDS SANS Manual tracing and automated segmentation</td>
<td>Right and left lateral ventricles: NDS&gt;HC</td>
<td>Right lateral ventricle: NDS &gt; DS</td>
</tr>
<tr>
<td>Cascella et al. 2008</td>
<td>DS 19 (16/3); NDS 31 (21/10); HC 90 (43/47)</td>
<td>35.1 (11.9); 44.4 (10.3); 46.3 (12.7)</td>
<td>11.8 (9.3); 19.7 (11.5)</td>
<td>SDS SANS VBM</td>
<td>GMV in temporal gyrus DS &lt; HC</td>
<td>GMV in superior and middle temporal gyrus: DS &lt; NDS</td>
</tr>
<tr>
<td>Galderisi et al. 2008</td>
<td>DS 34 (25/9); NDS 32 (26/6); HC 31 (21/10)</td>
<td>35.8 (7.4); 34.2 (8.1); 34.4 (8.3)</td>
<td>14.0 (8.0); 14.1 (6.6)</td>
<td>SDS SANS Manual tracing and automated segmentation</td>
<td>Lateral ventricles: NDS &gt; HC; DS=HC</td>
<td>Lateral ventricles: DS=NDN</td>
</tr>
</tbody>
</table>

DOI= duration of illness; SCZ=schizophrenia; HC=healthy controls; DS=deficit syndrome; NDS=non-deficit syndrome; SANS=Scale for the assessment of negative symptoms; PANSS=Positive and Negative Symptom Scale; SDS=Schedule for the Deficit Syndrome; GMV=gray matter volume; GMD=gray matter density; NS=negative symptoms; PS=positive symptoms; DLPFC=dorsolateral prefrontal cortex; VBM=voxel-based morphometry; EBPRS=Expanded Brief Psychiatric Rating Scale; AHC=amygdala-hippocampal complex; N/A=not applicable
1.7.3 Preliminary Evidence in First Episode Schizophrenia

Few studies have investigated the structural correlates of PNS in FES cohorts, however this represents a very important clinical population to examine this association at a time where potential confounds such as long term medication, chronicity and sedentary lifestyle are unlikely to contribute to this association. Nonetheless, preliminary evidence suggests an association between negative symptom severity and structural deficits. More specifically, in a group of FES patients who were assessed at baseline and 6 months after the initiation of treatment with neuroleptics, positive symptoms were shown to improve over time, while negative symptoms worsened (Ebdrup et al., 2011). In comparison to healthy controls, the FES group demonstrated marked structural declines in the striatum and hippocampus. Furthermore, although enlarged ventricles were not a significant structural deficit in the patient group, decrements in lateral ventricles were correlated with less improvements in negative symptoms (mean PANSS negative symptoms score of 21, which are considered mild) over a period of 6 months (Ebdrup et al., 2011).

1.8 Rational and Objectives of Thesis

It is well established that negative symptoms represent a widely heterogeneous clinical construct in psychosis. It may be more beneficial to create various subcategories of negative symptoms in order to foster research progress on the etiology of negative symptoms. Although there have been numerous studies on primary and enduring negative symptoms, or deficit syndrome, little is known about PNS which are proposed to be a broader negative symptom subtype presenting earlier in the course of illness. These
symptoms are thought to contribute to lower quality of life, higher levels of treatment discontinuation (Galderisi et al., 2012), lower rates of remission (Bodnar et al., 2008, Galderisi et al., 2012) and poor functional outcome (Rabinowitz et al., 2012). Many treatments have proven ineffective when targeting PNS (Moller, 2003). Thus, persistent negative symptoms remain a conundrum for both clinicians and researchers alike.

Although we have begun to better delineate DS, they can only be identified after the first year of treatment. If PNS can be identified earlier, then perhaps we can provide earlier treatment for these patients. Also, investigating PNS in FEP can help reduce the effects of illness chronicity, antipsychotics and sedentary lifestyle. Lastly, most studies will attempt to characterize negative symptoms in cross sectional studies; thus, there is a need for a longitudinal study investigating the impact of PNS on FEP patients.

1.8.1 Specific Objectives of This Thesis

Our literature review has indicated that there is a need to develop a PNS definition in FEP that takes into consideration the presence of moderate negative symptoms, the exclusion of potential confounds (e.g. depression) and the persistence in time of those negative symptoms. It is clear that these symptoms are detrimental to a patient’s prognosis and recovery, yet little is known about their etiology. In our review outlining the neurocognitive and neuroimaging correlates of negative symptoms, we have identified memory and white matter integrity as two potential markers of PNS that have not been
explored in this particular subgroup of FEP patients. Thus, the exploration of such markers in FEP is novel and exciting and unlike many studies before, there are fewer confounds such as sedentary lifestyle, long-term use of antipsychotics or long-term hospitalization in these younger patients.

1.8.2 Objective #1 – Prevalence of Persistent Negative Symptoms in First Episode Psychosis

First, the heuristic values of various PNS definitions were compared in a group of 158 first episode psychosis patients. The prevalence of PNS in FEP was explored. As a second objective, the heuristic value of those different PNS definitions were explored in terms of their association with functional outcome after 12 months of treatment in a first episode clinic. Lastly, although the deficit syndrome definition is usually applied later on in the course of illness, as exploratory analyses this definition was also included to help increase our understanding of the similarities and differences between persistent negative symptoms and deficit syndrome.

1.8.3 Objective #2 – Exploring Memory Domains in First Episode Patients with Persistent Negative Symptoms

A longitudinal study compared memory ability in first episode psychosis patients with and without persistent negative symptoms, as well as healthy controls to determine if PNS is characterized by greater memory impairments in a specific domain (verbal, visual or working memory). Furthermore, FEP patients were evaluated during a 1-year period to investigate the relative stability of memory over time.
1.8.4 **Objective #3 – White Matter Integrity in First Episode Patients with Persistent Negative Symptoms**

In this longitudinal study, a region of interest approach was used to investigate white matter integrity in patients with first episode psychosis and compared to non-PNS patients and healthy controls. A second exploratory objective was to assess the relationship between individual negative symptom domains and the selected white matter tracts.
Chapter 2: Identifying Persistent Negative Symptoms in First Episode Psychosis


PREFACE

Various studies have identified a subgroup of patients with first episode psychosis affected by negative symptoms that are both clinically significant and persist over time (Edwards et al., 1999, Bottlender et al., 2003b, Malla et al., 2004, Galderisi et al., 2012, Stauffer et al., 2012). These symptoms are referred to as persistent negative symptoms (PNS) (Buchanan, 2007). This subgroup of negative symptoms has been shown to contribute to a poor prognosis and resistance to treatment (Ho et al., 1998b). Research on PNS has recently gained momentum in the hopes of elucidating the etiology of these debilitating symptoms. However, there remains a lack of standardized criteria to identify PNS and estimates of its prevalence have varied across studies. Buchanan has proposed some criteria to identify PNS, stating that a patient must have at least moderate negative symptoms, negligible positive symptoms, minimal depressive or extrapyramidal symptoms, and clinical stability for an extended period of time (Buchanan, 2007).
However, this definition has not been applied to a group of FEP patients in order to obtain the prevalence of PNS.

In this longitudinal study, we compared three definitions previously applied in the literature to help identify first episode psychosis patients with persistent negative symptoms and obtain its prevalence. Symptoms were evaluated at the initial assessment and at months 1, 2, 3, 6, 9, and 12. Further, given previous evidence suggesting an association between negative symptom severity and poorer functional outcome, this relationship was also evaluated.
2.1 Abstract

**Background:** Although persistent negative symptoms (PNS) are known to contribute significantly to poor functional outcome, they remain poorly understood. We examined the heuristic value of various PNS definitions and their respective prevalence in patients with first episode psychosis (FEP). We also contrasted those definitions to the Proxy for the Deficit Syndrome (PDS) to identify deficit syndrome (DS) in the same FEP cohort.

**Methods:** One hundred and fifty-eight FEP patients were separated into PNS and non-PNS groups based on ratings from the Scale for Assessment of Negative Symptoms (SANS). PNS was defined in the following ways: 1) having a score of 3 or greater on at least 1 global subscale of the SANS (PNS_1); 2) having a score of 3 or more on at least 2 global subscales of the SANS (PNS_2); and 3) having a score of 3 or more on a combination of specific SANS subscales and items (PNS_H). For all three definitions, symptoms had to be present for a minimum of six consecutive months. Negative symptoms were measured upon entry to the program and subsequently at 1, 2, 3, 6, 9 and 12 months. Functional outcome was quantified at first assessment and month 12.

**Results:** PNS prevalence: PNS_1 (27%); PNS_2 (13.2%); PNS_H (13.2%). The prevalence of DS was found to be 3% when applying the PDS. Regardless of the definition being applied, when compared to non-PNS, patients in the PNS group were shown to have significantly worse functioning at month 12. All three PNS definitions showed similar associations with functional outcome at month 12.

**Conclusion:** Persistent negative symptoms are present in about 27% of FEP patients with both affective and non-affective psychosis. Although there has previously been doubt as to whether PNS represents a separate subdomain of negative symptoms, the current study suggests that PNS may be more applicable to FEP when compared to DS. Although all
three PNS definitions were comparable in predicting functional outcome, we suggest that
the PNS definition employed is dependent on the clinical or research objective at hand.
2.2 Introduction

Growing evidence has suggested that negative symptoms in psychotic disorders are intractable and associated with poor functional outcome (Eaton et al., 1995, Malla et al., 2004, Ventura et al., 2009). According to the most recent National Institute of Mental Health (NIMH) consensus statement, the negative symptom construct includes blunted affect, anhedonia, alogia, asociality and avolition (Kirkpatrick et al., 2006). However, broadly classifying negative symptoms into 5 categories does not take into account etiology and duration, which contribute to the heterogeneity of these symptoms (Buchanan, 2007). Thus, negative symptoms are further subdivided into the following subtypes: 1) primary or idiopathic negative symptoms, 2) secondary negative symptoms (caused by positive symptoms, depression, or extrapyramidal symptoms), 3) deficit syndrome (DS), believed to be a pathophysiological distinct disease within schizophrenia and is diagnosed based on the presence of primary enduring (minimum of 12 consecutive months) (Kirkpatrick et al., 1989), and 4) persistent negative symptoms (PNS) (primary or secondary negative symptoms evident for 6 consecutive months after the stabilization of a first episode of psychosis) (Buchanan, 2007).

Persistent negative symptoms have become a major concern given their resistance to treatment and persistence throughout the illness, leading to poor prognosis. Varying terminology and criteria have been used to describe and identify PNS. Consequently, the lack of a consensus definition has yielded mixed results in terms of structural, neuropsychological and functional correlates of PNS. Recently, Buchanan suggested that the duration and severity of negative symptoms must be taken into account when
identifying PNS. The following criteria were proposed: having at least moderate negative symptoms, having negligible positive, depressive or extrapyramidal symptoms, and clinical stability for an extended period of time (Buchanan, 2007). Empirical evidence on the proposed criteria for PNS has been scant.

Some have suggested that PNS may represent a broader concept than deficit syndrome (Buchanan, 2007, Foussias and Remington, 2010). Deficit syndrome, which is proposed to identify a putatively more homogenous subgroup in schizophrenia, highlights the manifestation of prominent, primary and enduring negative symptoms that are resistant to treatment. The criteria for DS requires that negative symptoms of significant severity be present for a minimum of one year, to have been present at baseline (during periods of relative remission) and are not secondary in nature (Kirkpatrick et al., 1989). Furthermore, patients must meet the DSM criteria for schizophrenia spectrum disorder (Kirkpatrick et al., 1989). Deficit syndrome is assessed using the Schedule for the Deficit Syndrome (SDS), which is a semi-structured interview measuring the persistence of 6 negative symptoms including restricted affect, diminished emotional range, poverty of speech, curbed interests, diminished sense of purpose, and diminished social drive (Kirkpatrick et al., 1989). An individual must have moderate to severe scores on at least 2 of these 6 symptoms. After the introduction of the SDS, the Proxy for the Deficit Syndrome (PDS) was introduced as a case identification for measuring deficit symptoms (Kirkpatrick et al., 1993). This tool allows one to administer common negative symptoms scales such as the Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) and to apply the PDS formula to obtain a score determining whether
the patient meets the criteria for DS. The PDS is defined as the sum of the scores for Anxiety, Guilt Feelings, Depressive Mood and Hostility items from the scales subtracted from the score of Blunted Affect (Kirkpatrick et al., 1993).

Unlike DS which is quantified using the SDS (Kirkpatrick et al., 1989), negative symptom severity for PNS can be measured using any validated negative symptom scale. According to the NIMH consensus statement (Kirkpatrick et al., 2006) the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) has the most extensive coverage. Other scales such as the PANSS (Kay et al., 1987) are also widely used, but do not provide as much detail on negative symptoms as the SANS. However, some concerns regarding these scales have been raised. For instance, early evidence suggests that some items from the SANS including, “poverty of content of speech” and “inappropriate affect” represent a disorganization dimension rather than negative symptoms of schizophrenia (Liddle, 1987). Exploratory and confirmatory factor analytical studies identified three underlying factors in the negative symptoms construct including 1) affective flattening 2) avolition/apathy and anhedonia/asociality and 3) inattention/alogia (Mueser et al., 1994b, Sayers et al., 1996, Peralta and Cuesta, 1999). Concordant factors have been documented in a FEP cohort (Malla et al., 2002). These factors are incorporated into the SANS (Andreasen, 1982). However, there is now a general consensus that inattention may not be conceptually related to negative symptoms (Blanchard and Cohen, 2006, Sergi et al., 2007, Foussias and Remington, 2010). Furthermore, some findings are suggestive of interrelated yet separate subdomains of negative symptoms in schizophrenia including, 1) diminished expression, composed of
affective flattening and poverty of speech, and 2) amotivation, consisting of avolition/apathy and anhedonia/asociality (Blanchard and Cohen, 2006, Kirkpatrick et al., 2006, Foussias and Remington, 2010). Similarly, in patients with DS, a principle component analysis using the Schedule for Deficit Syndrome indicated that DS is best described by two factors including avolition and reduced emotional expression (Kimhy et al., 2006). It is possible that this multidimensionality within negative symptoms is relevant not only to chronic schizophrenia but to FEP patients with PNS as well; this has not been investigated.

The lack of “gold standard” for PNS has brought up some major concerns (Leucht et al., 2005, Kirkpatrick et al., 2006, Kirkpatrick and Fischer, 2006, Makinen et al., 2008a). Also, studies have not employed comparable criteria to identify PNS. For instance, while one study included patients in the “negative symptom group” if they scored 2 or more on a minimum of 1 global SANS subscales (Bottlender et al., 2003a), others have used a score of 3 or more (Malla et al., 2004). In addition, some have also applied criteria that involve having clinically significant symptoms (score ≥3) on a minimum of 2 global items of the SANS (Edwards et al., 1999).

Given this variability, it is likely that using different criteria for identifying PNS will yield mixed results. Hence, there is a need for PNS criteria that are clinically useful in identifying PNS. The first episode of psychosis may be a critical time to identify individuals with PNS in order to potentially influence these symptoms through more focused intervention such as intensive psychosocial interventions. Further, given the lack
of consensus definition for PNS, its prevalence in FEP using well-defined criteria remains unknown. The main objective of this paper was to examine the heuristic value of various PNS definitions and their respective prevalence in patients with first episode psychosis. Second, given that DS also represents a subgroup of patients with enduring negative symptoms, we wanted to contrast the PNS definitions with the proxy definition for deficit syndrome in a FEP cohort. To substantiate the clinical predictive validity of the abovementioned definitions, all were explored in association with patient function followed over a 12-month period in a cohort of first-episode of psychosis patients. We hypothesize that patients meeting the PNS criteria will have poorer functioning than those not meeting the criteria (Ho et al., 1998a, Blanchard et al., 2005, Milev et al., 2005).

2.3 Methods

2.3.1 Subjects

All patients were part of a longitudinal naturalistic outcome study of first-episode psychosis and were recruited and treated through the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), a specialized early intervention service with integrated clinical, research, and teaching modules, at the Douglas Mental Health University Institute in Montreal, Canada. Individuals aged 14 to 35 years from the local catchment area suffering from either affective or non-affective psychosis that had not taken antipsychotic medication for more than one month and with an IQ higher than 70 were consecutively admitted to the program as either in- or out-patients. For complete program details see Malla et al. (Malla et al., 2003) or visit http://www.douglasresearch.qc.ca/pages/view?section_id=165. Patients were diagnosed
according to DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 1998). Written informed consent was obtained from all participants. Research protocols were approved by the Douglas Institute Human Ethics Review Board.

2.3.2 Clinical Assessment

For all subjects who met the inclusion criteria, an initial assessment was conducted on average, within one month after admission (in days; mean=22.7, s.d.= 8.6, range=8.3-54.8). At the initial assessment the following data were acquired: education level (number of school years completed), Full Scale IQ with the Wechsler Adult Intelligence Scale (Wechsler, 1997b), parental socio-economic status (SES) with the Hollingshead two-factor index (Miller, 1991b), The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), and handedness (Oldfield, 1971). Negative and positive symptoms were assessed with the Positive and Negative Symptoms Scale (PANSS) as well as the SANS (Andreasen, 1982) and SAPS (Andreasen, 1983), respectively. The domain of attention in the SANS scale was not included in our analyses. Evaluators at PEPP established an ICC of 0.74 on the SAPS and 0.71 on the SANS; all raters participated in inter-rater reliability sessions at least once a year to avoid rater drift (i.e. raters must maintain consistency with themselves as well as with other raters). Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) and extrapyramidal symptoms with the Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard and Margolese, 2005). If prescribed, based on the ESRS and attending physician’s discretion, type and dose of anticholinergic taken
were recorded. The type and dosage of antipsychotics taken were also recorded and subsequently converted into chlorpromazine equivalents (Woods, 2003). As part of the longitudinal study, severity of positive, negative, depressive and extrapyramidal symptoms was evaluated at initial assessment and 1, 2, 3, 6, 9 and 12 months later, using the SAPS, SANS, CDS and ESRS, respectively.

The period of “prodrome”, calculated through the Circumstances of Onset and Relapse Schedule (CORS) interview which is based on the Interview for the Retrospective Assessment of Schizophrenia (IRAOS) (Hafner et al., 1992), was defined as the time between the onset of any psychiatric symptoms and the onset of the presenting psychotic episode. From this interview, such variables as duration of untreated psychosis (DUP), duration if untreated illness (DUI), pre-morbid functioning levels, and socio-economic status are obtained. Psychiatric symptoms refer to symptoms indicating a behavioural change such as anxiety, depression, suicidal ideation, or social withdrawal as well as sub-threshold psychotic symptoms such as suspiciousness and odd ideas and behaviour and do not include developmental disorders. Duration of untreated psychosis was calculated as time from the first episode to the date of entry into the program. Finally, DUI was calculated as the time between the first ever onset of any psychiatric symptoms to the time of adequate treatment, as above (Malla et al., 2006). Duration of untreated illness included periods of psychiatric symptoms not necessarily contiguous with the psychotic episode and interspersed with relatively healthy periods. All other demographic data were obtained through the same interview.
2.3.3 Method for Identifying Persistent Negative Symptoms

Upon completing 12 months of the treatment program, clinical data were analyzed and PNS definitions were applied based on data collected from the first assessment, months 1, 2, 3, 6, 9, and 12. Negative symptoms were required to be present after the initial stabilization of symptoms (month 3) and maintained for 6 consecutive months (months 6, 9, and 12) with at least a moderate severity as measured on a validated scale (Buchanan, 2007). Although 6 months has often been employed as the point of initial stabilization (Edwards et al., 1999), our previous findings along with recent data in FEP, suggests a decrease of acute psychotic symptoms and an initial stabilization period closer to 3 months (Rodriguez-Sanchez et al., 2005, Rodriguez-Sanchez et al., 2008, Crespo-Facorro et al., 2009, Buchy et al., 2010). In addition, factor analytical studies have suggested that some items of the SANS including, “poverty of content of speech” and “inappropriate affect” poorly correlate with the scale (Sayers et al., 1996, Peralta and Cuesta, 1999). Hence, as suggested by Malla et al. (Malla et al., 2004), if the global rating on “affective flattening” or “alogia” was based entirely as a result of items “inappropriate affect” or “poverty of content of speech”, respectively, such patients were not included in the PNS group.

All subjects with secondary negative symptoms were excluded from analyses. Patients were required to have a global rating of mild (2) or less on all positive symptoms as measured by the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983), a total score of 4 or less on the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993), and extrapyramidal symptoms that were absent or too mild to require treatment with anticholinergic medication based on the ESRS (Chouinard and Margolese, 2005).
All of the above mentioned criteria had to be maintained for a period of at least 6 consecutive months (specifically between month 6 and 12 after admission). In addition to having negative symptoms for 6 consecutive months, patients with affective or non-affective psychosis were also required to have clinically significant negative symptoms (“clinically significant” symptoms were considered to be moderate to severe scores on SANS items, or scores of 3 or greater) on the SANS scale at month 3.

Lastly, three PNS definitions applied in various studies for identifying persistent negative symptoms during a 12-month longitudinal study and the PDS for identifying DS were explored (Kirkpatrick et al., 1993, Edwards et al., 1999, Malla et al., 2004):

**Persistent Negative Symptom:**

1. PNS_1: a score of 3 or more on at least 1 global item of the SANS (Malla et al., 2004).
2. PNS_2: a score of 3 or more on at least 2 global items of the SANS (Edwards et al., 1999).
3. PNS_H: a SANS score of 3 or more on either one or both of the following subdomains as previously described by Foussias and Remington (Foussias and Remington, 2010): 1) Diminished expression (must have a score of 3 or more for both affective flattening and poverty of speech) and/or 2) Amotivation (must have a score of 3 or more for both avolition/apathy and anhedonia/asociality).

**Deficit Syndrome:**

DS (using PANSS): PDS Score = Blunted Affect (n1) – [Anxiety (G2) + Guilty Feelings (G3) + Depressed Mood (G6) + Hostility Items (P7)]. In order to be classified as meeting the criteria for DS, patients were required to have a score greater than two on the PDS (Kirkpatrick et al., 1993). Similarly to PNS, this
criterion had to be met at months 3, 6, 9 and 12. In other words, the proxy
definition was not employed for 12 consecutive months, as it is required. Given
that this study examined a group with FEP, retrospectively assessing DSs would
have begun at the first episode when symptoms are not yet stable.

2.3.4 Statistical analysis

All analyses were conducted using PASW version 18 (SPSS, Chicago, IL) and were two-
tailed with a critical \( p \)-value of 0.05. Group differences with regard to the first assessment
variables for DUP, DUI, length of prodrome and SOFAS scores were analyzed using
independent t-tests. The following clinical characteristics were not normally distributed
(Shapiro-Wilks W test): DUP, DUI prodrome and CDSS scores. Prodrome, DUI and
CDSS scores were normalized using square root transformations, while DUP was
normalized using a logarithmic transformation. Group differences were also compared at
several time points (first assessment, months 3 and 12) for clinical symptoms including
SANS, SAPS and CDSS total scores as well as for SOFAS scores using independent t-
tests. Independent t-tests were also used to compare group differences between PNS and
non-PNS for age, DUI, DUP and prodrome. The prevalence of PNS in patients with FEP
was determined at month 12. Patients were categorized into PNS or non-PNS (and further
subdivided according to which PNS criteria they met). In addition, patients who met the
PDS criteria according to the previously published cutoff (≥2) (Kirkpatrick et al., 1993)
were categorized in the DS group. To determine the association between PNS and
function, repeated measures ANOVA were used to examine group differences between
PNS definitions (each definition separately) and SOFAS score (first assessment, month
12) used as the within subject variable and group (PNS, Non-PNS) as the between subject variable.

2.4 Results

2.4.1 Demographics and Symptoms

Data from a cohort of 280 FEP patients treated between 2003 and 2009 were collected. Of these, 100 had missing clinical data between months 3 and 12 due to one or more missed assessments. These subjects were excluded from further analyses since they could not be classified as PNS or non-PNS. Of note, no differences in age, DUP, DUI or prodrome were found between included patients and excluded patients due to missing data. Sixty-six of the 180 FEP patients had a score greater or equal to 3 on at least one SANS subscales. Twenty-two out of these 66 patients were excluded because of secondary negative symptoms (15 for moderate positive symptoms with SAPS score >2, six had clinically significant depressive symptoms, 3 for extrapyramidal symptoms and 1 for substance-induced symptoms (Note: two patients met the criteria for more than one secondary negative symptom). Hence, 44 FEP patients were included in the PNS group for analyses. Figure 2.1 illustrates patient classification for the current study.
Figure 2.1 Classification of FEP patients based on negative symptoms.
See Table 2.1 for results of patient demographics and clinical characteristics. Patients with PNS did not differ from patients without PNS in age, gender, DUI, DUP, and prodrome. The PNS group had significantly worse functioning at first assessment and at month 12 when compared to non-PNS groups. The PNS group had significantly worse negative symptoms scores than non-PNS at all time points. The PNS and non-PNS groups had similar scores on both positive symptom and depression scales. Mean negative and positive symptom scores for PNS and non-PNS were compared at each assessment and are presented in Figure 2.2A and 2.2B.
Table 2.1 Demographics and Clinical Characteristics of PNS Cohort (as per PNS_1 criteria). Data presented as mean ± SD ($\chi^2$ or t, p-value)

<table>
<thead>
<tr>
<th></th>
<th>PNS (n=44)</th>
<th>Non-PNS (n=114)</th>
<th>F, $\chi^2$ or t, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry, years</td>
<td>22.0±4.0</td>
<td>22.9±4.1</td>
<td>t=1.29, .195</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>30/14</td>
<td>82/32</td>
<td>$\chi^2=0.216, .697$</td>
</tr>
<tr>
<td>DUI, weeks $^b$</td>
<td>286.9±273.3</td>
<td>254.7±260.1</td>
<td>t= -0.679, .498</td>
</tr>
<tr>
<td>DUP, weeks $^b$</td>
<td>42.3±56.3</td>
<td>47.7±110.4</td>
<td>t=0.305, .761</td>
</tr>
<tr>
<td>Prodromal period $^b$</td>
<td>104.3±178.3</td>
<td>90.1±159.2</td>
<td>t= -0.478, .634</td>
</tr>
<tr>
<td><strong>SOFAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st assessment</td>
<td>40.0±12.7</td>
<td>47.0±14.5</td>
<td>t=2.403, .018*</td>
</tr>
<tr>
<td>Month 12</td>
<td>54.2±14.9</td>
<td>67.5±14.4</td>
<td>t=4.233, &lt;.001*</td>
</tr>
<tr>
<td><strong>SANS Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st assessment</td>
<td>31.2±12.4</td>
<td>31.6±13.7</td>
<td>t=-0.153, .878</td>
</tr>
<tr>
<td>Month 3</td>
<td>6.7±7.2</td>
<td>4.2±5.4</td>
<td>t=-2.320, .047*</td>
</tr>
<tr>
<td>Month 12</td>
<td>6.6±6.9</td>
<td>6.8±12.4</td>
<td>t=.103, .918</td>
</tr>
<tr>
<td><strong>SAPS Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st assessment</td>
<td>31.2±12.4</td>
<td>31.6±13.7</td>
<td>t=-0.153, .878</td>
</tr>
<tr>
<td>Month 3</td>
<td>6.7±7.2</td>
<td>4.2±5.4</td>
<td>t=-2.320, .047*</td>
</tr>
<tr>
<td>Month 12</td>
<td>6.6±6.9</td>
<td>6.8±12.4</td>
<td>t=.103, .918</td>
</tr>
<tr>
<td><strong>CDSS Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st assessment</td>
<td>5.3±4.8</td>
<td>4.9±5.3</td>
<td>t=-0.347, .729</td>
</tr>
<tr>
<td>Month 3</td>
<td>1.9±3.0</td>
<td>2.0±3.1</td>
<td>t=0.296, .768</td>
</tr>
<tr>
<td>Month 12</td>
<td>1.6±2.8</td>
<td>1.5±2.9</td>
<td>t=-0.314, .754</td>
</tr>
</tbody>
</table>

DUP= duration of untreated psychosis (from first episode to date of entry to PEPP); DUI=duration of untreated illness; SANS= Scale for the Assessment of Negative Symptoms; SAPS= Scale for the Assessment of Positive Symptoms; SOFAS = Social and Occupational

$^a$ Hollingshead Parental Socio-Economic Status, in which 1 = highest and 5 = lowest.

$^b$ Analyses were made with transformed data but values are presented in raw form.

Note: Secondary negative symptoms were removed from analyses.
Figure 2.2  Mean negative and positive symptom scores during the first year of treatment and individual negative symptom
domains.
Figure 2.2. A) SANS total scores from first assessment to month 12; B) SAPS total scores from first assessment to month 12 *= p<0.001; C) Frequency of patients that met PNS_1 criteria for the 4 subdomains of the SANS; D) Mean scores for the 4 subdomains of the SANS for patients meeting the PNS_1 criteria. N= 158 (44 PNS and 114 non-PNS) *= Domain was significantly different than all the other three SANS domains.

1st = First Assessment

Note: SANS total scores do not include the “Attention” domain.
Similar to previous findings (Rodriguez-Sanchez et al., 2005, Rodriguez-Sanchez et al., 2008, Crespo-Facorro et al., 2009, Buchy et al., 2010), we also documented an initial stabilization of symptoms by the third month of treatment. Individual domains were explored (Figure 2.2C and 2.2D). The frequency of patients with PNS who met the criteria (≥3) for any of the 4 domains SANS as well as the mean score of the PNS group for each domain was explored. Patients meeting the criteria for PNS_1 had higher levels of avolition/apathy as well as anhedonia/asociality both in terms of meeting the PNS criteria due to these domains as well as having higher mean scores in these domains. Primary diagnoses for all patients in the PNS groups are found in Table 2.2. The majority of patients in the PNS_1 group were diagnosed with schizophrenia (paranoid) (20.5%) or schizophrenia (undifferentiated) (20.5%). On the other hand, a greater number of patients in the PNS_2 and PNS_H groups were diagnosed with schizoaffective disorder or schizophrenia (undifferentiated).
Table 2.2 Primary Diagnosis on Admission. Data presented as frequency (percentage)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PNS_1</th>
<th>PNS_2</th>
<th>PNS_H</th>
<th>PDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia-Disorganized</td>
<td>4 (9.1)</td>
<td>2 (9.5)</td>
<td>2 (9.5)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>Schizophrenia- Paranoid</td>
<td>9 (20.5)</td>
<td>3 (14.3)</td>
<td>3 (14.3)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>1 (2.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>8 (18.2)</td>
<td>7 (33.3)</td>
<td>7 (33.3)</td>
<td>-</td>
</tr>
<tr>
<td>Schizophrenia- Undifferentiated</td>
<td>9 (20.5)</td>
<td>6 (28.6)</td>
<td>6 (28.6)</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>Bipolar I – With psychotic features</td>
<td>5 (11.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Major Depression – With psychotic features</td>
<td>2 (4.5)</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
<td>-</td>
</tr>
<tr>
<td>Bipolar I – Manic with psychotic features</td>
<td>2 (4.5)</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
<td>-</td>
</tr>
<tr>
<td>Bipolar I – Depressed recent episode</td>
<td>1 (2.3)</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
<td>-</td>
</tr>
<tr>
<td>Psychosis NOS</td>
<td>3 (6.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
2.4.2 Prevalence and Associations with Functional Outcome

*PNS_1 Definition:* Forty-four patients (27.8%) were identified with PNS and 114 (72.2%) were not. This liberal definition showed the highest prevalence of PNS compared to the other two definitions. The repeated measures ANOVA revealed a significant main effect of time ($F_{1,82}=71.762, p<0.001$) and a significant main effect of group ($F_{1,82}=10.065, p=0.002$). Figure 2.3 illustrates SOFAS scores over time for PNS_1, PNS_2 and non-PNS patients. A significant [time x group] interaction ($F_{1,83}=4.117, p=0.046$) was also observed. Further analyses revealed SOFAS scores for patients with PNS were significantly lower at both initial assessment ($F_{1,125}=4.343, p=0.039$) and at month 12 ($F_{1,109}=17.328, p<0.000$) compared to patients without PNS. Paired t-tests revealed that PNS_1 ($t_{23}=-4.335, p<0.000$) and non-PNS ($t_{59}=-9.414, p<0.000$) both significantly improved over time. A score of 60 or greater on the SOFAS is considered to represent good functioning (Koivumaa-Honkanen et al., 2008, Cassidy et al., 2010). Interestingly, only the non-PNS group had a mean score greater than 60 on the SOFAS scale at month 12. See Table 2.1 for SOFAS scores.
Figure 2.3 Mean SOFAS scores at the first assessment and month 12 follow-up for patients with and without PNS.
**PNS_2 Definition:** Twenty-one patients (13.3%) met the criteria for PNS_2, while 137 did not (86.7%). Similarly to the PNS_1 definition, repeated measures ANOVA revealed a significant main effect of time ($F_{1,82}=28.525$, $p<0.001$) and a significant effect of group ($F_{1,82}=14.661$, $p<0.001$). There was no significant [time x group] interaction ($F_{1,82}=2.956$, $p=0.089$) observed. Further analyses revealed that patients with PNS had significantly worse functioning at the initial assessment ($F_{1,126}=6.669$, $p=0.011$) and at month 12 ($F_{1,103}=20.981$, $p<0.001$) than patients in the non-PNS group. Paired t-test revealed that PNS_2 ($t_9=-2.239$, $p<0.052$) and non-PNS ($t_{73}=-10.072$, $p<0.000$) both significantly improved function over time. Similarly to the PNS_1 definition, the mean SOFAS score for the PNS_2 group was not greater than 60, which is considered to be “poor functioning”.

**PNS_H Definition:** Twenty-one patients (13.3%) met the criteria for PNS_H, while 137 (86.7%) did not. Repeated measures ANOVA revealed a significant main effect of time ($F_{1,82}=28.525$, $p<0.001$) as well as a significant effect of group ($F_{1,82}=14.661$, $p<0.001$). No significant [time x group] interaction was found ($F_{1,82}=2.956$, $p=0.089$). Group comparisons with a one-way ANOVA revealed significantly worse SOFAS scores for the PNS group at the initial assessment ($F_{1,126}=6.669$, $p=0.001$) and at month 12 ($F_{1,102}=20.981$, $p<0.001$). Paired t-tests revealed that both PNS ($t_9=-2.239$, $p<0.052$) and non-PNS ($t_{73}=-10.072$, $p<0.000$) groups improved in function over time. Only patients not meeting the PNS_H criteria achieved good functioning.
Prevalence of DS in FEP: Only five FEP patients (3%) met the criteria for deficit syndrome according to the proxy definition. All five patients in this group had an initial diagnosis of schizophrenia (disorganized, paranoid or undifferentiated).

Furthermore, as previously mentioned, when compared to any of the 3 PNS groups, only the cohort with non-PNS patients achieved a mean score of “good functioning” according to the SOFAS scale. Due to missing data, only 140 of the patients obtained a SOFAS score at month 12 (31 from the PNS cohort and 109 from the non-PNS cohort). However, of those with available SOFAS scores at the 12 month follow-up, 61% of patients from the PNS_1 group (19/31) were considered “poorly functioning” whereas only 26% of non-PNS patients (28/109) were “poor functioning”. Interestingly, of the 39% of PNS patients (12/31) with “good functioning”, 83% (10/12) met the PNS criteria for PNS_1 only and not PNS_2 or PNS_H.

2.4.3 Supplementary Analysis of the PNS_1 group

To further delineate whether a stringent PNS definition is more clinically significant, “liberal” and “stringent” subgroups were formed. More specifically, the “stringent” group was formed of both PNS_2 and PNS_H groups combined. To obtain a “clean” PNS_1 group, specific patients in the PNS_1 group were extracted and re-named as the “liberal” group. The “liberal” subgroup consisted of patients who only met the criteria for PNS_1 only and not PNS_2 and/or PNS_H (i.e. all patients who met the criteria for PNS_2 or PNS_H automatically also met the criteria for PNS_1, but not all patients in the PNS_1 group met the criteria for PNS_2 or PNS_H). Of the 44 patients in the PNS_1 group, 23 patients met the “liberal” criteria. Therefore, 21 patients were left in the “stringent” group. Using the “liberal” group, repeated
measures ANOVA were used to establish whether isolating this “liberal” group would impact the previous results with the entire PNS_1 group. Scores from the SOFAS scale were used as within subject variables (first assessment, month 12) and group (liberal, stringent) as the between subject variable. A main effect of time was observed ($F_{1,82}=48.089$, $p<0.001$). However, although there was a significant [time x group] interaction using the entire PNS_1 cohort, isolation of the “liberal” group from this definition failed to reveal any significant [time x group] interactions ($F_{1,82}=0.879$, $p=0.351$).

2.5 Discussion

2.5.1 Main Findings

The main findings of this study suggest the prevalence of PNS in FEP varies depending on the definition being applied. More specifically, the prevalence of PNS was shown to be between 13 and 27%. Patients identified as having PNS (regardless of the definition) were consistently shown to have poorer functional outcome at month 12. However, all three PNS definitions demonstrated similar associations with functional outcome. Both PNS and non-PNS cohorts improved function over a 1-year period; however, the PNS group never met the criteria for “good functioning” according to mean SOFAS scores. Interestingly, when patients who met the criteria solely for our PNS_1 definition were extracted, this “liberal” definition did not show any significant associations with functional outcome at the one-year follow-up. The majority of patients met the PNS criteria due to clinically significant global scores on either the Avolition/Apathy or Anhedonia/Asociality domains of the SANS scale. Lastly, applying the proxy definition to identify FEP patients with DS resulted in a prevalence rate of 3%.
2.5.2 Can the Deficit Syndrome Criteria be applied in First Episode Psychosis?

The prevalence of primary enduring negative symptoms, or deficit syndrome in first episode patients has been estimated to be around 15% (Kirkpatrick et al., 2001). However, when applying the PDS to identify individuals with DS in a FEP cohort, the current findings suggested a prevalence of 3% when compared to 13-27% using the PNS criteria. Initially, the PDS was validated with a chronic schizophrenia outpatient cohort (Kirkpatrick et al., 1993). While DS only applies to schizophrenia spectrum disorder, the current study demonstrates that prominent and enduring negative symptoms or PNS impacting functional outcome include FEP patients with several primary diagnoses including schizoaffective, bipolar I with psychotic features and major depression with psychotic features. Accordingly, this may suggest that this subgroup of negative symptoms is relevant not only to patients with a diagnosis of schizophrenia. In fact, a diagnosis of schizoaffective disorder fell within the top three most common diagnoses for any of the three PNS definitions. It may be possible that when compared to DS, PNS is a more appropriate subgroup found in FEP patients with both affective and non-affective diagnoses.

It has been suggested that affective flattening and alogia (poverty of speech) are strongly associated and represent the “core negative symptoms” contributing to poor functional outcome (Malla et al., 2002, Malla et al., 2004, Kirkpatrick and Fischer, 2006). In DS, affective flattening was previously shown to be significantly more severe in DS when compared to non-DS. The PDS case identification tool requires affective items to be subtracted from the blunted affect score of the PANSS or BPRS scales. In FEP patients, flat affect and
alogia have not always been shown to be the most prominent negative symptoms (Fennig et al., 1996). Similarly, the results of the current study demonstrated low levels of the “diminished expression” subdomain of negative symptoms in the PNS cohort. It is plausible that these low levels of affective flattening in FEP greatly impact the prevalence of DS. More recently, the PDS formula was further altered to include both blunted affect and poverty of speech items (Trotman et al., 2010). Adding this second negative symptom would possibly further decrease the prevalence of DS in chronic schizophrenia and more so in a FEP population. Thus, in a group of FEP patients PNS, blunted affect and/or alogia do not seem to be the driving forces of these persistent symptoms and this may elucidate why the prevalence of DS was lower than previously documented (Kirkpatrick et al., 1993).

2.5.3 Influence of Persisting Negative Symptoms on Functional Outcome

Similar to past findings in DS showing poorer functioning in DS when compared to non-DS (Arango et al., 2004), our results showed worse functional outcome at month 12 regardless of the PNS definition being applied. Several functional outcomes appear to be impacted by negative symptoms including psychosocial functioning, recreation, relationships, and occupational functioning (Herbener and Harrow, 2004, Milev et al., 2005, Bowie et al., 2006). An investigation by Milev et al. (Milev et al., 2005) assessed whether or not the severity of negative symptoms could predict functional outcome. Indeed, in comparison to positive and disorganized symptoms, negative symptom severity was shown to have the greatest predictability for poor psychosocial functioning. Concordantly, the current results demonstrated that applying the PNS_1 definition was sufficient to identify FEP patients with PNS at risk of poor functioning 12 months after entry into a FEP program.
Initial descriptions of schizophrenia included Kraepelin’s observation of avolition being prominent as key symptom (Kraepelin, 1919). Accordingly, several studies have demonstrated more severe negative symptoms in the SANS subscales of anhedonia/asociality and avolition/apathy (Malla et al., 2002, Atbasoglu et al., 2003, Blanchard et al., 2005, Avery et al., 2009). These SANS domains have also been associated with poor functional outcome, suggesting that the putative role of negative symptoms on functional outcome may be largely influenced by these domains. Similarly, our results showed greater mean scores on both these SANS domains as well as a greater number of FEP patients meeting the PNS criteria due to these SANS domains. Thus, the role of these two domains, which has been referred to as the “amotivation” subdomain of the SANS may play a pivotal role in PNS and its association with poor functional outcome (Foussias and Remington, 2010).

Individually, the apathy domain of negative symptomatology has also been shown to contribute to poor functioning at year 1 (Kiang et al., 2003, Faerden et al., 2009). However, given the content overlap observed when quantifying apathy and measuring functional outcome (Clarke et al., 2011), this may have some influence on their relationship due to their tautology. This is a concern raised by previous authors (Blanchard et al., 2010) and may have been a limitation in the current study. Nonetheless, improving social and occupational functioning is a major objective in the treatment of FEP patients and a step towards recovery. Given the results of the current study, it may be more beneficial to identify individuals with PNS who are at a greater risk of functional decline by applying more stringent criteria. This will help build a stronger foundation for a more concise PNS definition.
2.5.4 Secondary Negative Symptoms

Nineteen patients with PNS were removed from our analyses due to secondary negative symptoms. Secondary negative symptoms are thought to have a distinct etiology from that of primary negative symptoms (Remington et al., 1999). Thus, to increase homogeneity of a cohort it is preferable to characterize both features of negative symptoms. However, investigations have not always made this distinction (Honey et al., 2005, Bell and Mishara, 2006) - partly due to the difficulty in distinguishing primary from secondary negative symptoms (Peralta et al., 2000, Alphs, 2006, Chang et al., 2011). It was suggested that secondary negative symptoms not responding to treatment should be included in the criteria for PNS (Buchanan, 2007); albeit, the criteria proposed requires one to have minimal or no positive, depressive and extrapyramidal symptoms. It may be possible that patients with enduring secondary negative symptoms (due to positive symptoms not responding to treatment) may benefit specifically from interventions targeting PNS such as transcranial magnetic stimulation (TMS) (Goyal et al., 2007, Schneider et al., 2008, Dlabac-de Lange et al., 2010, Oh and Kim, 2011); however, this has not been empirically substantiated. Future studies should investigate the role these secondary negative symptoms have in PNS in order to provide a stronger rationale for including or excluding them from PNS.

2.5.5 Characterization of the PNS Cohort

Previous findings have documented longer DUP in patients with more prominent and enduring negative symptoms (Edwards et al., 1999, Malla et al., 2004, Chang et al., 2011). In a first episode cohort assessed during the first year of illness, DUP was also shown to predict PNS
(Malla et al., 2004). Furthermore, some studies have proposed that negative symptoms appear prior to the onset of positive symptoms, occurring in the prodromal period (Moller, 2007, Remington et al., 2011). The current study did not replicate these findings; no significant group differences were found for DUP or length of the prodromal period. Regardless of the lower DUP and prodromal period, patients still met the criteria for PNS suggesting that there may be other factors contributing to PNS. Furthermore, at the first assessment, our PNS group had significantly worse negative symptoms when compared to the non-PNS group while positive symptoms were similar between groups. This may support the idea that more severe negative symptoms occurring earlier on have a significant contribution to residual negative symptoms. Hence, clinically significant negative symptoms at the onset of psychosis may be a strong indicator of PNS.

2.5.6 Choosing a PNS Definition

Choosing which PNS definition to employ may be dependent on the research question being asked. From an intervention perspective, the number of patients needs to be maximized to have a stronger conclusion determining the efficacy of a given intervention. Hence, applying our PNS_1 definition may be more appropriate. Interestingly, all patients who met the criteria for PNS_2 also met the criteria for either of the two domains of the hybrid definition (diminished expression or amotivation). Future research should focus on identifying the neurobiological and physiological determinants of PNS_1 and PNS_2 in order to determine whether they are distinct or share similarities. Furthermore, as suggested by Buchanan (Buchanan, 2007), it may be beneficial to include patients with persistent secondary negative symptoms that have not responded to treatment when employing this particular research question.
2.5.7 Limitations

Some studies have suggested that a follow-up of two or more years may be more appropriate when exploring symptoms in FEP (Milev et al., 2005, Mane et al., 2009). Our study had a one-year follow up and this may have been a limitation in terms of understanding the trajectory of PNS. A 5-year follow up may have helped us better delineate the course of PNS in our FEP cohort.

2.6 Conclusions

Persistent negative symptoms are present in about 27% of FEP patients. Applying either of our PNS definitions for identifying PNS is a feasible method for identifying patients with PNS at risk of poor functioning. However, the definition being employed should depend on the research objectives. Given the association between PNS and poor functional outcome 12 months after entry into our treatment program, it is highly recommended to identify PNS within the first year of illness. When compared to the PDS, using a PNS criteria may be more applicable to a FEP cohort to identify enduring negative symptoms. As it has been stated ad nauseam, we need to standardize how to define PNS in order to obtain a better understanding of these symptoms. Further longitudinal, rather than cross-sectional studies on the development and treatment of PNS in a FEP population are warranted.
Chapter 3: Persistent Negative Symptoms in First Episode Psychosis: Relation to Memory


**PREFACE**

Cognitive impairments and negative symptoms are thought to be part of the core symptoms of schizophrenia (Bleuler, 1908, Kraepelin, 1919) and can be present as early as the prodrome and first episode of psychosis (Simon et al., 2007, Seidman et al., 2010, Gonzalez-Ortega et al., 2012). Although general cognitive deficits have been implicated in FEP (Gold et al., 1999), some studies have focused on the relationship between cognitive deficits and symptomatology and have highlighted increased cognitive impairments with greater negative symptoms severity (Heydebrand et al., 2004, Milev et al., 2005, Bora et al., 2009). Rather than assessing this relationship through correlational analysis applied in cross sectional studies, it might be of greater potential clinical utility to study this relationship longitudinally. However, this relationship has not been investigated in a well-defined FEP population with PNS.

The objectives of this longitudinal study were to investigate memory ability in a group of first episode patients identified as having persistent negative symptoms. Memory ability
in this group was compared to FEP patients without PNS and healthy controls. In addition, FEP patients were followed during a 1-year period and symptoms were evaluated at the initial assessment after entry into the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal) and at months 1, 2, 3, 6, 9, and 12. Hence, our second objective was to evaluate the relative stability of memory during the first year of illness.
3.1 Abstract

Negative symptoms are present early on during the first episode of psychosis (FEP). The severity of these symptoms has been linked to cognitive deficits, including memory; however, its relationship with persistent negative symptoms (PNS) remains unclear. Thus, the goals of the current paper were to explore memory profiles in FEP patients identified as having PNS and to delineate this relationship in PNS over a 1-year period. Patients diagnosed as having a first episode of psychosis were segregated into groups of patients who met the criteria for PNS (N=39) and patients who did not, or non-PNS (N=97). At an initial assessment, all subjects were administered neurocognitive tests for three memory domains including verbal, visual and working memory. In addition, in FEP patients, clinical symptoms including negative, positive and depressive symptoms were also measured at the initial assessment as well as months 1,2,3,6,9,12. A significant interaction of memory x PNS was observed (F=4.997, d.f. = 1,181, P=0.002), with post hoc comparisons indicating that the PNS group performed more poorly than non-PNS only in the verbal memory domain. All three-memory domains remained stable over time. Hence, in comparison to non-PNS patients, FEP patients with PNS appear to have greater (selective) verbal memory impairments throughout the first year of treatment.
3.2 Introduction

Since Kraepelin’s first description of dementia praecox (Kraepelin, 1971) and Blueler’s emphasis on primary vs. accessory (psychotic) symptoms, negative symptoms, as well as cognitive impairments, have been recognized as core features of schizophrenia. Negative symptoms refer to an impoverishment of normal behavior and include poverty of speech (alogia), reduced ability to feel pleasure (anhedonia), decreased motivation (avolition) and emotional unresponsiveness (blunted affect) (Andreasen, 1989, Kirkpatrick et al., 2006). Several studies suggest a modest association between poor cognitive ability and negative symptom severity (Gold et al., 1999, Fitzgerald et al., 2004, Harvey et al., 2006). This relationship is not as strongly evidenced with positive symptoms (Gold et al., 1999, Bilder et al., 2000, Keefe et al., 2006, Ventura et al., 2009).

Memory impairments manifesting across various memory domains including verbal, visual and working memory are well documented in schizophrenia (for review see Aleman et al., 1999) (Fridberg et al., 2010, Harvey et al., 2010, Leeson et al., 2010, Lepage et al., 2010, Bodnar et al., 2012, Ragland et al., 2012, Zhou et al., 2012); however, what is of clinical concern is the presence of these deficits earlier in the illness. Some have suggested that memory deficits documented during early stages of psychosis are associated with the severity of negative symptoms (Bodnar et al., 2008, Leeson et al., 2010), while others have shown that memory deficits present in the prodrome may predict transition to psychosis (Brewer et al., 2005, Lencz et al., 2006, Pukrop et al., 2006, Woodberry et al., 2010). Nonetheless, three major caveats of past studies...
investigating this relationship are: 1) the employment of correlational analyses, 2) variable degrees of negative symptoms between studies (O'Leary et al., 2000, Hughes et al., 2003, Bozikas et al., 2004, Rund et al., 2004) and 3) a lack of a clear distinction between PNS and non-PNS. Thus, identifying a group of FEP patients with set criteria for PNS may help strengthen findings and further our understanding of negative symptoms.

Research on persistent negative symptoms (PNS) has recently gained substantial momentum (Edwards et al., 1999, Heckers et al., 1999, Malla et al., 2004, Kirkpatrick et al., 2006, Buchanan, 2007, Chang et al., 2011, Hovington and Lepage, 2012, Stauffer et al., 2012). These symptoms are present at the first episode and represent approximately 24-27% of FEP patients (Malla et al., 2004, Chang et al., 2011, Hovington et al., 2012). Persistent negative symptoms must be present for a minimum of 6 consecutive months after the initial symptoms stabilization (Buchanan, 2007, Hovington and Lepage, 2012); hence, longitudinal rather than cross-sectional studies seem more suitable to investigate these symptoms. The stability of the relationship between memory and PNS remains unclear (Gold et al., 1999, Milev et al., 2005) [for review see (Bozikas and Andreou, 2011)].

Given the ambiguity of this relationship, it may be beneficial to assess a more homogenous subgroup of FEP. Thus, the objectives of this study were: 1) to compare memory ability (working, verbal and visual memory) in a sample of FEP subjects with PNS to subjects without PNS as well as healthy controls; and 2) to assess the trajectory of
these three memory domains in relation to PNS at 1-year follow-up. Based on previous reports on the relationship between the severity of negative symptoms and memory deficits, we hypothesize that the group with PNS will have greater memory deficits compared to non-PNS patients and healthy controls. Further, based on reports of relative stability of cognition over time (Aleman et al., 1999, Vaz and Heinrichs, 2002, Hughes et al., 2003), we hypothesized that all memory domains would remain stable.

3.3 Methods

3.3.1 Participants

All FEP patients were part of a longitudinal study and were treated in the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), a specialized early intervention service with integrated clinical, research, and teaching modules, at the Douglas Mental Health University Institute in Montreal, Canada. Individuals aged 14 to 35 years from the local catchment area suffering from either affective or non-affective psychosis who had not taken antipsychotic medication for more than one month and with an IQ higher than 70 were admitted to the program as either in- or out-patients (for details see (Malla et al., 2003) or visit http://www.douglasresearch.qc.ca/pages/view?section_id=165). Diagnosis of schizophrenia or related spectrum disorders was established with the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 1998). Written informed consent was obtained from all participants. Research protocols were approved by the Douglas Institute Human Ethics Review Board. Only baseline neuropsychological assessments were used
for the current study and clinical symptoms throughout the first year were employed to identify individuals with PNS. Sixty-two healthy controls were recruited through advertisements in local newspapers and were included only if they had no current or previous history of (a) any Axis I disorders, (b) any neurological diseases, (c) head trauma causing loss of consciousness, and (d) a first-degree family member with schizophrenia or related schizophrenia-spectrum psychosis. Current IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI-III) (Wechsler, 1997a).

3.3.2 Clinical Assessment

An initial assessment was conducted on average, within one month after admission (in days; mean=22.7, s.d.= 8.6, range=8.3-54.8). Education level (number of school years completed), parental socio-economic status (SES) with the Hollingshead two-factor index (Miller, 1991a), Social and Occupational Functioning Assessment Scale (SOFAS), The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) and handedness (Oldfield, 1971) were acquired at the initial assessment. As part of the longitudinal study, the following clinical variables were assessed at the initial assessment as well as at months 1,2,3,6,9 and 12 following the first evaluation. Negative and positive symptoms were quantified using the SANS (Andreasen, 1984) and the SAPS (Andreasen, 1983), respectively. The domain of attention in the SANS scale was not included in our analyses because previous factor analytical studies have shown that it loads on both negative and disorganization (Peralta and Cuesta, 1999, Malla et al., 2002). Evaluators at PEPP established an ICC of 0.74 on the SAPS and 0.71 on the SANS; all evaluator’s
participated in inter-rater reliability sessions at least once a year to avoid evaluator drift (i.e. evaluators must maintain consistency with themselves as well as with other evaluators). Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) and extrapyramidal symptoms with the Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard and Margolese, 2005). If prescribed, type and dose of anticholinergic medications taken were recorded. The type and dosage of antipsychotics taken were also recorded and subsequently converted into chlorpromazine equivalents (Woods, 2003).

3.3.3 Neuropsychological Assessment

Trained research staff administered a standardized battery of neuropsychological tests to all participants under the supervision of an accredited neuropsychologist (M.L). As part of a larger cognitive study, a total of seven cognitive domains as suggested by the NIMH-Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) group (Nuechterlein et al., 2004) were assessed at the first evaluation and at the 1-year follow-up in the patient group and only at the first assessment in the healthy control group. We have described these domains in further detail elsewhere (Bodnar et al., 2008, Lepage et al., 2008). The following cognitive domains were derived: verbal learning and memory from the Logical Memory (LM) subtests of the Wechsler Memory Scale - Third Edition (WMS-III) (Wechsler, 1997b); visual learning and memory from the Visual Reproduction subtests of the WMS-III; working memory from the Spatial Span subtests of the WMS-III and the Digit Span subtest of the Wechsler Adult
Intelligence Scale – Third Edition (WAIS-III); speed of processing from Trail Making Test A (completion time) (Reitan, 1992) and the digit symbol subtest of the WAIS-III; reasoning and problem solving from the Trail Making Test B (completion time) and the block design subtest of the WAIS-III; attention from the d2 Test of Attention (concentration performance score) (Brinkenkamp, 1998) and social cognition from the Four Factor Tests of Social Intelligence (O’Sullivan and Guilford, 1976) and Hinting Task (Corcoran et al., 1995).

3.3.4 Identifying Persistent Negative Symptoms

Clinical data from the first assessment as well as months 1, 2, 3, 6, 9, and 12 were analyzed to identify patients with PNS. PNS was defined as having a minimum score of three on one or more global items of the SANS (Malla et al., 2004) (Hovington et al., 2012). These negative symptoms were required to be present after the initial stabilization of positive symptoms (month 3) and to be maintained for 6 consecutive months (months 6, 9 and 12) (Buchanan, 2007) (Hovington et al., 2012). Subjects with global ratings on “affective flattening” or “alogia” entirely based as a result of items “inappropriate affect” or “poverty of content of speech”, respectively were excluded as having negative symptoms based on previous findings suggesting that these items are not part of the negative symptom construct (Malla et al., 2004). After the completion of the 12-month assessment, FEP patients were segregated into two groups (PNS and non-PNS).
Patients in the PNS group had primary negative symptoms absent of any positive (global rating of mild (2) or less, as measured by the SAPS), depressive (a total score of 4 or less on the CDSS) (Addington et al., 1993) or extrapyramidal symptoms (low to mild levels). Lastly, FEP patients who were administered their initial neuropsychological assessment later than nine months after entry into our program were also excluded since this was deemed too late given our PNS criteria.

### 3.3.5 Statistical Analysis

For clinical data, DUP and DUI were log transformed and duration of prodrome was square-root transformed; all other clinical data characteristics were normally distributed. Independent t-tests were used to compare clinical characteristics between PNS and non-PNS groups. Categorical variables were compared using a chi-squared test, while continuous variables were compared using independent t-tests. All clinical scales (SOFAS, SANS, SAPS, CDSS) were compared between groups at both first assessment and month 12.

For the neuropsychological data, all three visual reproduction variables from the initial assessment were square root transformed; all other neuropsychological data were normally distributed. Our first analysis focused on data from the initial assessment. To start, all pertinent subtests for each cognitive domain were transformed into standard equivalents (z-scores) using the mean and standard deviation of the healthy control group. Cognitive domains were then calculated by averaging the z-scores of the relevant
subtests and then normalized using the mean and standard deviation of the healthy control group. A repeated-measure multivariate analysis of variance (MANOVA) was used to compare the profile of memory performance among the groups, using group membership (PNS, non-PNS, and control) as the between-groups factor and the memory domains as the within-group factor. Univariate ANOVAs with post hoc Bonferroni pairwise contrasts were used to identify group differences where necessary. The critical P-value was set to 0.016 following the Bonferroni correction procedure to control for multiple comparisons.

To examine change over time, a repeated-measure MANOVA was used to compare the profile of memory performance between the patient groups, using group membership (PNS and non-PNS) as the between-groups factor and time (initial and follow-up) along with the memory domains as the within-group factors. Univariate ANOVAs were used to identify group differences where necessary. The critical P-value was set to 0.010. Please note, since control data was not collected at follow-up, this group was not included in this analysis. To maintain consistency with the previous analysis, the domains were re-calculated using the scaled scores. That is, all pertinent subtests for the memory domains were transformed into standard equivalents (z-scores) using a mean of 10 and a standard deviation of 3 (Weschler, 1997). Cognitive domains were then calculated by averaging the z-scores of the relevant subtests.

All statistical tests were two-tailed with the critical P-value set at 0.05 except where noted, and performed using SPSS version 18 for MAC.
3.4 Results

A group of 165 FEP patients with complete data from the first assessment up until the 12-month follow-up obtained between 2003 and 2009 were included. Figure 3.1 illustrates patient classification. Of the 165 patients admitted into the program, 29 were excluded from the analysis due to the presence of secondary negative symptoms or being administered a neuropsychological assessment later than nine months after entry into the FEP program (22 and 7, respectively). Of the rest, 39 were identified as having PNS (23.6%) with a primary diagnosis of: schizophrenia spectrum disorder, affective psychosis, or psychosis NOS. SOFAS scores were significantly worse for the PNS group at month 12. Of note, the relationship between PNS and function has been addressed in our previous study (Hovington et al., 2012). Based on SANS ratings, patients in the PNS group had significantly worse negative symptoms at both first assessment and month 12. Positive symptoms, depressive symptoms and antipsychotic dosage (CPZ equivalent doses) did not significantly differ between groups. Details regarding the diagnoses as well as clinical data are presented in Table 3.1.
Figure 3.1 Classification of FEP patients based on negative symptoms.
### Table 3.1 Socio-demographic data and Clinical Characteristics of groups (mean ± SD)

#### Socio-Demographic Data of PNS, Non-PNS and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>PNS group</th>
<th>Non-PNS group</th>
<th>Healthy Control Group</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=39)</td>
<td>(N=97)</td>
<td>(N=62)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>22.2 (3.9)</td>
<td>22.7 (4.1)</td>
<td>24.9 (3.3)</td>
<td>6.71</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>28/11</td>
<td>69/28</td>
<td>41/21</td>
<td>0.613</td>
</tr>
</tbody>
</table>

#### Clinical Characteristics of PNS and Non-PNS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>t</th>
<th>d.f</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUI (weeks)</td>
<td>303.9±284.</td>
<td>271.2±268.6</td>
<td>-.538</td>
<td>134</td>
<td>.591</td>
</tr>
<tr>
<td>DUP (weeks)</td>
<td>39.8±56.0</td>
<td>54.7±121.5</td>
<td>.756</td>
<td>134</td>
<td>.451</td>
</tr>
<tr>
<td>Prodrome</td>
<td>108.0±183.</td>
<td>95.8±169.6</td>
<td>-.267</td>
<td>134</td>
<td>.790</td>
</tr>
<tr>
<td>Antipsychotic Dose*</td>
<td>187.3±240.</td>
<td>142.6±125.4</td>
<td>1.103</td>
<td>134</td>
<td>.272</td>
</tr>
</tbody>
</table>

#### Type of Meds (N/%) | U=1880.50 | - | 0.954 |
| Risperidone            | 16 (41.0%)| 29 (29.9%)    | -            | -   |
| Olanzapine             | 17 (43.6%)| 49 (50.5%)    | -            | -   |
| Quetiapine             | 1 (2.6%)  | 6 (6.2%)      | -            | -   |
| Haloperidol            | 1 (2.6%)  | -             | -            | -   |
| Paliperidone           | -         | 2 (2.1%)      | -            | -   |
| Ziprasidone            | 1 (2.6%)  | 1 (1.0%)      | -            | -   |

#### Diagnosis (N) | U= 1705.50 | - | .296 |
| Schizophrenia Spectrum Disorders | 27(69.2%) | 58 (59.8%) | - | - |
| Affective Psychosis     | 9 (23.1%) | 28 (28.9%)  | - | - |
| Psychosis NOS           | 3 (7.7%)  | 11 (11.3%)   | - | - |

#### SOFAS Score

<table>
<thead>
<tr>
<th></th>
<th>1st Assessment</th>
<th>Month 12</th>
<th>t</th>
<th>d.f</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41.9±14.0</td>
<td>54.4±15.2</td>
<td>1.752</td>
<td>107</td>
<td>.083</td>
</tr>
<tr>
<td></td>
<td>67.1±14.5</td>
<td>-</td>
<td>3.823</td>
<td>91</td>
<td>&lt;.000*</td>
</tr>
</tbody>
</table>

Note: PNS = Psychosis NOS, Non-PNS = Non-Psychosis NOS, SOFAS = Social and Occupational Functions Assessment Scale.
<table>
<thead>
<tr>
<th></th>
<th>1st Assessment</th>
<th>Month 12</th>
<th>t-value</th>
<th>DF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SANS Score†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39.3±17.3</td>
<td>28.7±16.1</td>
<td>-</td>
<td>131</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td></td>
<td>32.6±14.1</td>
<td>15.5±10.9</td>
<td>-</td>
<td>117</td>
<td>&lt;.000*</td>
</tr>
<tr>
<td><strong>SAPS Score†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31.6±12.4</td>
<td>32.9±14.3</td>
<td>-</td>
<td>132</td>
<td>.613</td>
</tr>
<tr>
<td></td>
<td>6.6±7.2</td>
<td>7.2±12.8</td>
<td>-</td>
<td>117</td>
<td>.801</td>
</tr>
<tr>
<td><strong>CDSS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.1±4.9</td>
<td>5.2±5.3</td>
<td>-</td>
<td>131</td>
<td>.892</td>
</tr>
<tr>
<td></td>
<td>1.6±2.8</td>
<td>1.6±3.2</td>
<td>-</td>
<td>119</td>
<td>.983</td>
</tr>
</tbody>
</table>

DUI= duration of untreated illness; DUP= duration of untreated psychosis; SOFAS= Social and Occupational Functioning Assessment Scale; SANS= Scale for the Assessment of Negative Symptoms; SAPS= Scale for the Assessment of Positive Symptoms; CDSS= Calgary Depression Scale for Schizophrenia. * Mean cumulative chlorpromazine equivalent antipsychotic exposure at initial assessment. † Total SANS and SAPS scores do not include global items.
A significant interaction revealed that at the initial assessment, memory performance profiles in the three groups were not parallel (\(F=4.997, \text{ d.f.} = 1.181, \text{ P}=0.002\)). Subsequent univariate ANOVAs revealed significant mean differences among the groups in all memory domains. Post hoc comparisons indicated that z-scores for FEP patients (both PNS and non-PNS) were significantly worse than controls. Further, patients with PNS had poorer verbal memory in comparison to non-PNS and healthy controls (Table 3.2).
Table 3.2 Z-scores (mean±SD) for memory tests and IQ (mean±SD) of PNS and non-PNS groups at initial assessment

<table>
<thead>
<tr>
<th>Memory Domains</th>
<th>PNS (N=39)</th>
<th>Non-PNS (N=97)</th>
<th>Controls (N=62)</th>
<th>F</th>
<th>d.f.</th>
<th>P</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory</td>
<td>-1.81 (1.10)</td>
<td>-1.12 (1.24)</td>
<td>-0.01 (1.00)</td>
<td>31.51</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS&lt;non-PNS; ctrls&gt;patients</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>-1.34 (1.76)</td>
<td>-1.09 (1.48)</td>
<td>-0.00 (1.00)</td>
<td>14.66</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS=non-PNS; ctrls&gt;patients</td>
</tr>
<tr>
<td>Working Memory</td>
<td>-0.82 (0.94)</td>
<td>-0.69 (0.86)</td>
<td>0.04 (0.94)</td>
<td>12.12</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS=non-PNS; ctrls&gt;patients</td>
</tr>
<tr>
<td>IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>94.76 (16.28)</td>
<td>98.95 (15.0)</td>
<td>107.85 (15.0)</td>
<td>9.87</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS=non-PNS</td>
</tr>
<tr>
<td>Performance</td>
<td>91.56 (18.48)</td>
<td>92.95 (15.40)</td>
<td>104.02 (14.38)</td>
<td>11.06</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS=non-PNS</td>
</tr>
<tr>
<td>Overall</td>
<td>93.38 (17.45)</td>
<td>96.39 (15.14)</td>
<td>107.90 (14.76)</td>
<td>13.56</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS=non-PNS</td>
</tr>
</tbody>
</table>

PNS=persistent negative symptoms; ctrls=controls; <= performed worse; >= performed better
Follow-up data from 88 non-PNS FEP patients and 34 FEP patients with PNS were assessed to investigate whether there was a change over time. Analysis of the change over time for all three-memory domains in the PNS and non-PNS group revealed no significant three-way interaction (F=0.695, p=0.498); thus, suggesting that 1) significant differences observed between PNS and non-PNS remain stable over time (verbal) and 2) lack of significant memory differences documented between PNS and non-PNS also remains stable over time (visual and working memory). A main effect of group (F=5.222, d.f 1,122 p<0.001) and types of memory (F=13.527, d.f 1,122, p.0.001) was observed. See Figure 3.2 for Z-scores of all three memory domains at baseline and at month-12.
Figure 3.2  Z-Scores at initial assessment and at 12-month follow-up for patients with and without PNS for A) verbal memory, B) visual memory and C) working memory.

A) Verbal Learning and Memory

B) Visual Learning and Memory

C) Working Memory
Given the significant verbal memory impairments in patients with PNS, this relationship was further explored to delineate whether specific negative symptoms correlate more strongly with verbal memory. Exploratory Spearman’s correlations were performed between global scores of individual SANS subdomains and verbal memory at initial assessment (see Table 3.3 for details). When all patients were included in the analysis, affective flattening, alogia and avolition/apathy significantly correlated with verbal memory. On the other hand, when the PNS group was isolated from the non-PNS group, only alogia maintained a significant with verbal memory.

<table>
<thead>
<tr>
<th></th>
<th>Verbal Memory Domain at Initial Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire FEP Cohort (PNS and Non-PNS group)</strong></td>
<td></td>
</tr>
<tr>
<td>Affective Flattening</td>
<td>-.361**</td>
</tr>
<tr>
<td>Alogia</td>
<td>-.449**</td>
</tr>
<tr>
<td>Avolition-Apathy</td>
<td>-.303**</td>
</tr>
<tr>
<td>Anhedonia-Asociality</td>
<td>-.102</td>
</tr>
<tr>
<td><strong>PNS Group (Non-PNS group removed)</strong></td>
<td></td>
</tr>
<tr>
<td>Affective Flattening</td>
<td>-.291</td>
</tr>
<tr>
<td>Alogia</td>
<td>-.515**</td>
</tr>
<tr>
<td>Avolition-Apathy</td>
<td>-.225</td>
</tr>
<tr>
<td>Anhedonia-Asociality</td>
<td>-.078</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01
3.5 Discussion

The present study assessed memory ability in FEP patients with and without PNS and compared these patients to healthy controls. In addition, memory was evaluated in patients at a 1-year follow-up. Our results suggest that PNS, and verbal memory impairments are related, such that FEP patients with PNS had poorer verbal memory ability when compared to patients without PNS or healthy controls. Our findings are in line with previous studies identifying verbal memory deficits with increasing negative symptom severity in FEP (Bilder et al., 2000, Putnam and Harvey, 2000, Heydebrand et al., 2004, Bodnar et al., 2008). Our results also showed that FEP patients with PNS maintain verbal memory impairments up to at least 1-year after starting treatment. Both visual and working memory domains did not change over time. Further, alogia was shown to have significant negative associations with verbal memory at the initial assessment in our PNS sample.

The specificity of cognitive impairments in patients with pronounced negative symptoms has previously been highlighted, with deficits being more pronounced in verbal learning and memory (McGurk et al., 2000a, Putnam and Harvey, 2000). Accordingly, greater verbal memory deficits were observed in our group of patients with PNS, suggesting that this relationship may be more pronounced between verbal memory and PNS. Growing evidence for the association between negative symptoms and verbal memory impairments has been documented during these early stages of psychosis (Milev et al., 2005). However, the degree of overlap between negative symptoms and cognition remains
unclear. One factor that may have an influence on this variability is the instability of negative symptoms (Chang et al., 2011), which in turn can hinder our understanding of the aforementioned relationship. However, while most have focused on the instability of negative symptoms with regards to severity, we propose that the persistence, rather than the severity of PNS has a much greater influence on this relationship. Our current and previous findings suggest an initial stability of negative symptoms three months after entry into the FEP program (Buchy et al., 2010, Hovington et al., 2012). Past findings have highlighted the role of the amygdala-hippocampal complex and prefrontal cortex in both negative symptoms (Rajarethinam et al., 2001, Anderson et al., 2002, Malaspina et al., 2004) and verbal memory (Baare et al., 1999, O'Driscoll et al., 2001, Killgore et al., 2009, Qiu et al., 2010), hence, it may be plausible that they share common neural substrates. We recently highlighted the right parahippocampal gyrus as a key brain region of grey matter loss in FEP patients with PNS (Benoit et al., 2012). Nonetheless, future longitudinal studies should place a greater importance on delineating the neural substrates of PNS as well as verbal memory in FEP patients with and without PNS.

In support of the neurodevelopmental theory of schizophrenia, which is based on the hypothesis that cognitive deficits precede the onset of a first frank psychotic episode, verbal memory deficits observed in our PNS group were maintained after a 1-year follow-up. In line with our results, Becker and colleagues also reported the presence of cognitive deficits at first episode and a lack of cognitive deterioration (Becker et al., 2010). The influence verbal memory and negative symptoms have on each other over time has been investigated in several studies (Censits et al., 1997, Gold et al., 1999,
Schuepbach et al., 2002, Schuepbach et al., 2004, Bell and Mishara, 2006). While some have proposed that improving symptomatology can have an effect on cognition (Censits et al., 1997, Schuepbach et al., 2002, Schuepbach et al., 2004) others have argued that they are distinct (Bowie and Harvey, 2005). Our results suggest that FEP patients identified after 12 months of treatment have worse negative symptoms and verbal memory throughout the first year. Given our current findings, it would be of interest to investigate whether a treatment specific to PNS would help improve these symptoms and whether this would be paralleled with memory improvements.

Previous studies (Mueser et al., 1994b, Sayers et al., 1996, Peralta and Cuesta, 1999, Blanchard and Cohen, 2006, Foussias and Remington, 2010), including our earlier findings (Malla et al., 2002), suggest that alogia and flat affect may represent a combined negative symptom domain referred to as “diminished expression”, rather than two separate factors. In the current study, a significant correlation was observed between alogia and verbal memory impairments in patients with PNS. Verbal fluency has shown a relationship with negative symptoms (Stolar et al., 1994), and given that alogia is a diminished output of spontaneous language, this relationship seems plausible. Interestingly, imaging studies have observed lower fractional anisotropy (FA) of the uncinate fasciculus in patients with recent onset schizophrenia as well as similar FA abnormalities in schizophrenia patients with severe negative symptoms (Szeszko et al., 2008, Voineskos et al., 2013). Thus, showing support the prefronto-temporolimbic model of negative symptoms (Sigmundsson et al., 2001, Szeszko et al., 2008) as well as highlighting a plausible key relationship between neurocognition and negative symptoms.
Our findings highlight this relationship to some degree; however, future studies in imaging investigating PNS could help elucidate this model and might benefit from investigating negative symptoms as separate domains rather than as a whole.

We would like to note that a significant limitation of the present study is the lack of control group at the follow-up assessment. Although past findings have shown a relative stability in cognitive functioning (Albus et al., 2002, Hoff et al., 2005, Bonner-Jackson et al., 2010), the lack of control group limits us from knowing whether they would have shown any improvements over time due to practice effects.

In conclusion, our results provide evidence for selectively poorer verbal memory ability as of the initial assessment in FEP patients with PNS relative to non-PNS and for the maintenance of these deficits over a 1-year period. Thus, it may be beneficial to assess memory and clinical symptoms early on in the illness in order to provide more tailored therapeutic treatments (cognitive remediation, repetitive transcranial stimulation etc.) for these individuals. Clinically, PNS can also be identified at an individual level and accordingly, the appropriate treatment could be provided to these specific individuals. Given that during these early stages of illness, applying the DS criteria would not be possible, we recommend applying PNS criteria to help identify this subgroup of FEP patients with poor verbal memory and poor functional outcome (Hovington et al., 2012). Characterization of the relationship between PNS and verbal memory may help target
specific individuals in need of an explicit treatment and can help optimize functional outcome, which is often compromised.
Supplementary Table. Z-scores for Speed of Processing, Reasoning and Problem Solving, Attention and Social Cognition between PNS, Non-PNS and Controls.

<table>
<thead>
<tr>
<th></th>
<th>PNS (N=39)</th>
<th>Non-PNS (N=97)</th>
<th>Controls (N=62)</th>
<th>F</th>
<th>d.f</th>
<th>P</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of Processing</td>
<td>-0.31 (1.23)</td>
<td>-.40 (1.14)</td>
<td>0.41 (1.00)</td>
<td>10.42</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS=non-PNS ;ctrls&gt;patients</td>
</tr>
<tr>
<td>Reasoning and Problem Solving</td>
<td>-0.88 (1.40)</td>
<td>-0.84 (1.28)</td>
<td>0.00 (1.00)</td>
<td>10.18</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS=non-PNS ;ctrls&gt;patients</td>
</tr>
<tr>
<td>Attention</td>
<td>-1.1 (1.48)</td>
<td>-0.92 (1.05)</td>
<td>0.00 (1.00)</td>
<td>14.96</td>
<td>2,181</td>
<td>&lt;.000</td>
<td>PNS=non-PNS ;ctrls&gt;patients</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>-0.66 (1.00)</td>
<td>-0.48 (1.15)</td>
<td>0.01 (1.00)</td>
<td>4.82</td>
<td>2,154</td>
<td>0.009</td>
<td>PNS=non-PNS ;ctrls&gt;patients</td>
</tr>
</tbody>
</table>
Chapter 4: White Matter Microstructure in First Episode Psychosis Patients with Persistent Negative Symptoms

**Article in Preparation:** Hovington CL, Bodnar M, Chakravarty M, Joober R, Malla AK, Lepage M. Investigation of white matter abnormalities in first episode psychosis patients with persistent negative symptoms.

**PREFACE**

Some studies have put forward a disconnectivity hypothesis of schizophrenia (Crow, 1998, Burns et al., 2003, Cheung et al., 2008). Using diffusion tensor imaging as a tool, researchers have been able to investigate white matter microstructure in patients with psychotic disorders including schizophrenia. The negative symptomatology of psychosis contributes greatly to poor clinical outcome. More specifically, persistent negative symptoms (PNS) are related to poor functional outcome (Galderisi et al., 2012), increased cognitive deficits (O'Leary et al., 2000) and lower remission rates (Bodnar et al., 2008). Several studies have observed decreased FA values in white matter tracts connecting frontal, temporal and limbic structures in psychosis patients with more severe negative symptoms (Szeszko et al., 2008, Kitis et al., 2012). However, there is a need for a longitudinal study to assess negative symptoms at multiple time points in patients with FEP to better delimitate white matter integrity in patients with PNS.
Thus, the primary objective of this longitudinal study were to explore microstructure in the neurocircuitry of first episode psychosis proposed to be involved in persistent negative symptoms by using a region of interest (ROI) approach. Secondly, the relationship between individual negative symptom domains and the selected white matter tracts were explored.
4.1 Abstract

White matter integrity has previously been studied in patients with schizophrenia identified as having deficit syndrome. However, scant research has focused on white matter integrity in patients presenting with a first episode of psychosis (FEP) with persisting negative symptoms. This study aimed to explore microstructure in the neurocircuitry in first episode psychosis proposed to be involved in persistent negative symptoms (PNS) by using a region of interest (ROI) approach. Secondly, the relationship between individual negative symptom domains and the selected white matter tracts were explored. To meet the criteria for persistent negative symptoms, patients were required to have a score of three or greater on a minimum of one global items of the Scale for the Assessment of Negative Symptoms (SANS) without the presence of depression, positive or extrapyramidal symptoms. These symptoms needed to be maintained between months 6-12 of their first year of treatment. Fractional anisotropy (FA) was measured in the fornix and three other tracts bilaterally including the uncinate fasciculus, superior longitudinal fasciculus and the cingulate. A group of 12 patients with PNS were compared to a non-PNS group (51) and a healthy control group (51). Results showed that the PNS group had significantly lower FA values in the fornix when compared to healthy controls and that the non-PNS group had significantly lower FA values in the right uncinate fasciculus compared to healthy controls. In addition, when the PNS group was isolated, a relationship was found between SANS global score for anhedonia-asociality and lower FA values in the right cingulum. Our results suggest that white
matter in the limbic system might be more closely related to PNS and that this relationship may possibly be mediated by greater avolition in PNS patients.
4.2 Introduction

The negative symptomatology of psychotic disorders is of considerable interest to researchers due to their contribution to poor functional outcome (Ho et al., 1998b, Wood et al., 2006), role in lower remission rates (Bodnar et al., 2008) and neurocognitive deficits such as verbal memory (Bilder et al., 2000, Heydebrand et al., 2004, Hovington et al., 2013). Although there have been several theories put forward to explain the psychopathology of negative symptoms in psychotic disorders, many questions remain. Part of this discrepancy may be attributed to the diversity of symptoms in psychosis. “Negative symptoms” is an all-encompassing term used to describe several categories of symptoms such as lack of facial expressions, amotivation, lack of volition and diminished emotional expression. While some individuals with psychosis and negative symptoms might experience an improvement over time, a substantial percentage in FEP (about 27%) (Hovington et al., 2012) will have negative symptoms that are resistant to treatment, or persisting negative symptoms (PNS), characterized as primary or secondary negative symptoms (Malla et al., 2004, Buchanan, 2007). These negative symptoms are present for a minimum of 6 consecutive months (during periods of clinical stability) and with the minimal presence of positive, depressive and extrapyramidal symptoms (Buchanan, 2007, Hovington et al., 2012). Identifying a clinically homogenous subgroup of patients specifically in early psychosis may help better delineate the etiology of negative symptoms.
It has been postulated that frontal and medial temporal gray matter regions might be involved in the pathophysiology of negative symptoms (Baare et al., 1999, Anderson et al., 2002, Szaszko et al., 2008, Rowland et al., 2009, Benoit et al., 2012, Hovington and Lepage, 2012). Hence, it does not appear that the neural correlates of negative symptoms are localized to a specific grey matter structure. It may also be plausible that the white matter connecting the above-mentioned gray matter structures may be involved. Evidence of reduced white matter volume has also been reported in patients with schizophrenia (Wible et al., 2001, Zetzsche et al., 2008) and FEP (Chua et al., 2007, Price et al., 2010). Some have suggested that decreases in white matter may be specific to patients with greater negative symptoms severity (Sanfilipo et al., 2000, Wible et al., 2001) as shown by moderate associations between these symptoms and reductions in prefrontal white matter volume.

There has been great interest surrounding the disconnectivity model of schizophrenia, which suggests that the underlying pathophysiology of schizophrenia is caused by alterations in white matter pathways. Diffusion tensor imaging (DTI) allows for the in vivo study of white matter microstructure and integrity (Basser et al., 1994). There are various approaches to analyzing DTI data including region of interest (ROI), voxel-based and tract-oriented methods. Studies applying these types of analysis have provided evidence for fronto-temporal abnormalities in FEP (Price et al., 2008, Rowland et al., 2009) and fronto-temporo-limbic impairments (Ardekani et al., 2003, Koutsouleris et al., 2008). With regards to white matter integrity, fractional anisotropy (FA) (a measure of white matter integrity) has been assessed in FEP patients as well as patients with DS. In patients with recent onset
schizophrenia, lower FA values (or decreased white matter integrity) were reported in the uncinate fasciculus (UF), superior longitudinal fasciculus (SLF) and inferior fronto-occipital fasciculus (Szeszko et al., 2008) when compared to healthy controls. Furthermore, lower FA values in the UF (bilaterally) correlated with negative symptom severity, or specifically alogia and affective flattening (Szeszko et al., 2008). Similarly, in DS, findings have suggested a reduction in FA values in the SLF (Rowland et al., 2009) and the left UF (Kitis et al., 2012, Voineskos et al., 2013). Finally, other groups have also shown that negative symptoms severity is associated with decreased FA in the right fornix (Kunimatsu et al., 2012). Hence, the above-mentioned findings have led to various disconnectivity models for negative symptoms including fronto-temporal and fronto-temporo-limbic models.

Although there has been a large support for the disconnectivity model of psychosis, many questions remain in terms of the relationship between white matter microstructure and negative symptoms. Furthermore, PNS are often assessed cross-sectionally rather than at multiple time points to thoroughly measure their persistence over time. Thus, the primary objective of this longitudinal study was to explore microstructure in the neurocircuitry of first episode psychosis proposed to be involved in persistent negative symptoms by using a region of interest (ROI) approach. Due to previous studies highlighting the role of fronto-temporo-limbic connections in negative symptoms, we hypothesized that white matter related to these three areas might have lower FA values. Secondly, the relationship between individual negative symptom domains and the selected white matter tracts were explored. Due to the exploratory nature of this objective, no hypothesis was made.
4.3 Methods

4.3.1 Subjects

All FEP patients were part of a longitudinal study and were treated in the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), a specialized early intervention service with integrated clinical, research, and teaching modules, at the Douglas Mental Health University Institute in Montreal, Canada. Individuals aged 18 to 35 years from the local catchment area suffering from either affective or non-affective psychosis who had not taken antipsychotic medication for more than one month and with an IQ higher than 70 were admitted to the program as either in- or out-patients (for details see (Malla et al., 2003). Diagnosis of schizophrenia or related spectrum disorders was established with the Structured Clinical Interview for DSM-IV (SCID-IV) (First et al., 1998). Written informed consent was obtained from all participants. Research protocols were approved by the Douglas Institute Human Ethics Review Board. Healthy controls were recruited through advertisements in local newspapers and were included only if they had no current or previous history of (a) any Axis I disorders, (b) any neurological diseases, (c) head trauma causing loss of consciousness, and (d) a first-degree family member with schizophrenia or related schizophrenia-spectrum psychosis. Current IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI-III) (Wechsler, 1997a).
4.3.2 Clinical Assessment

Education level (number of school years completed), parental socio-economic status (SES) with the Hollingshead two-factor index (Miller, 1991a), Social and Occupational Functioning Assessment Scale (SOFAS), The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) and handedness (Oldfield, 1971) were acquired. As part of the longitudinal study, the following clinical variables were assessed at an initial assessment as well as at months 1, 2, 3, 6, 9 and 12 following the first evaluation. Negative and positive symptoms were quantified using the SANS (Andreasen, 1984) and the SAPS (Andreasen, 1983), respectively. The domain of attention in the SANS scale was not included in our analyses because previous factor analytical studies have shown that it loads on both negative and disorganization (Peralta and Cuesta, 1999, Malla et al., 2002). Evaluators at PEPP established an ICC of 0.74 on the SAPS and 0.71 on the SANS; all evaluator’s participated in inter-rater reliability sessions at least once a year to avoid evaluator drift (i.e. evaluators must maintain consistency with themselves as well as with other evaluators). Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) and extrapyramidal symptoms with the Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard and Margolese, 2005). If prescribed, type and dose of anticholinergic medications taken were recorded. The type and dosage of antipsychotics taken were also recorded and subsequently converted into chlorpromazine equivalents (Woods, 2003).
4.3.3 Identifying Persistent Negative Symptoms

Clinical data from months 3, 6, 9, and 12 were analyzed to identify patients with PNS. PNS was defined as having a minimum score of three on one or more global items of the SANS (Malla et al., 2004) (Hovington et al., 2012). These negative symptoms were required to be present after the initial stabilization of positive symptoms (month 3) and to be maintained for 6 consecutive months (months 6, 9 and 12) (Buchanan, 2007) (Hovington et al., 2012). Subjects with global ratings on “affective flattening” or “alogia” entirely based as a result of items “inappropriate affect” or “poverty of content of speech”, respectively were excluded as having negative symptoms based on previous findings suggesting that these items are not part of the negative symptom construct (Malla et al., 2004). After the completion of the 12-month assessment, FEP patients were segregated into two groups (PNS and non-PNS).

Patients in the PNS group had primary negative symptoms absent of any positive (global rating of mild (2) or less, as measured by the SAPS), depressive (a total score of 4 or less on the CDSS) (Addington et al., 1993) or extrapyramidal symptoms (low to mild levels). Lastly, FEP patients who were administered their initial neuropsychological assessment later than nine months after entry into our program were also excluded since this was deemed too late given our PNS criteria.

4.3.4 Scanning Procedures

Scans were acquired at the Montreal Neurological Institute (MNI) on a 1.5T Siemens Sonata whole body MRI system. These scans were acquired as part of the patient’s initial assessment along with the clinical assessments mentioned above. Structural T1 volumes
were acquired for each participant using a three-dimensional (3D) gradient echo pulse sequence with sagittal volume excitation (repetition time=22ms, echo time=9.2ms, flip angle=30°, 180 1mm contiguous sagittal slices. The rectangular field of view (FOV) for the images was 256mm (SI) x 204mm (AP).

4.3.5 Diffusion tensor imaging

Two successive whole-brain diffusion tensor images (DTI) were acquired using a single-shot echo planar imaging (EPI) sequence parallel to the anterior-posterior commissural plane. The two images were average for analyses. Diffusion sensitive gradients were applied in 60 non-collinear, non-coplanar directions (b=1000 s/mm²), together with one acquisition with no diffusion weighting (b=0 s/mm²). Sixty contiguous axial slices were acquired with a slice thickness of 2.2 mm and no gap. To reduce signal to noise ratio, each direction was scanned twice and averaged. The acquisition parameters were as follows: TR=9800 ms; TE=102 ms; FOV=280 mm; image matrix 112x128. These parameters resulted in 2.2 x2.2 x 2.2 mm³ acquisition voxel dimensions.

All MINC diffusion tensor images were transformed to a 4D Nifti format on a Linux workstation. Preprocessing was performed using Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) [The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain] Software Library, http://http://www.fmrib.ox.ac.uk/fsl). First, to correct for shearing and motion between volumes, eddy current corrections were performed to align all images to the b0 image using affine transformations. Second, a binary brain extraction tool-generated mask was
applied suing the BET2 tool (Smith, 2002). Fractional anisotropy and mean diffusivity was obtained by fitting a diffusion tensor model at each voxel with DTIFit.

4.3.6 Region of Interest Analysis

Due to previous findings in schizophrenia and first episode psychosis highlighting a relationship between higher negative symptoms and lower FA values in white matter tracts connecting frontal and temporal regions (Luck et al., 2011, Kitis et al., 2012, Voineskos et al., 2013), as well as fronto-temporo-limbic regions (Hazlett et al., 2011, Kunimatsu et al., 2012) the following regions were chosen for analyses: uncinate fasciculus, superior longitudinal fasciculus, fornix and cingulate. Structural T1 images were non-linearly registered to the stereotaxic white matter atlas, or ICMB152 template (Mori et al., 2008) using automatic normalization tools (ANTs) algorithm (Avants et al., 2008, Avants et al., 2011). Fractional anisotropy maps were then matched to the subject’s T1 scan using a rigid body transformation and this atlas was warped to each subject’s FA map. A conservative probability threshold was set at 80% for all selected white matter tracts; therefore excluding voxels with a low probability of being located in the regions of interest. Finally, mean FA values were then extracted from each region of interest and analyzed for group differences.

4.3.7 Statistical Analysis

Statistical analyses were conducted by means of PASW version 18 (SPSS, Chicago IL). All analyses were two-tailed with a critical p-value set at 0.05, except where
noted. Multiple group comparisons for demographic data were analyzed using one-way analysis of variance (ANOVA) with Tukey’s for post hoc comparisons. The following clinical characteristics were not normally distributed: CPZ equivalents, DUP and DUI. These variables were normalized using square root transformations. For multiple group comparisons of categorical variables, the Kruskal-Wallis H-test was applied (Mann-Whitney U test for post hoc). For two-group comparisons, independent t-tests, Mann-Whitney U-test or cross-tabulation and Chi-square tests were applied. For each region of interest, group differences for fractional anisotropy were compared using a one-way ANOVA. Exploratory Spearman rho correlations of white matter and global scores of the SANS were conducted to further investigate the relationship between negative symptoms and white matter abnormalities.

4.4 Results

See Table 4.1. for socio-demographic and clinical data of all groups. Sixty-four first episode patients were divided into PNS (n=12) and non-PNS (n=52) groups and compared to 51 healthy controls. Post hoc tests revealed lower education in both patient groups compared to controls. As per design, total SANS scores were lower in non-PNS compared to the PNS group. When individual SANS global items were compared between PNS and non-PNS groups, the PNS group had worse negative symptoms for anhedonia-asociality. Both groups had similar scores for total positive symptoms measured with the SANS. Patients did not differ on other clinical parameters such as DUP, DUI, prodrome or positive symptoms.
Table 4.1 Clinical data, socio-demographic information and fractional anisotropy values at initial assessment.

<table>
<thead>
<tr>
<th></th>
<th>PNS N=12</th>
<th>Non-PNS N= 51</th>
<th>Controls N=51</th>
<th>Statistics</th>
<th>d.f.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.67±4.77</td>
<td>23.44±3.35</td>
<td>23.76±3.16</td>
<td>F=.115</td>
<td>2</td>
<td>.891</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>10/2</td>
<td>32/20</td>
<td>36/15</td>
<td>χ²=2.421</td>
<td>2</td>
<td>.298</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.5±2.17</td>
<td>12.31±2.42</td>
<td>14.67±2.64</td>
<td>F=17.768</td>
<td>2</td>
<td>&lt;.000*</td>
</tr>
<tr>
<td>Handedness (R/L/ambidextrous)</td>
<td>11/0/1</td>
<td>41/3/7</td>
<td>48/2/1</td>
<td>χ²=4.795</td>
<td>2</td>
<td>.098</td>
</tr>
<tr>
<td>Duration of untreated psychosis (weeks)</td>
<td>35.86±60.08</td>
<td>52.01±100.22</td>
<td>-</td>
<td>t=-.577</td>
<td>61</td>
<td>.983</td>
</tr>
<tr>
<td>Duration of illness (weeks)</td>
<td>453.02±289.92</td>
<td>314.12±262.94</td>
<td>-</td>
<td>t=1.563</td>
<td>61</td>
<td>.123</td>
</tr>
<tr>
<td>Prodrome (weeks)</td>
<td>174.80±258.14</td>
<td>133.20±201.87</td>
<td>-</td>
<td>t=.558</td>
<td>52</td>
<td>.579</td>
</tr>
<tr>
<td>Antipsychotic dose</td>
<td>817.45±899.33</td>
<td>810.59±726.38</td>
<td>-</td>
<td>t=.136</td>
<td>61</td>
<td>.893</td>
</tr>
<tr>
<td>Diagnosis (N%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>U = 287.50</td>
<td>-</td>
<td>.741</td>
</tr>
<tr>
<td>Schizophrenia Spectrum Disorder</td>
<td>10 (76.9%)</td>
<td>33 (64.7%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective Psycosis</td>
<td>3 (23.1%)</td>
<td>8 (15.7%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis NOS</td>
<td>0 (0%)</td>
<td>10 (19.6%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFAS</td>
<td>32.67±20.44</td>
<td>41.27±22.51</td>
<td>-</td>
<td>t=-1.211</td>
<td>61</td>
<td>.230</td>
</tr>
<tr>
<td>SAPS total score</td>
<td>34.25±14.85</td>
<td>35.59±16.66</td>
<td>-</td>
<td>t=-.255</td>
<td>61</td>
<td>.799</td>
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<tr>
<td>CDSS total score</td>
<td>5.5±4.66</td>
<td>4.39±5.29</td>
<td>-</td>
<td>t=.667</td>
<td>61</td>
<td>.508</td>
</tr>
<tr>
<td>SANS total score</td>
<td>34.75±14.64</td>
<td>25.74±12.44</td>
<td>-</td>
<td>t=2.182</td>
<td>61</td>
<td>.033*</td>
</tr>
<tr>
<td>Blunted Affect</td>
<td>2.83±1.33</td>
<td>2.09±1.30</td>
<td>-</td>
<td>χ²=7.374</td>
<td>5</td>
<td>.194</td>
</tr>
<tr>
<td>Alogia</td>
<td>1.83±1.46</td>
<td>1.50±1.39</td>
<td>-</td>
<td>χ²=2.072</td>
<td>4</td>
<td>.723</td>
</tr>
<tr>
<td>Avolition-Apathy</td>
<td>3.58±1.40</td>
<td>3.10±1.10</td>
<td>-</td>
<td>χ²=8.633</td>
<td>5</td>
<td>.125</td>
</tr>
<tr>
<td>Anhedonia-Asociality</td>
<td>3.75±1.05</td>
<td>2.70±1.10</td>
<td>-</td>
<td>χ²=13.462</td>
<td>5</td>
<td>.019*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fractional Anisotropy</th>
<th>PNS</th>
<th>Non-PNS</th>
<th>Controls</th>
<th>Statistic</th>
<th>d.f.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fornix</td>
<td>.218±.09</td>
<td>.257±.11</td>
<td>.309±.11</td>
<td>F=4.760</td>
<td>112</td>
<td>.010*</td>
</tr>
<tr>
<td>Right Uncinate Fasciculus</td>
<td>.264±.12</td>
<td>.268±.11</td>
<td>.330±.09</td>
<td>F=4.624</td>
<td>112</td>
<td>.012*</td>
</tr>
<tr>
<td>Left Uncinate Fasciculus</td>
<td>.229±.12</td>
<td>.265±.09</td>
<td>.298±.12</td>
<td>F=2.491</td>
<td>112</td>
<td>.087</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>.360±.16</td>
<td>.336±.15</td>
<td>.375±.14</td>
<td>F=.970</td>
<td>112</td>
<td>.382</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>F-value</td>
<td>df</td>
<td>p-value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>---------</td>
<td>----</td>
<td>---------</td>
</tr>
<tr>
<td>Right Superior Longitudinal Fasciculus</td>
<td>0.304±0.08</td>
<td>0.321±0.09</td>
<td>0.355±0.09</td>
<td>2.571</td>
<td>112</td>
<td>0.081</td>
</tr>
<tr>
<td>Left Superior Longitudinal Fasciculus</td>
<td>0.315±0.07</td>
<td>0.322±0.12</td>
<td>0.340±0.09</td>
<td>0.581</td>
<td>112</td>
<td>0.561</td>
</tr>
</tbody>
</table>

* Significant at p<0.05. SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; SOFAS = Social and Occupational Functioning Assessment Scale. ‡Analyses of duration of untreated illness, duration of untreated psychosis and chlorpromazine equivalents were made with transformed data but values are presented in raw form.
Fractional anisotropy was measured in four white matter tracts connecting fronto-temporal areas and limbic structures. The tracts included the fornix, cingulum, superior longitudinal fasciculus and uncinate fasciculus. Group differences for white matter integrity were found in the fornix (bilaterally) ($F=4.760$, df=112, $p=0.010$) and the uncinate fasciculus ($F=4.624$, df=112, $p=0.012$). Post-hoc analyses showed that PNS patients had significantly lower fornix FA in comparison to healthy controls in the fornix ($p=0.033$). Patients in the PNS group had numerically lower fornix FA compared to non-PNS, but this did not reach significance ($p=0.805$). Regarding the uncinate fasciculus in the right hemisphere, the non-PNS group had lower FA values than healthy controls ($p=0.015$). There were no significant differences between PNS and non-PNS groups. See Figure 4.1 for details.
Figure 4.1 Fractional anisotropy values for the fornix and right uncinate fasciculus in PNS, non-PNS and healthy control groups.
Correlational analyses with both patient groups revealed a negative correlation between left uncinate fasciculus and scores on blunted affect. When the PNS group was isolated, a moderate negative correlation between the right cingulum and anhedonia-asociality global scores of the SANS was found (see Table 4.2 for details).
Table 4.2 Spearman rho correlations for SANS global scores and ROI's in the PNS group only.

<table>
<thead>
<tr>
<th></th>
<th>Blunted Affect</th>
<th>Alogia</th>
<th>Avolition-Apathy</th>
<th>Anhedonia-Asociality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PNS and Non-PNS Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fornix</td>
<td>-.065</td>
<td>-.089</td>
<td>.006</td>
<td>.058</td>
</tr>
<tr>
<td>Right UF</td>
<td>-.225</td>
<td>-.063</td>
<td>.168</td>
<td>-.092</td>
</tr>
<tr>
<td>Left UF</td>
<td>-.363**</td>
<td>-.215</td>
<td>.080</td>
<td>-.109</td>
</tr>
<tr>
<td>Right SLF</td>
<td>-.190</td>
<td>-.057</td>
<td>.176</td>
<td>-.102</td>
</tr>
<tr>
<td>Left SLF</td>
<td>-.162</td>
<td>-.091</td>
<td>.071</td>
<td>-.208</td>
</tr>
<tr>
<td>Right Cingulum</td>
<td>-.054</td>
<td>-.005</td>
<td>.022</td>
<td>-.038</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>.032</td>
<td>-.002</td>
<td>.070</td>
<td>.056</td>
</tr>
<tr>
<td><strong>PNS Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fornix</td>
<td>.206</td>
<td>.026</td>
<td>.300</td>
<td>-.059</td>
</tr>
<tr>
<td>Right UF</td>
<td>-.303</td>
<td>-.475</td>
<td>-.124</td>
<td>-.233</td>
</tr>
<tr>
<td>Left UF</td>
<td>-.090</td>
<td>-.139</td>
<td>-.333</td>
<td>-.023</td>
</tr>
<tr>
<td>Right SLF</td>
<td>-.430</td>
<td>-.358</td>
<td>-.015</td>
<td>-.341</td>
</tr>
<tr>
<td>Left SLF</td>
<td>-.501</td>
<td>-.479</td>
<td>-.264</td>
<td>-.564</td>
</tr>
<tr>
<td>Right Cingulum</td>
<td>-.445</td>
<td>-.263</td>
<td>-.523</td>
<td>-.587*</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>-.034</td>
<td>-.044</td>
<td>-.135</td>
<td>-.094</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001

SLF=superior longitudinal fasciculus; UF=uncinate fasciculus; PNS=persistent negative symptoms.
4.5 Discussion

The relationship between the negative symptomatology of psychotic disorders and white matter integrity is a conundrum to many researchers. Our lack of understanding may be partly due to various methods used to assess white matter integrity, the inherent heterogeneity of psychosis and the cross-sectional nature of these studies. Our study examined white matter integrity in a subpopulation of first episode patients with PNS. We addressed two of the above issues by investigating a more homogenous subgroup of FEP patients and evaluated clinical symptoms at multiple time points. No differences were found between both patients groups (PNS and non-PNS). Hence, our findings did not identify a specific white matter marker for PNS; however, lower fornix FA values in the PNS group compared to healthy controls were found. In addition, when our PNS group was isolated, FA values in the right cingulum significantly correlated with the anhedonia-asociality global score of the SANS. Fractional anisotropy in the right uncinate fasciculus was lower in the non-PNS group compared to healthy controls. Reductions of white matter integrity in frontal and temporal regions in association with negative symptom severity have previously been documented (Kitis et al., 2012, Voineskos et al., 2013). Our results complement these findings and suggest that white matter tracts of the limbic system may also be impaired in patients with psychosis and PNS. In contrast, our result are in disagreement with some studies such that we did not find lower uncinate fasciculus FA values in the PNS group compared to non-PNS or healthy controls.
In our sample, patients with PNS had significantly greater anhedonia-asociality scores than the non-PNS group. Our previous findings (Malla et al., 2004, Hovington et al., 2012), as well as other studies have also documented that anhedonia may be the most frequent and prominent negative symptoms in patients with more severe negative symptoms (Nesvag et al., 2009, Green et al., 2011, Leitman et al., 2011, Lyne et al., 2012, Stauffer et al., 2012). Avolition-apathy has often been a close second (Lyne et al., 2012, Stauffer et al., 2012). Recently, there has been a movement towards a 2 negative symptoms subdomains (Mueser et al., 1994a, Blanchard and Cohen, 2006, Kimhy et al., 2006, Blanchard et al., 2010, Foussias and Remington, 2010) rather then the previously 5-construct model proposed by the MATRICS (Kirkpatrick et al., 2006). These 2 constructs include: 1) diminished expression (blunted affect and poverty of speech) and 2) amotivation (avolition-apathy and anhedonia-asociality) (Foussias and Remington, 2010) (Forbes et al., 2010, Horan et al., 2011, Barch, 2013). It is possible that these 2 constructs have separate, yet overlapping etiologies, and may help provide a rationale for the equivocality in previous negative symptoms studies. Hence, it might be beneficial for future studies to assess individual negative symptom constructs within a negative subgroup, such as PNS and DS, to further elucidate the etiology of negative symptoms.

White matter integrity has previously been shown to be impaired in patients with more severe negative symptoms. For instance, Kunimatsu et al. found that patients with schizophrenia and a more severe severity of negative symptoms also had decreased FA in the right fornix (Kunimatsu et al., 2012). Similarly, decreased FA
values in the right cingulum have been associated with greater severity of negative symptoms (Hazlett et al., 2011). Our results converge with these findings and suggest a role of limbic white matter structures in PNS. The most visible neural pathways connecting the limbic system to cortical and subcortical structures are the fornix and cingulate. The fornix connects the hippocampus to project its fibers to other brain regions such as the prefrontal cortex, whereas the cingulum connects the entorhinal cortex and the cingulate gyrus (Concha et al., 2005). The limbic system is central to motivation, emotions, hedonic impact and reward as well as cognition (Bush et al., 2000, Ikemoto, 2010, Keedwell et al., 2012). Given that our sample had more prominent anhedonia symptoms, which are also part of the “amotivation” construct, this may have contributed to the group difference and the correlations with white matter tracts of the limbic system. Intriguingly, amisulpride, being a second-generation antipsychotics shown to be effective at decreasing negative symptoms, antagonizes postsynaptic dopamine D2 and D3 receptors in the limbic system (Moller, 2003); thus providing further suggesting that the core of PNS might involve the limbic system.

The uncinate fasciculus is one of the major association fibers connecting frontal and temporal regions of the brain via several clusters (Mori et al., 2008). This ventral limbic pathway is associated with memory and emotions (Barbas, 2000). Altered integrity of the uncinate fasciculus has previously been shown in patients with first episode schizophrenia (Price et al., 2008). Some reports have extended previous
findings by suggesting that the reduced FA might be attributed to increased negative symptom severity in patients with recent onset schizophrenia (Szeszko et al., 2008) or enduring schizophrenia (Rowland et al., 2009, Kitis et al., 2012, Voineskos et al., 2013). Results of the present study revealed lower FA values in the right uncinate fasciculus only in the non-PNS group compared to healthy controls and did not find this difference in the PNS group. This suggests that in FEP, lower FA in the uncinate fasciculus may not be necessarily specific to negative symptoms. On the other hand, it may be that even within the subdivisions of “deficit syndrome” and “persistent negative symptoms”, there still remains some level of heterogeneity, which may contribute to discordant findings even within DS studies.

4.6 Limitations

Our conclusions have to be regarded with caution given certain limitations. First, there are inherent limitations when obtaining FA values such as structural limitations, which can have an effect on the results. Also, although white matter tracks were selected due to previous evidence, there remains the possibility of other white matter tracts being associated with PNS, but not having been one of our regions of interest. A second limitation is the small sample size in the PNS group (n=12). No differences were found between PNS and non-PNS, which is why we cannot conclude that the fornix is selectively associated with PNS. However, given the correlations observed in the PNS group, we can posit that limbic structures are related to PNS. Lastly, the possible effects of cannabis on white matter integrity were not taken into account in the current study. Although, substance induced psychosis was excluded, one still cannot rule out the
possible contribution of cannabis to our results. Studies have suggested that volume changes may be more widespread in first episode patients who use cannabis more extensively (Rais et al., 2008).

4.7 Conclusions

Previous studies have shed light on various brain anomalies that may be implicated in psychosis and its symptomatology; however, many conundrums remain. A possible tool to help increase our understanding of the negative symptoms of psychosis might be DTI and the measure of white matter integrity. Furthermore, the heterogeneity of negative symptoms contributes greatly to our lack of understanding of their etiology. Identifying a subgroup of patients with PNS in a longitudinal study can help delineate their role. Our results suggest that white matter of the limbic system may be altered in FEP patients with PNS; however, this warrants further study with a larger PNS group. Even within negative symptom subgroups such as DS, findings are discordant. This may suggest that there are other underlying factors contributing to these varied results. Our findings propose that there are more prominent negative symptom constructs within well-defined subdomains such as PNS. Future studies may want to place emphasis on the role of individual negative symptoms in PNS. Moreover, larger longitudinal studies assessing FEP patients meeting the criteria for PNS should focus on the role of the limbic system in addition to fronto-temporal white matter.
CHAPTER 5: Conclusions and Significance
The goal of this thesis was to characterize persistent negative symptoms in first episode psychosis patients and to determine the relationship between these symptoms and functional outcome, memory performance and white matter integrity. A longitudinal design was applied to investigate these symptoms in a large cohort of first episode psychosis patients.

Varying terminology has been applied to define FEP patients with “enduring negative symptoms” or negative symptoms that do not respond to treatment. More recently, the term “persistent negative symptoms” has been used to describe these symptoms and as described in this thesis, PNS has been defined as primary or secondary negative symptoms persisting for a minimum of 6 consecutive months with minimal or absent positive, depression and extrapyramidal symptoms (Buchanan, 2007). In this thesis, first episode of psychosis patients were followed for 12 months after the start of their treatment. In our first study, we compared various PNS definitions and found that all patients in the PNS group, regardless of the definition being applied, had poorer functional outcome compared to patients in the non-PNS group. Hence, our first hypothesis was supported. Results from study 1 suggest that the prevalence of PNS in FEP is estimated at 27%, which is in line with previous estimations (Malla et al., 2004). Interestingly, when individual SANS global scores were explored to better characterize the PNS group, it was found that a higher frequency of patients met the PNS criteria due to moderate scores in avolition-apathy and anhedonia-asociality global items. Higher scores on anhedonia items compared to other negative symptoms have previously been documented.
(Nesvag et al., 2009, Leitman et al., 2011, Stauffer et al., 2012). If there are specific negative symptoms in PNS that are more frequent and prevalent, it may be important for studies to perform exploratory analyses to assess this and may have partly contributed to discordant findings in the literature. Our findings suggest that as of the first assessment, clinicians should be vigilant for individuals with moderate negative symptoms and provide a more robust treatment targeting negative symptoms as early as possible.

In our second study, our first hypothesis, which stated greater memory impairments in PNS, was supported. Memory impairments were found to be specific to verbal memory. Secondly, as hypothesized, memory ability was stable over the first 12 months of treatment for a first episode of psychosis. This is in accordance with previous studies showing a relative stability of cognition over time (Aleman et al., 1999, Vaz and Heinrichs, 2002). Previous studies have also shown that verbal memory may be the most affected cognitive domain in patients with more pronounced negative symptoms (McGurk et al., 2000b, Putnam and Harvey, 2000, Hill et al., 2004). Our results also provide some support for the neurodevelopmental theory given that verbal memory impairments were evidenced as of the first assessment and did not deteriorate over the course of treatment. Verbal memory has been shown to significantly contribute to poor functional outcome (Landro and Ueland, 2008, McDowd et al., 2011). Cognitive remediation has been implemented as a treatment to improve cognitive function including verbal memory (Fiszdon et
al., 2005, Twamley et al., 2012). While verbal memory ability improved in some studies as a result of cognitive remediation (Fiszdon et al., 2005, Twamley et al., 2012), concurrent improvements of negative symptomology have only been shown in some (Twamley et al., 2012) but not all studies (Fiszdon et al., 2005). Our longitudinal study suggests that patients identified as having PNS have memory impairments, which are specific to verbal memory. These findings complement the findings from study 1, by providing further evidence of the impairments present as of the initial assessment and stress the importance of early intervention for both clinical symptoms (negative symptoms) and cognition (verbal memory).

Finally, our third hypothesis, stating that white matter related to the fronto-temporo-limbic areas of the brain is impaired in FEP patients with PNS, was not supported. Patients in the PNS group had lower FA values in the fornix compared to healthy controls; however, no differences were found between PNS and non-PNS groups. Hence, we were not able to identify a white matter marker specific to PNS. These unexpected results may have been due to a small number of subjects in our PNS group. Nonetheless, moderate correlations were also found between the cingulum and anhedonia scores in the PNS group. Both the fornix and cingulum are structures of the limbic system that are known to play a critical role in cognition (Kern et al., 2012) (Metzler-Baddeley et al., 2012). More specifically, lower FA values in the fornix have been associated with poorer verbal memory (Metzler-Baddeley et al., 2012), which is in line with both study 1 and 2 of this thesis.
Although previous studies have highlighted fronto-temporal tracts such as the uncinate fasciculus (Perez-Iglesias et al., 2010, Voineskos et al., 2013) to be specific to PNS, it is plausible that the limbic tracts are also implicated given their role in cognition, emotions and motivation (Bush et al., 2000, Ikemoto, 2010, Keedwell et al., 2012). Our third study provides some preliminary evidence for the potential implication of white matter abnormalities in patients with PNS; however, further studies are needed with larger sample of patients with PNS to provide robust empirical evidence of this relationship.

Limitations:

Despite containing longitudinal studies with large sample sizes, limitations of this thesis still exist. First, although patients were followed for 12 months, some studies show that negative symptoms are still relatively unstable during the first year. However, in our study, negative symptom data during the first year showed that patients experience an initial stabilization at month 3. Data was not taken prior to month 3 to identify PNS and consequently, symptomatology in our sample was relatively stable. This particular knowledge of our sample was obtained due to the multiple assessments that were administered. Second, although the PNS definition recommended by Buchanan (Buchanan, 2007) suggests that both primary and secondary negative symptoms be included, this thesis only included primary negative symptoms. Previous studies have shown that secondary negative symptoms may have a separate etiology than primary negative symptoms and may
not be as severe (Brazo et al., 2005). For this reason, many studies have chosen to include only primary negative symptoms (Buchanan et al., 1993, Benoit et al., 2012, Voineskos et al., 2013). However, further studies are needed to determine if the homogeneity of the PNS sample would be significantly altered if secondary negative symptoms were included. Third, patients were not antipsychotic-naïve, and consequently an effect of medication cannot be entirely ruled out. However, only primary negative symptoms were included in our PNS definition to avoid the effect of medication on secondary negative symptoms.

**Contributions:**

Notwithstanding the limitations of this study, there were also aspects of this thesis that contributed to the current literature regarding persistent negative symptoms in FEP. First, a great strength of this thesis was the fact that the same PNS definition was applied in all three studies. One of the major contributions to our lack of understanding of PNS is the fact that each study will apply their own terminology and definition. This leads to inconsistencies in conclusions. In this thesis, the same definition for PNS was applied throughout the studies; therefore providing consistency. Secondly, several exploratory analyses conducted in this thesis helped shed some light on the role of individual negative symptoms in a FEP patients with PNS. A consistent finding across studies was that although patients met the criteria for PNS, the SANS subdomains of avolition-apathy and anhedonia-asociality, which combined are known as the amotivation subdomain of negative symptoms, were
more prominent in PNS than alogia and blunted affect. This suggests that, in agreement with recent studies (Blanchard and Cohen, 2006, Kimhy et al., 2006, Foussias and Remington, 2010), viewing negative symptoms as fitting in either the diminished expression or amotivation subdomain, even in terms of persistence, might help reduce variability of findings. Lastly, in all studies included in this thesis, negative symptoms were assessed at multiple time points between a patient's initial assessment and month 12. Most studies will assess negative symptoms cross sectionally rather than longitudinally and this may introduce some inaccuracies. Quantifying negative symptoms monthly allows for a more in-depth understanding of the course of negative symptoms in patients with PNS. For instance, in our first study, we found that negative symptoms are relatively stable after the third month of treatment, which is question that was raised in the NIMH consensus statement on negative symptoms (Alphs, 2006).

Future Studies and Closing Remarks:
In addition to the suggested future studies stated for each study of this thesis, there are also other possible considerations for further research that arise from the results of this thesis. First, it may be more beneficial to avoid defining negative symptoms from a broader perspective; hence, more focus should be placed on various subcategories of negative symptoms. Future studies need to consider the two subdomains (diminished expression and amotivation) and to determine whether each subdomain has a distinct etiology. Second, a general consensus for defining PNS needs to be established. It is
pivotal for investigators to adopt a diligent method of identifying individuals with PNS in order to standardize the negative symptom construct of schizophrenia. Applying similar criteria will help shed light on the etiology of PNS. Third, results of this thesis suggest that first episode psychosis represents a key period to explore the relation between PNS and neurocognition/ neuroimaging. In more chronic samples, it is not straightforward to separate the contribution of different factors (long term medication, sedentary lifestyle, etc.) and the actual impact of negative symptoms. Lastly, evidence is starting to emerge that interventions can be developed to improve negative symptoms. These include neuromodulation techniques such as rTMS (Slotema et al., 2010), cognitive behavioral therapy (Rector et al., 2005), and the use of add on pharmacotherapy (e.g. glycine). It will be of the utmost importance to determine whether treatment that improves negative symptoms can also affect positively these cognitive/neural markers of negative symptoms.

In the upcoming years, a number of issues are likely to be at the center of PNS research. First, as previously mentioned there is a need to develop a consensual definition of PNS that can easily be based on common clinical rating scales (e.g. PANSS, SANS, etc.). Secondly, we have not touched the topic of the validity of those measures of negative symptoms, but this is a current hot topic in the field with work of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) negative symptoms initiative and the recent development of the Clinical Assessment Interview for Negative Symptoms (CAINS) (Blanchard et al., 2010, Forbes et al., 2010).
In closing, PNS represents a subdomain of negative symptoms that impacts a significant number of FEP patients. These individuals have negative symptoms of moderate severity that persist during the first year of treatment, which in turn contributes to poor functional outcome, verbal memory impairments and although the etiology of these symptoms remains unclear, white matter microstructure may also be affected. Upon our understanding of the exact nature of PNS and their neurobiological underpinnings, we will be able to establish more effective interventions with the hopes of improving functional outcome in these individuals.
APPENDICES
Appendix A: Published Articles
Appendix B: Other Publications
Appendix C: Consent Forms
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