Universitat Autònoma de Barcelona

NEUROLOGICAL SOFT SIGNS, TEMPERAMENT AND SCHIZOTYPY IN PATIENTS WITH SCHIZOPHRENIA AND UNAFFECTED RELATIVES: AN FMRI STUDY

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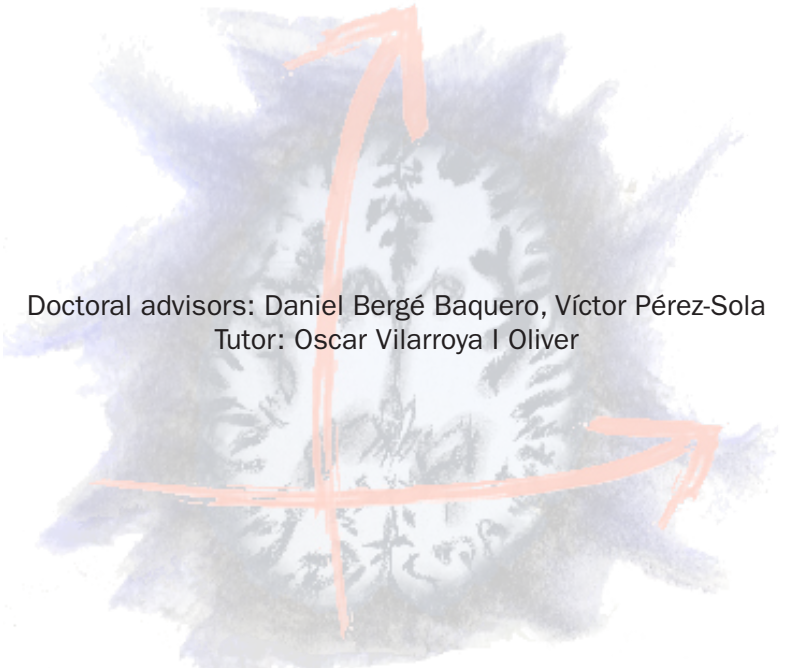
Thesis Doctoral of Liliana Galindo Guarin



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INAD Institut de Neuropsiquiatria i Addiccions · Parc de Salut MAR Barcelona · Instituto de Salud Carlos III · cibersam Centro de Investigación Biomédica En Red de Salud Mental · IMIM Parc de Salut MAR Barcelona · Institut Hospital del Mar d'Investigacions Mèdiques

A la belleza e imperfección de la vida, a la armonía de la música, a la libertad, al amor.
A mi familia, a mis amigos, a mis maestros.

"In order to begin to understand it, to get a glimmer of understanding, we need to take a step back and look at the way that the normal healthy person in the world processes that world [...] and I think through looking at that we get a glimmer of the possibility that actually many of us are in a pretty much psychotic state all the time"

Prof. Paul Fletcher
Psychosis: Bending Reality to See Around the Corners
TED talk. Cambridge University
https://www.youtube.com/watch?v=tV2RLLtOgL4
February 13, 2016

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The present study aims to establish the correlation between the neurological soft signs, the personality traits and the results of the functional magnetic resonance in resting state images comparing the group of patients with non-affected relatives and healthy controls. The results are expected to contribute to the better understanding of the development of the disorder and to have an impact in the future clinical approach.

List of Abbreviations:

ANOVA	Analysis of Variance
ACC	Anterior Cingulate Cortex
BA	Brodmann Area
BOLD	Blood-Oxygen-Level Dependent
C	Cooperativeness
CCTCC	Cortical-Thalamic-Cerebellar-Cortical Circuit
CEIC	Comité Ético de Investigación Clínica del Parc de Salut Mar
CPFM	Cortex Prefrontal Medial
CONN- FMRI	Functional Connectivity Toolbox
DALY	Total Disability-Adjusted Years
DLPFC	Dorsolateral Prefrontal cortex
DMN	Default Mode Network
DMPFC	Dorsal Medial Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental disorders
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EPI	Single Shot Echo Sequence
FA	Fli Angle
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging
FP	Fronto Parietal
FPI	Fluid percussion injury

FPm	Fronto Parietal Medial
FPo	Fronto Parietal Occipital
FWE	Family Wise Error
GAF	Global Adaptive Functioning
GIFT	Group ICA fMRI Toolbox
GLM	General Linear Model
HA	Harm Avoidance
HC	Hippocampus
ICA	Independent Component Analysis
iFC	Intrinsic Functional Connectivity
IPL	Inferior Parietal Lobule
IQ	Intelligence Quotient
ITG	Inferior Temporal Gyrus
MATLAB	Matrix Laboratory
MPFC	Medial Prefrontal Cortex
MNI	Montreal Neurological Institute
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MTG	Medial Temporal Girus
MTL	Medial Temporal Lobe
NC	Neurocognition
NES	Neurological Evaluation Scale
NS	Novelty Seeking
NSS	Neurological Soft Signs

P	Persistence
PCA	Principal component analysis
PCC	Posterior Cingulate Cortex
PCu	Precuneus
PFC	Prefrontal Cortex
PHG	Parahippocampal Gyrus
PANSS	Positive And Negative Scale Symptoms
RD	Reward Dependence
ROI	Region Of Interest
SPD	Schizotypal Personality Disorder
SPQ	Schizotypal Personality Questionnaire
SCID	Structured Clinical Interview for DSM
SD	Self-Directedness
ST	Self-Transcendence
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for Social Sciences
TCI	Temperament and Character Inventory
TCI-R	Temperament and Character Inventory Revised version
TE	Echo Time
TPJ	TemporoParietal-Junction
TR	Repetition Time
WAIS	Weschler Adult Intelligence Scale
WMH	White Matter Hyperintensity

Contenido

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1.Abstract:

Schizophrenia is a severe psychiatric disorder that has a profound effect on both the individuals affected and society. This common mental illness is a complex, heterogeneous behavioural and cognitive syndrome that seems to originate from disruption of brain development caused by genetic or environmental factors, or both. The genetic basis may be present in individuals without disease, as in the case of relatives of patients, being detectable through biological markers. Neurological soft signs (NSS) are discrete sensorimotor impairments associated with deviant brain development that were postulate as an endophenotype of schizophrenic spectrum disorder. Also the personality traits have been proposed as a vulnerability marker in schizophrenia. A specific profile of temperament and character and the schizotypal personality traits have also been correlated with schizotypal personality traits. These traits and some neurological abnormalities have been shown to aggregate in the relatives of schizophrenia patients. The etiopathogenesis of schizophrenia suggests it may be a "progressive neurodevelopmental disorder". This view postulates a disruption in functional circuits involving hetero modal association areas rather than a specific abnormality in a single brain region.

The aim of this study is to explore the abnormalities in the functional connectivity of the default mode network related to the association between neurological soft signs and personality in schizophrenia.
To investigate this a cross-sectional study is proposed, comparing a group of patients with schizophrenia, a group of unaffected relatives and a group of healthy controls.
In order to explore the association of these potential biomarkers of schizophrenia the study was composed of two parts:

a) To explore the association between neurological soft signs and personality traits in schizophrenia, two personality examinations

(Temperament and Character Inventory and the Schizotypal Personality Questionnaire) and an evaluation of Neurological Soft Signs were performed.

b) To explore the association between cerebral connectivity changes in the default mode network with the presence of neurological soft signs in schizophrenia a functional magnetic resonance scan was performed on participants in a resting state.

The major finding in this study was that patients with schizophrenia and non-psychotic relatives display a unique profile of temperament and character and more schizotypal traits that correlate with higher presence of NSS.

Our results reveal an association between these hypothesized vulnerability markers, as temperament (especially harm avoidance, reward dependence and persistence) and character (especially self-directedness and cooperativeness) correlated with the presence of NSS in the entire sample. Also the schizotypal traits (total scores and subscores) showed a very strong correlation with the presence of NSS in the entire sample.

The results showed that susceptibility to NSS and to schizophrenia are both related to individual differences in personality features in non-psychotic relatives of patients with schizophrenia. These findings highlight the value of using both assessments to study high risk populations.

The neuroimaging results showed connectivity changes in the default mode network with a possible association with the presence of neurological soft signs. These findings support the theory of cognitive dysmetria as a possible dysfunction in cortical-thalamic-cerebellar connectivity. This model also could explain the diversity of symptoms

in schizophrenia and their associations (like this study that includes personality and sensory and motor functions).

One strength of the study is that the relatives of patients with schizophrenia had no familial ties to the patients used, thus decreasing the possibility that similar upbringing would confound the results.

INTRODUCTION

2.1. Context of the study

2.1.1 Schizophrenia- Generalities

Schizophrenia is a severe psychiatric disorder that has a profound effect on both the individuals affected and society. This common mental illness is associated with cognitive deficits and also a deficit of personal, social and occupational functionality. Schizophrenia occurs worldwide, and for decades it was generally thought to have a uniform lifetime morbid risk of 1% across time, geography, and sex. The implication is either that environmental factors are not important in conferring risk or that the relevant exposures are ubiquitous across all populations studied. The incidence per 100000 population per year of roughly 15 in men and 10 in women, a point prevalence of 4·6 per 1000, and a lifetime morbid risk of around 0.7% (McGrath, Saha, Chant, & Welham, 2008; Owen, Sawa, & Mortensen, 2016).

In general, the evidence showed that only between 10 and 20% of patients with schizophrenia have a good evolution. Between 20 and 30% can lead a relatively normal life and between 40 and 60% functional impairment persists for life. Although outcomes might not be as uniformly negative as is commonly believed, more than 50% of individuals who receive a diagnosis have intermittent but long-term psychiatric problems, and around 20% have chronic symptoms and disability. Unemployment is staggeringly high at 80–90%, and life expectancy is reduced by 10–20 years. (Owen et al., 2016). Most patients schizophrenia need some degree of formal or informal financial and daily-living support, the perspective now is one of recovery, where the patient takes an active role in the development of new meaning and purpose while growing beyond the misfortune of mental illness (van Os & Kapur, 2009). Schizophrenia was postulated as one of the most frequent causes of disability, accounting for 1.1%

of the total disability-adjusted years (DALY) and 2.8% of the years lived with disability. This entails a direct cost of $ 19 trillion (1991) and a cost of productivity loss of $ 46 trillion (WMH) (AlAqeel & Margolese, 2012; Keshavan et al., 2010; Soundy et al., 2015).

Schizophrenia is a complex, heterogeneous behavioural and cognitive syndrome that seems to originate from disruption of brain development caused by genetic or environmental factors, or both. Since the first half of the last century, the study of the aetiology of schizophrenia has centred on the fact that it has the necessary genetic base that predisposes to the development of the disease in the presence of environmental factors (Owen et al., 2016; van Os & Kapur, 2009). This genetic basis may be present in individuals without disease, as in the case of relatives of patients, being able to be detected through biological markers.

To date, several candidates for biological markers of schizophrenia have been suggested. For example, recent studies propose the presence of cognitive deficits, as markers of vulnerability for schizophrenia. These deficits have been observed in several cognitive domains in unaffected relatives of patients, including attention, working memory, verbal memory, visual memory, processing speed, aspects of social cognition and general intelligence (Keshavan et al., 2010). Despite the vast knowledge and a large number of studies around cognitive deficits in schizophrenia, the transfer of this knowledge to the generation of therapeutic hypotheses or markers has been quite unsuccessful, which raises the need to look for new approaches and new candidates for biological markers.

The tremendous heterogeneity in the clinical symptoms and cognitive/emotional/motor deficits seen in patients with schizophrenia has made it challenging to determine the underlying pathogenesis of the illness. The theory that genes and environment combine to confer

susceptibility to the development of diseases surfaced in the early half of the last century, but the use of such a framework for exploring the aetiology of schizophrenia and other psychiatric disorders is more recent (Braff, Schork, & Gottesman, 2007). One technique to help identify underlying genetic factors is the use of heritable intermediate phenotypes, or endophenotypes. Endophenotypes provide mechanisms to study the genetic underpinnings of the disorder by focusing on measureable traits that are more proximal to gene regulation and expression than are symptoms (Gottesman & Gould, 2003).

Criteria for the identification of **vulnerability markers** to apply to endophenotypes (Gottesman & Gould, 2003):

1. Associated with illness in the population.
2. Heritable.
3. Primarily state-independent (manifests in an individual whether or not illness is active).
4. Within families, the vulnerability marker and illness are co-segregate.
5. Founded in affected family members is found in nonaffected family members at a higher rate than in the general population.

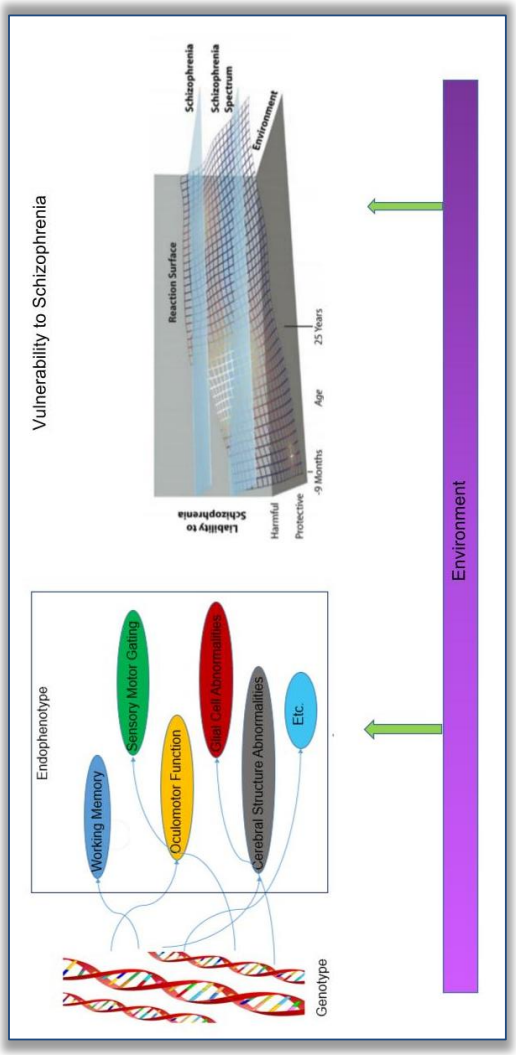


Figure 2.1 Vulnerability to Schizophrenia

2.2Personality

The personality has been proposed as a vulnerability marker in schizophrenia (Bolinskey et al., 2017; Bolinskey & Gottesman, 2010). Several studies have shown an association between schizophrenia and certain personality traits, however, the nature of this relationship is not clarified (Silberschmidt & Sponheim, 2008; Smith, Cloninger,

Harms, & Csernansky, 2009). One such avenue of discovery was the observation of individuals with schizophrenia and their relatives, who often display attenuated signs of the disorder, including odd or eccentric personality and withdrawal from others (Kraepelin, 1909). Also significantly greater numbers of symptoms of paranoid, schizoid, schizotypal, and avoidant personality disorders were reported in siblings of schizophrenia patients (Bolinskey et al., 2015; Cuesta, Peralta, & Caro, 1999; Webb & Levinson, 1993). Several studies showed siblings of individuals with schizophrenia exhibit symptoms of Cluster A personality disorders at a greater rate compared to healthy controls (Torti et al., 2013). The Cluster A personality disorders have also been found to be present in the prodromal phase of schizophrenia (Rodríguez Solano & González De Chávez, 2000). Additionally, avoidant personality disorders symptoms also occur in relatives of individuals with schizophrenia at higher rates than in controls, even when controlling for the presence of paranoid and schizotypal personality disorders, and these symptoms are related to poorer neurocognitive performance in relatives (Fogelson et al., 2007, 2010).

2.2.1. Temperament and Character

The initial Cloninger's psychobiological model of personality suggests that a person's temperament is heritable and regulated by neurotransmitters involved in the pathophysiology of schizophrenia. (Cloninger, 1994; Cloninger, Adolfsson, & Svrakic, 1996; Heath, Cloninger, & Martin, 1994; Stompe et al., 1998). Among the different models of studying personality, Cloninger's model is one that has shown greater biological correlation (Cloninger et al. 1993). Both temperament and character traits are equally heritable (Gillespie, Cloninger, Heath, & Martin, 2003), but character is more shaped by sociocultural influences as it develops across a lifespan (Josefsson,

Jokela, Cloninger, et al., 2013; Josefsson, Jokela, Hintsanen, et al., 2013). The temperament are individual differences in perceptions based on habits and skills (procedural memory and associative learning-preconceptual), whereas character are individual differences based in goals and values (propositional memory, verbal and conceptual learning or reorganization of self) (Silberschmidt & Sponheim, 2008; Van Schuerbeek, Baeken, Luypaert, De Raedt, & De Mey, 2014). Environmental factors do impact on both temperament and character traits, however, these factors are more critical for the development of character than temperament. Character is the result of social adaptation and the interaction between environment and heredity (Cloninger et al., 1993). In fact, both temperament and character are equally heritable but character is more influenced by parental rearing and other sociocultural learning (Gillespie et al., 2003; Josefsson, Jokela, Cloninger, et al., 2013; Josefsson, Jokela, Hintsanen, et al., 2013).

Recent studies showed the neurobiological basis of temperaments by identifying their anatomical fibre connectivity correlates within the subcortical–cortical neural networks (Lei et al., 2014)

By using this model, patients with schizophrenia have shown a temperament and character profile that is distinct from the general population (Bora & Veznedaroglu, 2007; Glatt, et al. 2006; Kurs, Farkas, & Ritsner, 2005; Ritsner & Susser, 2004) Specifically, people with schizophrenia and their non-psychotic relatives are higher in the temperament of harm avoidance (i.e., more anxious and shy) and lower in the temperament of reward dependence (i.e., more detached and cold emotionally), so that they are more socially distant than controls (Bolinskey et al., 2017; Smith et al., 2009). More recently, evidence has emerged showing that the dimensions of character are heritable and may also influence the risk of schizotypy (Silberschmidt

& Sponheim, 2008). Specifically, people with schizophrenia and their non-psychotic relatives have the schizotypal character profile of low self-directedness (i.e., aimless and tending to blame others for their problems), low cooperativeness (i.e., suspicious and lacking in empathy), and high self-transcendence (i.e., prone to fantasy and magical thinking). Thus Cloninger's TCI-R provides a reliable way to quantify personality traits related to susceptibility to the schizophrenia spectrum (Smith et al., 2009).

The association between personality and schizophrenia has been reinforced by several studies that relate these personality traits with other abnormalities in schizophrenia. For example, the correlation between some dimensions of temperament and changes in monoaminergic activity has been postulated as the biological basis of schizophrenia (Mitsuyasu et al., 2001). In addition, an interaction has been observed between polymorphisms of these two systems that predicts the scores on harm avoidance (Benjamin et al., 2000).

Also studies of cohorts with people with psychosis found that reward dependence and persistence were significantly correlated with PANSS negative symptoms. Also persistence scores predicted higher social and occupational functioning, and higher harm avoidance predicted a higher likelihood of being on a disability pension. This findings suggest that the understanding of personality dimensions support better understanding of outcome and symptom expressions in psychotic disorders (Poustka et al., 2010).

Studies of structural neuroimaging found higher social RD in men was significantly associated with increased gray matter density in the orbitofrontal cortex, basal ganglia and temporal lobes. These regions been previously shown to be involved in processing of primary rewards (Lebreton et al., 2009).

2.2.2. Schizotypal personality

Schizotypy refers to latent personality organization that indicates an individual proneness to psychosis and, in particular, to schizophrenia, as a complex construct that can be understood as an attenuated form of schizophrenia, representing a premorbid or prodromic phase (Adrian Raine, 2006). The dimensional model of schizotypal personality posits that the degree of schizotypal traits varies on a continuum where normality lies on one extreme, non-clinical to clinical schizotypy in the middle, and clinically expressed schizophrenia on the opposite extreme. Along this continuum we might encounter “intermediate” phenotypic expressions of these set of traits, which, though not reaching clinical levels, would be associated with greater current psychopathological intensity (Chmielewski & Watson, 2008; Fonseca-Pedrero et al., 2011). In accord with this view, several lines of evidence have demonstrated a range of abnormalities in relation to schizotypal personality that are intrinsically similar to those seen in schizophrenia (Hazlett et al., 2008). More recent formal family studies confirm the association between schizophrenia and personality disorders, including schizotypal traits, in families (Kendler et al., 1993) and that higher degrees of genetic relatedness to relatives with schizophrenia are associated with higher rates of schizotypal symptoms (Torgersen, 1994).

Previous studies reported a significantly higher incidence rate of meeting diagnostic criteria for each of the disorders at baseline among psychometrically identified schizotypic individuals in comparison to a matched comparison sample (Bolinskey et al., 2015). Studies of functional neuroimaging, and in particular the study of brain activity in idle state has allowed to relate some brain networks (resting state networks) with personality traits. Also, other studies found a positive correlation between schizotypy and visual networks and a negative correlation between schizotypy and auditory networks (R.C.K. Chan et al., 2010).

Schizotypal personality features and some neurological abnormalitities have been shown to aggregate in the relatives of schizophrenia patients, supporting the view that both are likely to reflect genetic contributions to liability to schizophrenia (Siever et al., 2002).

2.2Neurological soft signs

Neurological soft signs (NSS) are subtle but observable impairments in simple motor coordination, complex motor sequencing, sensory integration and disinhibition signs that are not localized to a specific area of the brain nor characteristic of any specific neurological condition (Bombin, Arango, & Buchanan, 2005a; Raymond C K Chan & Gottesman, 2008). NSS are discrete sensorimotor impairments (e.g. discrete motor discoordination, impairment in sequencing, balance, and sensory integration (Krebs & Mouchet, 2007) associated with deviant brain development (Gay et al., 2013)

It is generally accepted that NSS are more prevalent in schizophrenia patients compared to healthy subjects. They have consistently been demonstrated in neuroleptic-naïve first-episode patients, i.e., prior to medication exposure, supporting the assumption that NSS constitute an intrinsic feature of schizophrenia (Bachmann, Degen, Geider, & Schröder, 2014).

Thus, NSS have been suggested as markers of disease vulnerability, which are present prior to the start of treatment and are independent of illness state (as well as type of antipsychotic treatment) (Bombin et al., 2005; Raymond C K Chan, Xu, Heinrichs, Yu, & Wang, 2010, Chan et al., 2010; Bombin, Arango & Buchanan, 2003.)

Recent studies suggesting that schizophrenia spectrum disorders may be characterized by developmental abnormalities in the central nervous system, and support the notion that NSS may be schizophrenia spectrum disorder biomarkers (Wang, Cai, Li, Yang, & Zhu, 2016). NSS have been frequently reported in schizophrenia

spectrum disorders and sometimes also in related psychotic disorders (E. Y. H. Chen et al., 2005; Heinrichs & Buchanan, 1988).

Validating their status as endophenotypic markers reflecting vulnerability to schizophrenia, NSS are found in relatives of patients and within families, and follow the transmission of the genetic risk (Caldani et al., 2016; Gourion, Goldberger, Olie, Lôo, & Krebs, 2004). Evidence supports that motor coordination in particular, meet criteria to be a vulnerability marker of schizophrenia (Raymond C K Chan & Gottesman, 2008). NSS were found to have moderate but significant heritability in the healthy twin sample. Moreover, patients with schizophrenia correlated closely with their first-degree relatives on NSS. NSS are highly heritable and show familial association. The motor coordination and the sensory integration subscales showed high heritability estimates based on both the classical heritability equation and the genetic model analysis (Xu et al., 2016). Similar significant correlations of the NSS subscale and total scores were reported between patients with schizophrenia and their first-degree relatives, regardless of whether the comparison was made between patient–sibling pairs or patient–parent pairs (Xu et al., 2016).

Recent studies NSS were found to have moderate but significant heritability in the healthy twin sample. Moreover, patients with schizophrenia correlated closely with their first-degree relatives on NSS in tweens showed the genetic heritability of the NSS in Schizophrenia (Xu et al., 2016). However, the reason for the high prevalence rate of NSS in psychosis is still unsolved.

A very high quantity of evidence in the last years demonstrated that NSS are correlated with structural and functional brain abnormalities related to schizophrenia (Caldani et al., 2016; Raymond C K Chan et al., 2015; Hirjak et al., 2015; Mouchet-Mages et al., 2011; Zhao et al., 2014). In cortical networks negative correlations were found between

NSS levels and functional connectivity of the right precuneus, right superior frontal areas, supplementary motor area, and left paracentral gyrus (Hirjak, Wolf, Kubera, Stieltjes, & Thomann, 2016; Thomann, Hirjak, Kubera, Stieltjes, & Wolf, 2015).

Findings from structural MRI and functional MRI meta-analyses further support the conceptualization of NSS as a manifestation of the "cerebello-thalamo-prefrontal" brain network model of schizophrenia and related psychotic disorders (Zhao et al., 2014). Also, the distribution of NSS in schizophrenia, and in first-degree relatives, is consistent with the endophenotype criterion of familial association (Zhao et al., 2014). However, belonging to the same family could act as a confounding factor because it includes environmental influence and common genetic factors unrelated to the illness. In this respect, no studies are available comparing both NSS and personality in patients with schizophrenia and non-psychotic relatives.

2.2.1 Clinical correlate of neurological soft signs

Recent studies propose that the NSS scores could be identified as course predictors. NSS scores decrease in the clinical course of schizophrenia with remission of psychopathological symptoms; and an indication that this effect is more pronounced in patients with a remitting course than in those with non-remitting schizophrenia. Also, NSS was associated with more chronic and severe forms of the illness (Bachmann et al., 2014) Patients who had a favourable course showed more reduction in NSS. Predictors of follow-up NSS scores were baseline NSS scores and compliance with treatment (Bachmann et al., 2014). Other studies also showed at 4-year follow-up, NSS were closely related to psychopathology (Whitty et al., 2003).

The level of NSS was lower for patients with a shorter duration of untreated psychosis. A relationship between NSS and negative

symptoms became apparent 1 year after the initial episode. At follow-up, overall severity of the NSS was significantly higher in non-remitters than in remitters. A significant reduction of NSS, with the exception of sensory integration, occurred in remitters (Prikryl, Ceskova, Kasparek, & Kucerova, 2006).

NSS at baseline were significantly associated with baseline positive and negative symptoms. NSS showed a strong trend toward improvement during 6 weeks of the prospective haloperidol trial. Hierarchal linear regression analyses indicated that more severe baseline NSS predicted poorer response to haloperidol treatment (Mittal et al., 2007).

Also, studies described a progressive increase over 3 years in these NSS in schizophrenia, mainly motor coordination, sensory integration and disinhibition associated to the clinical curse (E. Y. Chen, Kwok, Au, Chen, & Lau, 2000).

Some authors even proposed a hypothetical "protective" action of antipsychotics on neurological dysfunction, based on data from 5-year follow-up showing that patients who had been free of medication throughout had more marked increase in NSS scores (Madsen, Vorstrup, Rubin, Larsen, & Hemmingsen, 1999).

Therefore, NSS at untreated baseline seem to be associated with symptom severity, and elevated NSS are predictive of a smaller degree of improvement in symptoms after antipsychotic treatment. These findings are consistent with the hypothesis that NSS are linked to the neuropathology that underlies schizophrenia symptomatology and course (Neelam, Garg, & Marshall, 2011; Varambally, Venkatasubramanian, & Gangadhar, 2012).

2.3Neurological Soft Signs and Personality

Furthermore, several studies of schizophrenia have suggested an association between the presence of schizotypal personality traits correlates more strongly with the presence of neurological soft signs. Specifically, the presence of schizotypal personality traits correlates with the presence of neurological soft signs in relatives of patients with schizophrenia (Mechri et al., 2009, 2010). Alterations in motor coordination and integration of stimuli are positively correlated with both the total scores and with the cognitive perceptive component of scales measuring schizotypy (Barrantes-Vidal et al., 2003; Raymond C K Chan, Wang, et al., 2010; Kaczorowski, Barrantes-Vidal, & Kwapil, 2009).

Healthy individuals with schizotypy have been found to demonstrate increased numbers of NSS (Raymond C K Chan, Wang, et al., 2010). Alterations in motor coordination and integration of stimuli are positively correlated with total scores and the cognitive perceptive aspect of schizotypy scales (Raymond C K Chan, Wang, et al., 2010; E. Y. H. Chen et al., 2005) .

Several studies in the last years examined the first-degree relatives of schizophrenic patients. Results of these studies were divergent: some reported no association between NSS and schizotypal traits (Obiols, Serrano, Caparrós, Subirá, & Barrantes, 1999) while others showed by one hand that NSS were associated with schizotypal features in a sample of healthy controls (Bollini et al., 2007). An other study showed that the overall NSS score was correlated with the total SPQ score in both unaffected siblings and healthy controls and with the SPQ disorganization sub-score only in unaffected siblings of patients with schizophrenia (Mechri et al., 2009, 2010).

In respect to temperament and character, interestingly, temperament and character features and NSS have been shown to aggregate in the relatives of schizophrenia patients (Krebs et al., 2000; Andreasen et

al., 2005), supporting the view that both are likely to reflect genetic liability to schizophrenia.

No comparison of patients with schizophrenia avoiding family ties has been made by researchers before. Belonging to the same family could act as a confounding factor, because it would also include upbringing as a major environmental influence.

2.4. Default Mode Network in schizophrenia

One leading hypothesis that has come to the forefront over the past several decades is that schizophrenia is caused by aberrant connectivity between brain regions. In fact, a new field of connectomics has emerged to study the effects of brain connectivity in health and illness (White & Gottesman, 2012). The default mode network (DMN) is active during rest and deactivated when goal-directed behaviour is required and is thought to play a role in appraising external and internal stimuli, self-referential and reflective processes. Regions representing the DMN consist of the medial prefrontal cortex (MPFC), the posterior cingulate cortex (PCC) extending into the precuneus (PCu), the lateral parietal cortices, lateral temporal cortex, hippocampus (HC) and parahippocampal gyrus (PHG) (Garrity et al. 2007; Gusnard & Raichle 2001). Structural and functional alterations in these regions have been associated with schizophrenia. In addition, the DMN has been implicated in self-referential processing (Schilbach et al. 2008), perspective-taking, self-other judgments (Lindner et al. 2008), processing of agency and memory functions (Farrer et al. 2003), all of which appear to be altered in individuals with psychotic disorder (Peeters et al. 2015).

The MPFC is a key node of the DMN and is essential in self-referential processing and emotional regulation (Yu et al. 2014; Liu et al. 2013; F. Liu et al. 2012). The MPFC is an important node of the DMN and the connectivity and activation abnormalities have been found in

schizophrenia (Zhou et al. 2015). A recent meta-analysis reported reduced resting-state connectivity of MPFC and temporal regions in schizophrenia and suggested that these findings are to be linked to disturbed selfreference processing (Pankow et al. 2015; Kühn & Gallinat 2013).

In previous studies abnormal connections were found in the DMN in schizophrenic patients, showing a reduced functional connectivity between bilateral temporoparietal-junction (TPJ) and the PCC. In addition, the left TPJ showed gradually weaker functional connectivity with PCC and the MPFC in DMN as the duration of schizophrenia increased (Zhang et al. 2014). The results suggested that in the disease process patients have decreased connectivity functional networks wich is negatively correlated with illness duration, which provided evidence for progressive brain abnormalities in early schizophrenia (Zhang et al. 2014).

Studies in Patients with schizophrenia

Many studies reveal that the causal connectivity of the integrated prefrontalthalamic (limbic)-cerebellar (sensorimotor) circuit was partly affected by structural deficits in first-episode, drug-naive schizophrenia as follows: (1) unilateral prefrontalsensorimotor connectivity abnormalities (increased driving effect from the left MPFC to the sensorimotor regions); (2) bilateral limbic-sensorimotor connectivity abnormalities (increased driving effect from the right anterior cingulate cortex [ACC] to the sensorimotor regions and decreased feedback from the sensorimotor regions to the right ACC); and (3) bilateral increased and decreased causal connectivities among the sensorimotor region (Guo et al. 2014).

The different findings suggest that the schizophrenia patients show impaired interaction among DMN subsystems, with a reduced central role for PCC and MPFC hubs as well as weaker interaction between

dorsal medial prefrontal cortex (dMPFC) subsystem and medial temporal lobe (MTL) subsystem (Du et al. 2016).

Negative correlations were also observed between the PANSS negative/total score and the increased driving connectivity from the left MPFC to the left MTG in patients. Increased frontal connectivity is previously reported to be negatively correlated with the severity of negative symptoms in schizophrenia (Mingoia et al. 2012) .

Studies in unaffected siblings of patients with schizophrenia

Sharing similar genetic and environmental background with the patients, unaffected siblings have a higher risk of developing schizophrenia than individuals without a family history of schizophrenia (Gottesman et al. 2003). Unaffected siblings also exhibit similar but mild brain abnormalities as the patients (Jang et al. 2011; van Buuren et al. 2012). Hence, unaffected siblings provide a unique opportunity to examine functional connectivity abnormality associated with the neurobiology of schizophrenia (Guo et al. 2015).

Some studies founded that compared to controls, patients and siblings had increased PCC connectivity with the IPL, PCu and MPFC. In the IPL and PCu, the functional connectivity of siblings was intermediate to that of controls and patients. (Peeters et al. 2015).

Combined with the results from the patients, the siblings and the patients shared increased functional connectivity between the left Crus I and the left superior MPFC, as well as between the lobule IX and the left MPFC (orbital part), which could serve as candidate endophenotypes for schizophrenia (Guo et al. 2015).

Also, the increased functional connectivity in individuals with (increased risk for) psychotic disorder may reflect trait-related network

alterations. The association between familial risk and DMN connectivity was not conditional on environmental exposure (Peeters et al. 2015).

Studies on DMN connectivity in schizophrenia have shown conflicting results as to the direction of associations, decreased, increased and mixed patterns of functional connectivity (Broyd et al. 2009; Chang et al. 2014; Khadka et al. 2013), or no significant alterations in patients with schizophrenia (Repovs et al. 2011) have been reported. Similarly, in individuals at higher than average risk for psychotic disorder (first-degree relatives) both increased (in the MPFC, bilateral inferior temporal gyrus (ITG), PCu) (van Buuren et al. 2012; H. Liu et al. 2012), as well as an absence of significant differences with respect to controls (Khadka et al. 2013; Repovs et al. 2011) have been reported (Peeters et al. 2015).

Taken together, most studies have shown increased connectivity in patients with schizophrenia and first-degree relatives, though the larger studies (n = 258 and n = 799) suggest that patients have reduced DMN connectivity and that relatives have reduced (Nanodevices et al. 2014) or no differences (Khadka et al. 2013) in DMN connectivity with respect to controls.

Studies reveal that patients and siblings had a similar pattern of increased connectivity between the PCC seed and other regions of the DMN (i.e., left IPL, left PCu and right MPFC) compared to controls. DMN connectivity was not associated with (subclinical) psychotic or cognitive symptoms. The association between familial risk and DMN connectivity was not conditional on environmental exposure(Peeters et al. 2015).

Others studies found that compared to controls, relatives showed significantly less suppression of DMN activity in the left parahippocampal gyrus. Left hippocampal and posterior parahippocampal volumes were inversely and significantly associated

with DMN processing (smaller volumes, less suppression) in relatives (Seidman et al. 2014). These results provide support for the hypothesis that expressions of the liability to schizophrenia include a smaller left hippocampus and reduced DMN suppression in the left PHG as well as altered structure and function in MPFC (Whitfield-Gabrieli et al., 2009; Rosso et al., 2010). Thus, structural and functional DMN abnormalities in MTL and MPFC appear to be markers of familial vulnerability to schizophrenia, observable by the teenage years, and likely to precede the onset of psychosis (Seidman et al. 2014).

This study aims to deepen the neurobiological, neuroanatomical and neurofunctional basis of the association between personality traits and neurological soft signs in schizophrenia. For this purpose, two personality examinations were performed, the neurological soft signs were evaluated and a functional magnetic resonance acquisition was performed in resting state in a group of patients with schizophrenia, a group of non-affected relatives and to a group of healthy controls.

3. Objectives and Hypothesis

3.1 General Objective

The aim of this study is to explore the abnormalities in the functional connectivity of the default mode network related to the association between neurological soft signs and personality in schizophrenia.

For that objective the study will be composed of two parts:

c) To explore the association between neurological soft signs and personality traits in schizophrenia.

d) To explore the association between cerebral connectivity changes in the default mode network with the presence of neurological soft signs in schizophrenia.

3.2 Specific objectives

3.2.1 Neurological soft signs and personality in schizophrenia

a) To determine the association of neurological soft signs and the temperament and character in patients with schizophrenia and their non-affected relatives in comparison to healthy controls.

b) To determine the association between neurological soft signs and the schizotypal personality traits in patients with schizophrenia and their non-affected relatives in comparison to healthy controls.

3.2.2 Functional Neuroimaging

To explore the abnormalities in the connectivity of the default mode network by functional magnetic resonance imaging (fMRI) during resting state and the association between neurological soft signs and personality traits in the three groups of subjects.

3.3. General Hypothesis

The general hypothesis is that there is an association between higher presence of neurological soft signs, a temperament with higher harm avoidance, low reward dependence, low novelty seeking, low persistence (according to Cloninger's personality model), schizotypy and functional brain alterations in areas of the default mode network in patients with schizophrenia and their non-affected relatives.

In this sense, our study hopes to explore the association between the clinical vulnerability markers and their neurofunctional abnormalities associated with schizophrenia.

3.4 Specific Hypothesis

3.4.1 Neurological soft signs and personality in schizophrenia

a) A temperament with higher harm avoidance, low reward dependence, low novelty seeking and low persistence traits will show a positive correlation with the neurological soft signs across the three groups of subjects.
b) Higher scores in schizotypal personality traits will show a positive correlation with the neurological soft signs, across the three groups of subjects.

3.4.2 Functional Neuroimaging

a) There is a set of abnormalities in functional connectivity in the default mode network and personality traits that will be present in patients with schizophrenia and their non-affected relatives with higher neurological soft sign scores.
b) This set of alterations in functional connectivity in the default mode network and neurological soft signs will not be present in the control subjects or in the unaffected relatives who do not have high scores for the aforementioned personality traits.

c) Subjects with higher neurological soft sign scores will show a significant correlation with changes in functional connectivity patterns, in regions involved in reward dependence (ventral striatum), harm avoidance (medial and dorsolateral prefrontal cortex), persistence (inferior frontal cortex) and novelty seeking.

4. Methods: Procedures

To explore the association between neurological soft signs, personality and the abnormalities of the functional connectivity of the default mode network in schizophrenia, the study included a clinical exploration and an fMRI in resting state.

4.1 Subjects

This study was developed at the Neuropsychiatry and Addictions Institute of the Parc de Salut Mar de Barcelona between 2012 and 2015. The patients and the non-psychotic relatives were recruited from outpatient mental health services and clinics. The patients were diagnosed with schizophrenia from their medical records and confirmed by the Structured Clinical Interview for DSM Disorders. Unaffected relatives and healthy controls were also evaluated. All the patients had a disease duration from 5 to 15 years, were treated with atypical antipsychotics, had never received electroconvulsive therapy and had been clinically stable for the last six months (all positive items of the Positive and negative Scale Symptoms (PANSS) positive subscale scoring 4 or lower) (Peralta & Cuesta, 1994).

The non-psychotic relatives were from the same mother and father of a patient with a diagnosis of schizophrenia according to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) (APA, 2000). The non-psychotic relatives were not from the same families of the patients included in the study, to avoid the effects of similar upbringing that could induce potential similarities in temperament and character between patients and siblings. Control subjects were recruited by advertisements in public places.

All subjects were between 25 and 50 years old and had an estimated IQ > 80 as measured by WAIS subscales (Digit, cubes, vocabulary,

arithmetic, symbol search) (Wechsler, 2008) All participants had lived in Spain for more than five years and were fluent Spanish speakers.

The exclusion criteria for all the subjects included the presence of a substance dependence disorder (except nicotine dependence) according to DSM-IV-TR, and the presence any other psychiatric disorder from axis I or II of DSM-IV-TR, as well as the personal history of severe somatic or neurological disorders.

The study was approved by the ethics committee of the CEIC-Parc de Salut Mar Hospital (2011/4141/I). All subjects gave written informed consent and were assured of the confidentiality of the collected data.

Selection criteria for all subjects

1. Age: Between 25 and 50 years old
2. Estimated IQ > 80 as measured by WAIS subscales
3. Live in Spain for more than five years and be fluent Spanish speakers
4. Absence of a substance dependence disorder (except nicotine dependence) according to DSM-IV-TR
5. Absence of any other psychiatric disorder from axis I or II of DSM-IV-TR, as well as the personal history of severe somatic or neurological disorders.

Patients selection criteria

1. They were diagnosed with schizophrenia from their medical records and confirmed by the Structured Clinical Interview for DSM Disorders.
2. Disease duration from 5 to 15 years
3. Were treated with atypical antipsychotics
4. Had never received electroconvulsive therapy
5. Had been clinically stable for the last six months.

Unaffected relatives selection criteria

1. They have the same mother and father of a patient with a diagnosis of schizophrenia according to DSM-IV-TR
2. Absence of diagnostic criteria of schizophrenia according to DSM-IV-TR
3. They were not from the same families of the patients included in the study, to avoid the effects of similar upbringing that could induce potential similarities in temperament and character between patients and siblings.

Healthy Control group selection criteria

1. Absence of any family or personal history of mental illness.
2. They were recruited by advertisements in public places.

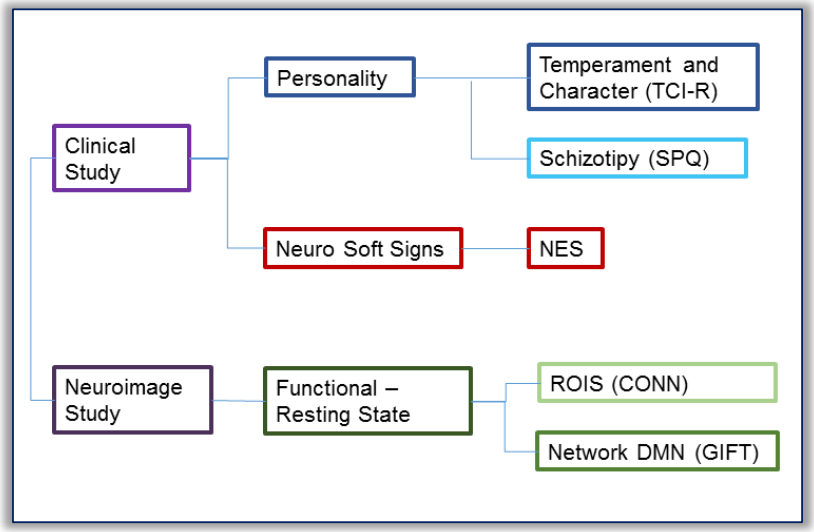
4.2 Design

A cross-sectional study with a comparison between groups and correlations between variables was performed. The detailed statistical analyses are described in section 5.

4.2.1 General scheme aim of the study

To explore the abnormalities in the functional connectivity of the default mode network related to the association between neurological soft signs and personality in schizophrenia, a clinical and a neuroimage MRI study were performed.

Figure 4.1: General Scheme



4.2.2. Clinical Procedures

Basic socio-biographical data were collected from the patients' medical history. This information was recorded in order to facilitate further analysis of possible confounding variables between and within groups. These data included years of education, socio-economic level, psychiatric and medical history, years since disease onset, administered treatment and psychiatric history of first degree relatives. The number of previous psychiatric admissions, years since the onset

of the illness, a chronological summary of antipsychotic treatment, and a first-degree family psychiatric history were collected as a clinical psychiatric background.

To assess positive and negative symptoms of schizophrenia, patients were clinically assessed using the Positive and Negative Syndrome Scale (PANSS) (Peralta & Cuesta, 1994) and the overall functioning of the subjects was assessed using the Global Adaptive Functioning (GAF) (Jones, Thornicroft, Coffey, & Dunn, 1995) . We introduced these measurements in order to further reduce the influence of these symptoms in the study of the association between other clinical variables. The IQ was estimated by WAIS subscales (Digits, cubes, Vocabulary, Arithmetic, symbol search). The pharmacological treatments were compared by calculating equivalent doses of chlorpromazine.

To explore the association between neurological soft signs and personality traits in schizophrenia, all subjects were assessed with the Spanish version of the Temperament and Character Inventory (TCI-R) (Gutiérrez-Zotes et al., 2004.), the schizotypal personality questionnaire (SPQ) (Raine, 1991; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000) and the Neurological Soft Signs Scale (Buchanan & Heinrichs, 1989).

4.2.2.1 Personality

Several studies have described an association between certain personality traits and schizophrenia without further clarifying the nature of that relationship (Silberschmidt & Sponheim, 2008; Webb & Levinson, 1993). To explore the different personality traits in patients with schizophrenia and their unaffected relatives in comparison to healthy controls two different approaches to evaluate personality were performed. To evaluate personality traits among the different models

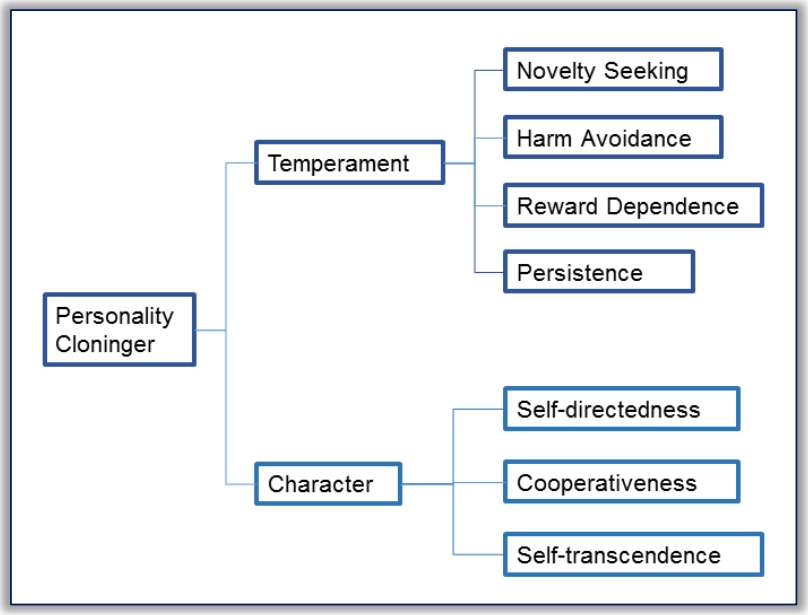
of studying personality, Cloninger's model is one that has shown greater biological correlation (Cloninger et al., 1993).

Schizotypy refers to latent personality organization that indicates an individual proneness to psychosis and, in particular, to schizophrenia (Mohr & Claridge, 2015) as a complex construct that can be understood as an attenuated form of schizophrenia, representing a premorbid or prodromic phase (Barrantes-Vidal, Grant, & Kwapil, 2015). To explore the schizotypal personality in patients with schizophrenia and their non-affected relatives in comparison to healthy controls the SPQ was performed.

4.2.2.1.1 Temperament and Character

According to Cloninger's model, personality can be evaluated using the temperament and character inventory (TCI-R) and divided into temperament, which in turn has four dimensions - novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P) - and character, also constituted by three dimensions - self-directedness (SD), cooperativeness (C), and self-transcendence (ST). This model provides a useful framework for studying the biological basis of personality and their relationship with several mental disorders. The TCI-R sub-scores for each of the seven dimensions were calculated (Cloninger, 1994).

Figure 4.2: Cloninger’s Personality model



In the TCI-R the response method is a five point rating scale (1, definitively false; 2, mostly or probably false; 3, neither true nor false, or about equally true or false; 4, mostly or probably true; 5, definitively true). In comparison with the TCI (previous model of the questionnaire) (Cloninger et al., 1994), this method is meant to improve the reliability of the responses, because moderate answers are possible; various currently used personality questionnaires include this response pattern with satisfying psychometric characteristics. In particular, the more informative response set was designed to improve the precision of measuring the subscales without increasing the number of items. The TCI-R is composed of 240 questions. In comparison with the TCI; 37 items have been eliminated (mostly related to character dimensions), only 189 items are common, and 51 new items have been introduced in the TCI-R including five validity items. The TCI-R also has an increase of subscales measuring RD and P for a total of 29 TCI-R subscales (Pelissolo et al., 2005) (table 4.1 and 4.2).

Table 4.1 : Temperament Subscales			
Novelty seeking	**Harm Avoidance**	**Reward dependence**	**Persistence**
Exploratory excitability	Anticipatory worry	Sentimentality	Eagerness of effort
Impulsiveness	Fear of uncertainty	Openness to warm communication	Work hardened
Extravagance	Shyness	Attachment	Ambitious
Disorderliness	Fatigability	Dependence	Perfectionist

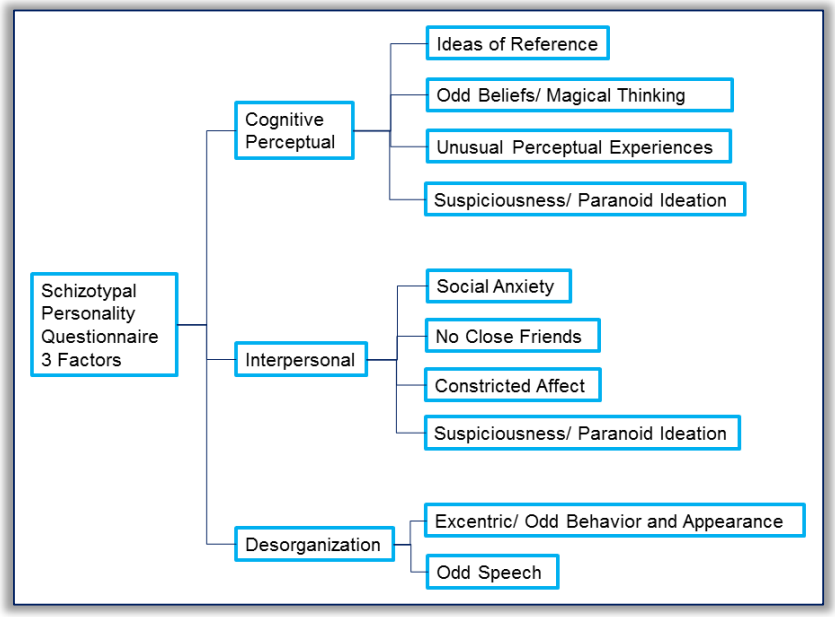
Table 4.2: Character Subscales		
Self-directedness	**Cooperativeness**	**Self-transcendence**
Responsibility	Social acceptance	Self-forgetful
Purposeful	Empathy	Transpersonal identification
Resourcefulness	Helpfulness	Spiritual acceptance
Self-acceptance	Compassion	
Enlightened second nature	Pure-hearted conscience	

4.2.2.1.2 Schizotypal personality

Raine developed the Schizotypal Personality Questionnaire (SPQ), a 74-item self-reporting instrument, based on DSM-II-R criteria for schizotypal personality disorder (SPD) and including nine subscales to evaluate the nine features of SPD listed in DSM-III-R. This questionnaire has shown to have a three-factor structure, namely Cognitive-Perceptual Deficits (ideas of reference, magical thinking, unusual perceptual experiences and paranoid ideation), Interpersonal Deficits (Social Anxiety, No close Friends, Blunted affect, Paranoid

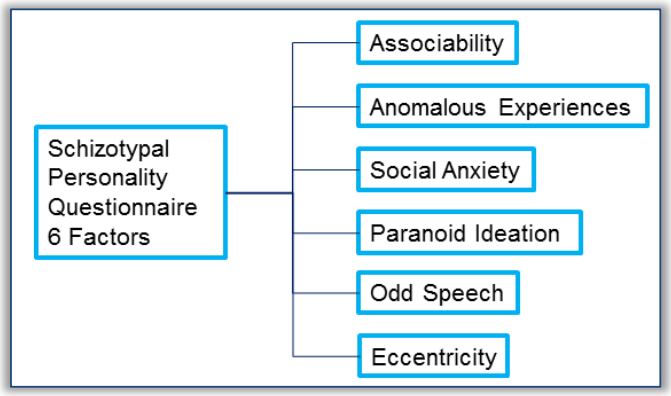
Ideation), and Disorganization (Odd Behaviour, Odd Speech) (Raine, 1991; Reynolds et al., 2000).

Figure 4.3: Schizotypal Personality Questionnaire (SPQ- 3 Factors)



Literature-derived factorial structures of the SPQ either fit the data poorly or had redundant, non-distinct dimensions. A novel 6-factor solution outperformed novel and literature-derived structures while maintaining distinct dimensions. All 6 dimensions were adequately unidimensional, had high internal consistency, had reasonable measurement precision over levels of severity, could be used reliably as sum scores and showed at least no bias in factorial structure over age and sex. These results support little advantage in using the 9 subscales of the SPQ and strongly question the validity of the three-factor and four-factor models that are often considered to be the basic structure of schizotypy (Davis et al., 2017).

Figure 4.4: Schizotypal Personality Questionnaire (SPQ- 6 Factors)



4.2.2.2 Neurological soft signs

To explore the differences in neurological soft signs in patients with schizophrenia and their non-affected relatives in comparison to healthy controls, the Neurological Evaluation Scale (NES) was used. The examination was performed using the neurological assessment scale of Buchanan & Heindrichs (Buchanan & Heinrichs, 1989). NES is composed of 28 items, rated from 0 to 2, composed by three subscores:

1. Integrative sensory dysfunction, reflected in traits such as bilateral extinction, agraphesthesia, astereognosis, right/ left confusion, and impaired audiovisual integration.

2. Motor coordination, reflected in items such as tandem walk, finger to nose, finger to thumb opposition, and dysdiadochokinesis.

3. Impaired sequencing of complex motor acts. As a relevant limitation in the use of this measure in this study, in the item of Rhythm Tapping Test, the part B was not made.

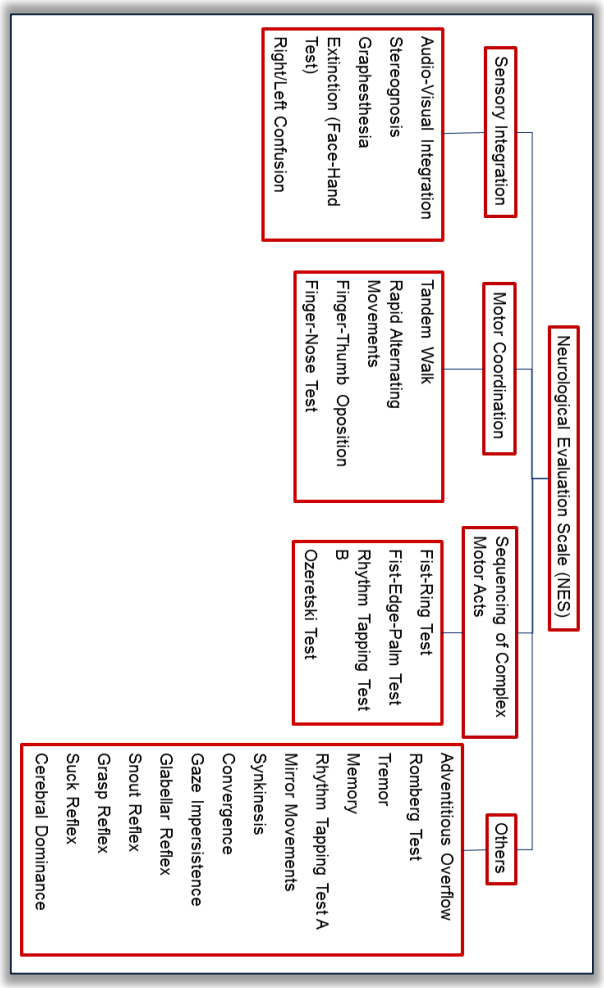


Figure 4.5: Neurological Evaluation Scale (NES)

The NSS total score and sub-scores for each of the factors were calculated. Two assessors were trained to perform the neurological assessment. The inter-assesor reliability of the NES assessment was established by the two assessors and jointly examined 20 independent subjects. The intra-class correlation coefficient (SPSS: two-way Mixed Effect Model, confidence interval=95%) was 0.90 [0.77–0.95].

4.2.2 Neuroimage Procedures

To explore the abnormalities in the connectivity of the default mode network a 15 minute brain functional magnetic resonance during Resting State was performed. Because the aim was to explore the association between two very different clinical vulnerability markers (neurological soft signs and personality traits) with the abnormalities in the connectivity of the default mode network, we decided that functional MRI was during resting state instead of another functional task.

The total neuroimaging acquisition process also includes 5 minutes of diffusion tensor imaging acquisition. The structural neuroimages and diffusion tensor images were not analysed for this specific study.

4.2.3 Imaging data acquisition

Functional MRI images were acquired on a Philips Achieva 3T scanner equipped with an 8 head coil. For anatomical reference, a T1-weighted pulse sequence was employed using the following parameters:

- repetition time (TR) = 500 ms,
- echo time (TE) = 50 ms,
- fli angle (FA) = 8º,
- matrix size = 240 x 200
- slice thickness=1mm

for the structural acquisition. The sequence of functional images was a T2- weighted-gradient, single shot echo sequence (EPI) which allowed the functional volumes to be obtained, each comprising thirty 3mm thick slices (TR 3000 ms, TE: 35 ms, FOV=230 x 230 cm FA: 90º, gap = 1.0 mm, matrix size: 76 x 75). The acquisition process was completed in 94 subjects. In one patient with schizophrenia the acquisition was voluntarily ended early because of anxiety.

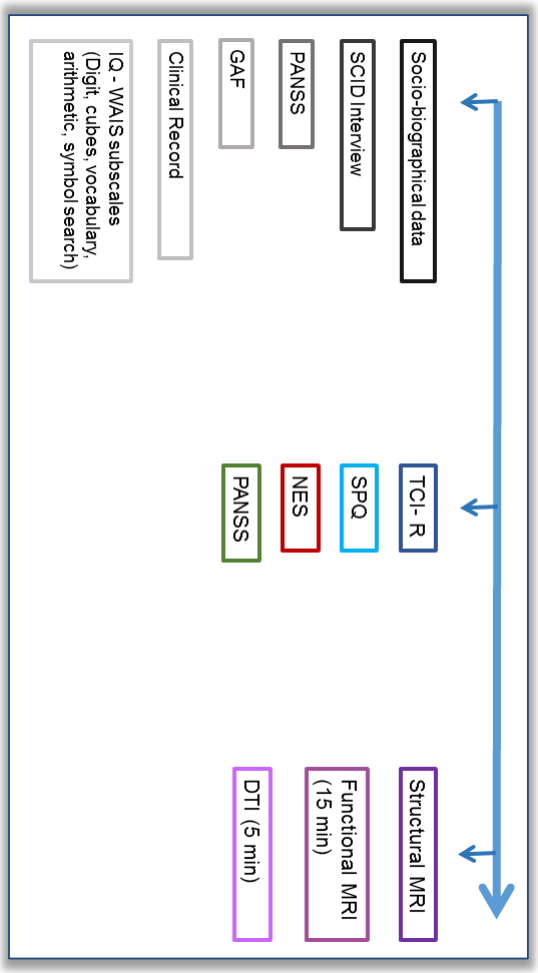


Figure 4.6: Summary of the procedures

5. Methods: Analysis

5.1 Variables

Independent Variables

Origin of the subjects (patients affected by schizophrenia, siblings of schizophrenia patients, healthy controls).

Main variables:

- Neurological Soft Signs: Total scores and motor coordination, sequencing of complex motor acts and sensory integration subscores.
- Temperament and Character:
    - Temperament in four dimensions: search for novelty; avoidance of harm; dependence of reward; and persistence.
    - Character is evaluated in three dimensions: self-direction; cooperativism; and self-transcendence.
- Schizotypy: Total scores and three subscores: cognitive-perceptual, interpersonal and disorganised. Changes in connectivity of the default mode in resting state network by Functional MRI

Covariables:

- The socio-demographic data was collected using a form, with questions about age, sex, number of siblings, years of study and socio-economic level (Hollingshead Readlich Scale) (Nunes, 2010).

5.2 Clinical statistical analysis

Clinical and behavioural data were analysed with the SPSS 20 (Statistical Package for Social Sciences for Windows Rel 20 SPSS Inc, Chicago IL). Analysis of Variance (ANOVA) followed by the Bonferroni posthoc test were employed in order to perform a mean comparison for the quantitative data and the chi-squared test ($\chi 2$ –test) for the qualitative data.

First, univariate analyses of the sociodemographic data were performed. Differences in age and years of education were determined by the Analysis of Variance (ANOVA), and the *chi*-squared test was applied for gender differences. As there were statistical differences in years of education, it was added as a covariable in the rest of the analyses.

Total scores and sub scores of TCI-R. SPQ and NSS were analysed with the Levene test. Then, to study differences of personality and NSS between groups, and depending on the results on Levene tests, the analysis was performed with ANOVAs followed by the Bonferroni posthoc test or a Kruskal-Wallis test followed by Mann-Whitney U test, adding years of education as a covariate.

To determine the association of NSS and the temperament and character in patients with schizophrenia and their non-affected relatives in comparison to healthy controls including the entire population between the total NSS scores and sub-scores for the SPQ, adding years of education as a covariable.

To determine the association between NSS and the schizotypal personality traits in patients with schizophrenia and their non-affected relatives in comparison to healthy controls. Pearson correlations were performed using the entire population between the total NSS scores and sub-scores for the SPQ, adding years of education as a covariable.

Sample Size: Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 23 subjects are necessary for the first group and 23 in the second to recognise as statistically significant a difference

greater than or equal to 1 unit. The common standard deviation is assumed to be 1.2. It has been anticipated a drop-out rate of 0%.

Clinical statistical analysis

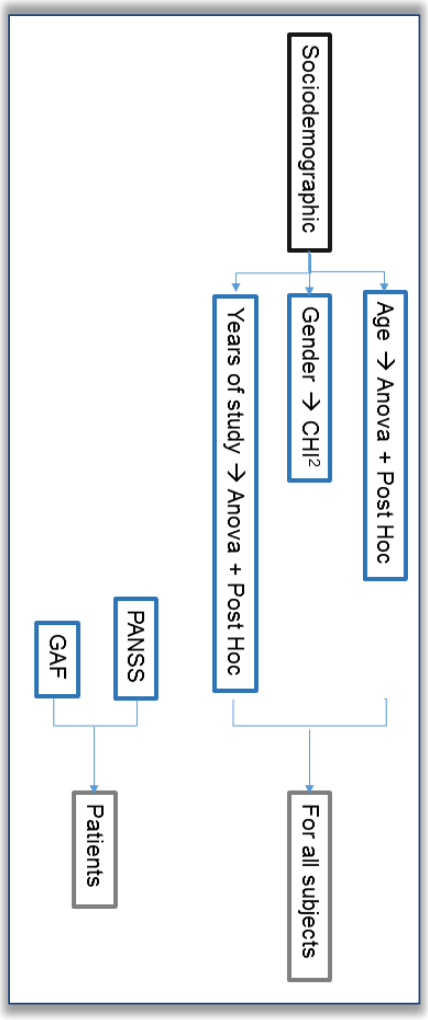
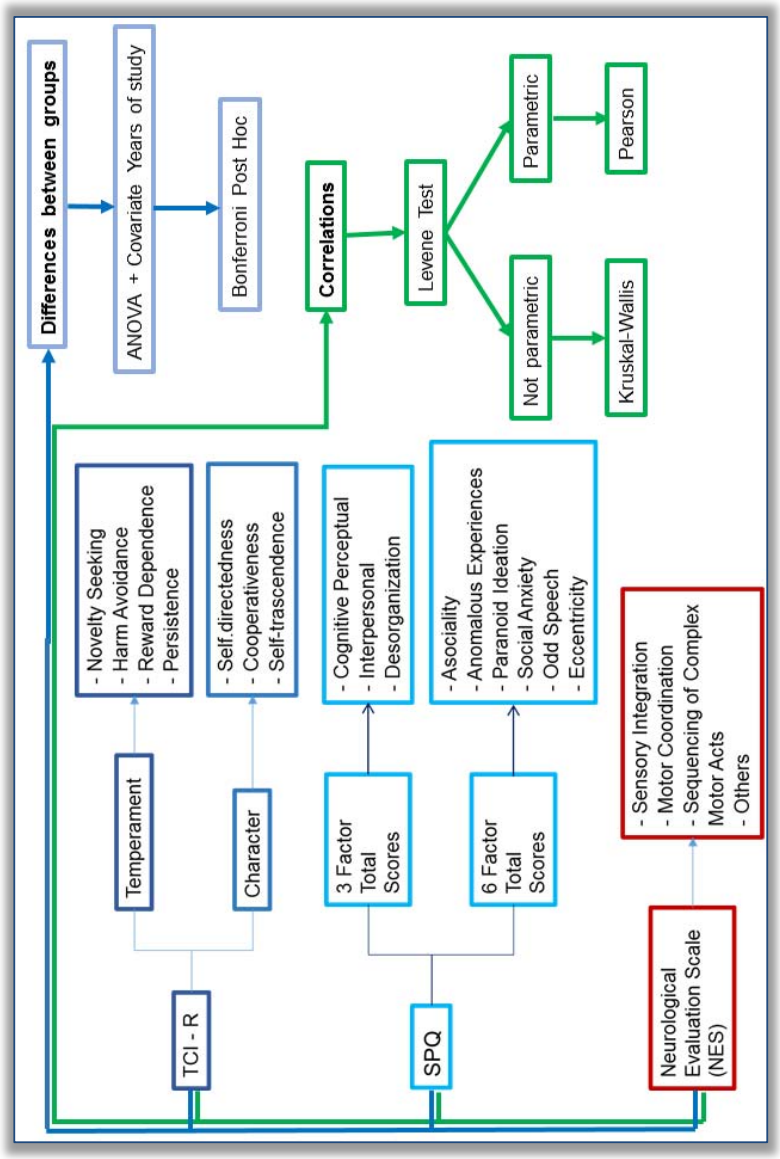


Figure 5.1: Sociodemographic and clinical analysis

Figure 5.2: Clinical statistical analysis



5.3 Neuroimaging Statistical Analysis

5.3.1 Image pre-processing

Functional MRI data were preprocessed with the software package SPM8 (Welcome Department of Imaging Neuroscience, London, United Kingdom). The pre-processing was performed with a bespoke script based on SPM and Matlab functions. After the scripts, 10 random images were also pre-processed manually to confirm the precision of the script.

Preprocessed steps:

0) Ensure image quality

1) **Slice time correction**: Correct for the acquisition time of the slice.

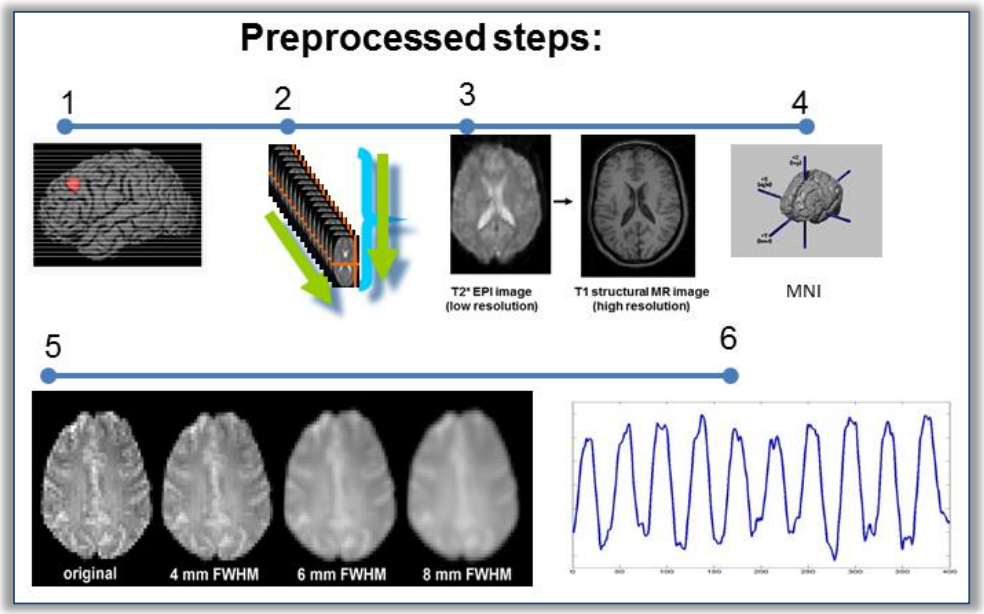
2) **Motion correction/Realign**: Correct the head movements inside the scanner.

3) **Coregister**: Matching images of the same subject but different modalities.

4) **Spatial normalization**: Normalize/standardize. Modify the shape/ size of a brain to match the atlas of a standardized brain.

5) **Spatial filtering/smooth**: Smooth/blur images.

6)**Temporal filtering**: Remove or preserve different frequency components present in the signal.

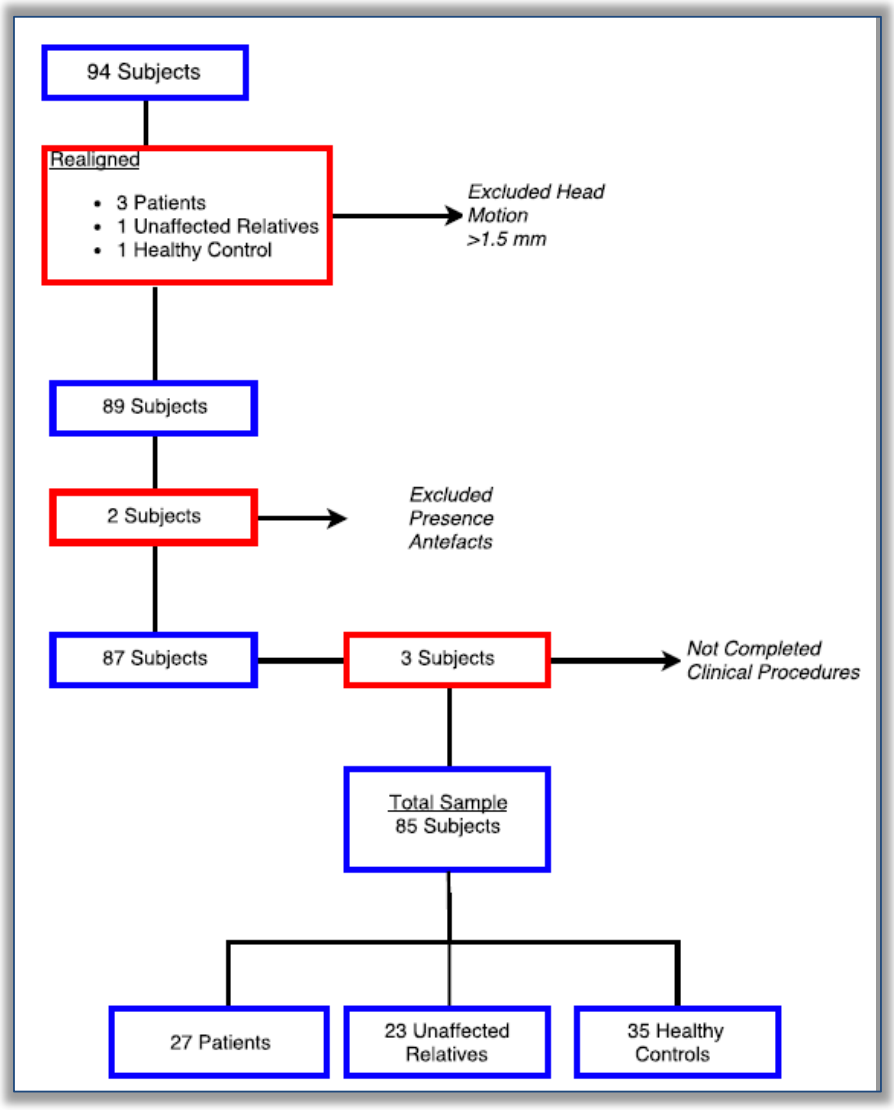


All-time series were converted from Dicom into the statistical parametric mapping SPM8 format. Image preprocessing and statistical analysis were performed using SPM8 (and custom software (spm8w, Dartmouth College) implemented in Matlab 9 (The Mathworks Inc. USA). First, the anatomical scan was rigid-body transformed to match

the first functional volume. Functional images were **realigned** to correct for motion-related artefacts. Subjects with head motion greater than 4 mm translation or 4 degrees rotation in any of the x, y or z directions were disregarded. This led to the exclusion of three patients with schizophrenia, one unaffected relative and one healthy control. Two additional subjects were excluded due to either error during fMRI acquisition or the presence of artefacts. In order to correct for between-scan movements, all volumes were realigned to the first volume. Following realignment, **coregistration** with the anatomical image was performed. Then, functional images were spatially normalised **(**linear and non-linear transformations) into the Montreal Neurological Institute (MNI) reference system, generating normalization parameters, which were applied to all functional images. For high accuracy filtering of the images a **smoothing** with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel filter was also applied. Specifically smoothing is used in fMRI studies to increase the signal-to-noise ratio and to compensate for inter-individual differences in the location of corresponding functional areas. For **temporal filtering**, all data were high-pass filtered (128 s) to remove low-frequency noise.

Finally, three additional subjects were excluded for not completing the clinical procedures. The final sample consisted of 85 subjects: 27 patients with schizophrenia, 23 unaffected relatives and 35 healthy controls.

Figure 5.3: Sample subjects for fMRI

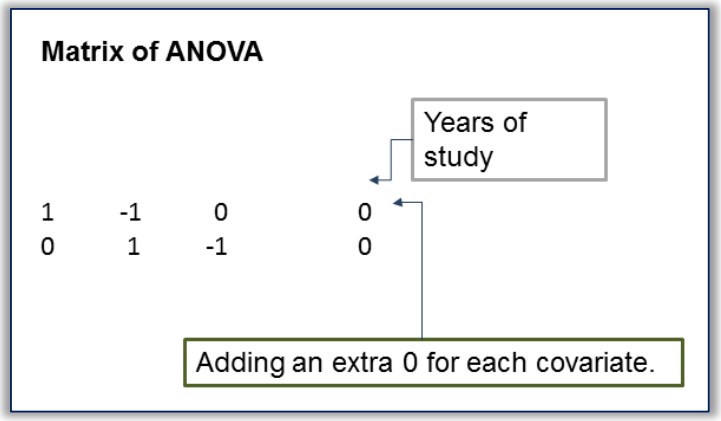


5.3.2 Second level analysis

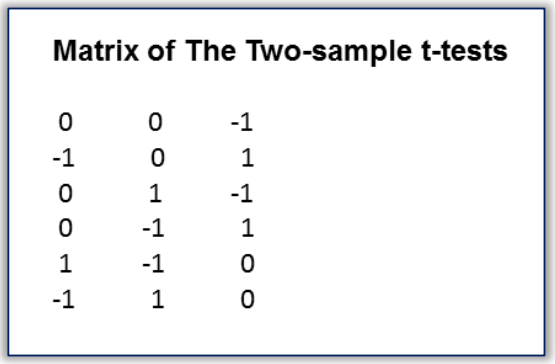
Functional MRI data were analysed with the software package SPM12 (Welcome Department of Imaging Neuroscience, London, United Kingdom). The General Linear Model (GLM) matrix design included

the correlation with the total scores or neurological soft signs. Age and years of study were included as covariables.

Following the individual preproccesing analyses mentioned above, and after seed-based or independent component anaylisi (ICA) was performed, a second-level group analysis was conducted using SPM. To find the differences between the three groups, an ANOVA was performed using the following contrast:



As a posthoc analysis of the ANOVA, Two-sample t-tests were performed in order to compare the differences in the functional connectivity between groups. The two-sample t-tests included three single comparisons between: patients and unaffected relatives, patients and controls, and unaffected relatives and controls.



Additionally, correlations between funtional connectivity within the DMN and clinical data (items from the Neurological soft signs, harm avoidance, persistence and selfdirectness) were conducted using SPM.

5.3.1.1 Region-of-interest analysis

To detect the abnormalities in neuronal connectivity in schizophrenia, a region-of-interest analysis of the areas that compose the default mode network was performed. A whole-brain exploration was performed with a threshold of $p < .05$ corrected for multiple comparisons using the false discovery rate (FDR; Genovese, Lazar, & Nichols, 2002). The CONN- FMRI Toolbox v1.2 was used to create individual subject seed-to-voxel connectivity maps, to the corresponding seeds of the default mode network. ANOVA with Extend P FEW- corrected ($p<0.01$) to evaluate differences between the three groups. Then a *Post-hoc* analysis (Voxel-vise FDR corrected $p<0.05$) with Extent P FWE- corrected was performed.

Mean iFC values in clusters showing significant group differences were extracted to examine their relationship with clinical measures.

5.3.2 Independent component analysis

Pre-processed images were subjected to spatial ICA, employing the Group ICA fMRI Toolbox (GIFT v3.0a; http://mialab.mrn.org/software/), performed in three stages:

(1) Principal component analysis (PCA) was employed first to reduce the dataset at subject level to 30 components, and then to reduce it to 20 components at group level. Subject-level PCA allows preservation of differences between subjects at the same time that it emphasises the similarities between subjects by projecting data into a common space; this allows for the acquisition of mean data for each subject and renders the data computationally tractable. With group level PCA, data

are further reduced into a set number of components and independent group spatial maps.
(2) The infomax algorithm was used to decompose the reduced dataset into maximally independent component images.
(3) Back reconstruction of the components was performed.

After these analyses, a spatial mask of the default mode network avaible in the GIFT software was applied and then the component with the maximum spatial correlation with this template was selected as the default mode network component of our sample. This component was exported to SPM 12 for the second level analyses.

To test the effect of group membership on intrinsic functional connectivity (iFC) of the selected default mode network component, one-way ANOVA models controlling for age were conducted in SPM12. A grey matter mask was used from the SPM as an inclusive mask for all comparisons. Significant main effects of groups were followed up with pairwise comparisons.
Results were interpreted at a voxel-wise threshold of $p < 0.001$ uncorrected and a cluster-wise threshold of $p < 0.05$ FWE corrected, with a minimum cluster size of 50 contiguous voxels.

6. Results

6.1 Clinical Results

6.1.1 Sociodemographic Characteristics

The study was conducted on 31 patients with schizophrenia, 24 unaffected relatives of patients and 40 controls. In total two patients and two controls were excluded because they did not complete the entire clinical and neuroimaging process. No significant differences between groups were observed regarding age or gender; although patients with schizophrenia and unaffected relatives showed significantly fewer years of education than controls (Table 6.1).

Table 6.1 Demographic characteristics in healthy controls, unaffected relatives and patients with schizophrenia

	Healthy Controls	Unaffected Relatives	Patients	p
	n=38	n=24	n=29	
Mean Age (years) ± SD	36.47 ± 7.68	40.92±10.32	37.97±7.13	0.16
Gender (M/F)	18/20	11/13	16/13	0.71
Mean school Level (years) ± SD	12.81±1.73	11.37±2.56	10.00±2.80	<0.05*

6.1.2 Personality

6.1.2.1 Temperament and Character

Table 6.2 Temperament and Character scores in healthy controls, unaffected relatives and patients with schizophrenia

		Healthy Controls n=38	Unaffected Relatives n=24	Patients n=27	F	p
Temperament						
	Harm Avoidance (mean ± SD)	86.18 ± 10.67	101.08 ± 23.31	109.48 ± 16.29	16.60	<0.01 *
	Reward Dependence (mean ± SD)	108.03 ± 12.32	100.08 ± 15.02	99.52 ± 19.94	3.03	<0.05 *
	Novelty Seeking (mean ± SD)	103.97 ± 9.62	102.81 ± 14.66	96.56 ± 13.57	2.94	>0.05
	Persistence (mean ± SD)	114.45 ± 17.16	104.33 ± 26.26	98.81 ± 18.67	5.10	<0.01 *
Character						
	Self-Directedness (mean ± SD)	156.13 ± 18.06	141.75 ± 22.68	137.15 ± 24.21	7.09	<0.01 *
	Cooperativeness (mean ± SD)	145.24 ± 14.17	135.63 ± 14.29	135.37 ± 21.33	3.80	<0.05 *
	Self-Transcendence (mean ± SD)	56.95 ± 16.24	56.58 ± 13.28	63.52 ± 21.56	1.39	>0.05

Table 6.2 shows the scores obtained for each temperament and character dimension in patients, unaffected relatives and healthy controls.

Harm Avoidance scores were significantly different between the groups [F (2,89) = 16.60, p<0.01]. Subsequent post-hoc analysis revealed that patients with schizophrenia and unaffected relatives obtained significantly higher scores on harm avoidance than controls, and patients showed significantly higher scores than relatives (Fig.6.1).

In addition, significant differences between the groups were observed in Reward Dependence [F (2,89) =3.03, p<0.05] and persistence [F(2,89) =5.10, p<0.01] scores. The post-hoc test revealed that patients obtained significantly lower Reward Dependence scores than controls and both patients and unaffected relatives had lower persistence scores than controls. No significant differences between groups were observed for novelty seeking scores (Fig.6.1).

Figure 6.1: Temperament Scores

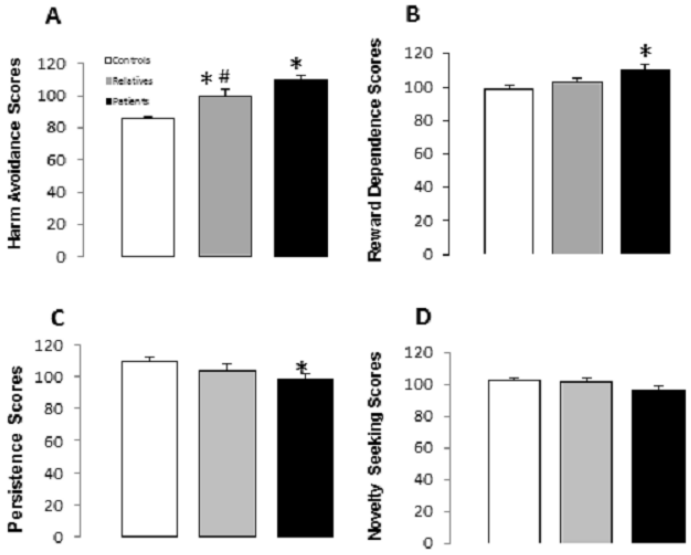


Figure 6.1. Temperament scores in controls, unaffected relatives and patients with schizophrenia. Harm avoidance (A), Reward dependence (B), Persistence (C) and Novelty seeking (D) scores. The data are represented as mean + SD. * p<0.05 vs controls; # p<0.05 vs relatives.

Figure 6.2: Character Scores

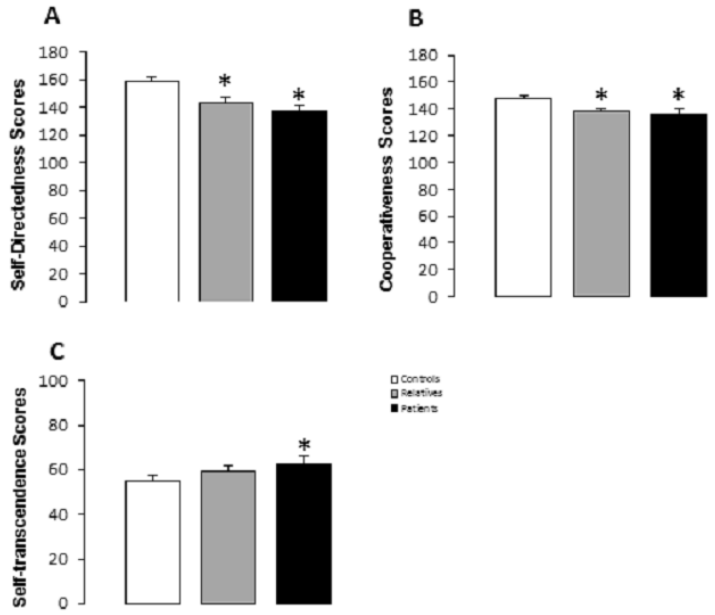


Figure 6.2. Character scores in controls, unaffected relatives and patients with schizophrenia. Self-directedness (A), Cooperativeness (B) and Self-transcendence (C) scores. The data are represented as mean + SD. * $p<0.05$ vs controls

Table 6.2 shows the scores obtained for each character dimension in controls, unaffected relatives and patients. Significant differences between groups were observed in self-directedness, cooperativeness and self-transcendence scores. A subsequent subgroup analysis revealed that both patients and relatives obtained significantly lower scores on self-directedness and cooperativeness than the controls. In addition, no significant differences were observed in self-directedness or cooperativeness scores between patients and relatives. Finally, significantly higher self-transcendence scores were observed in patients with schizophrenia than in the controls.

6.1.2.2 Schizotypal personality

Table 6.3 SPQ scores in healthy controls, unaffected relatives and patients with schizophrenia

		Healthy Controls n=38	Unaffected Relatives n=24	Patients n=25	F	p
3 Factors	Cognitive-Perceptual (mean ± SD)	1.45 ± 2.47	8.46 ± 6.81	12.28 ± 8.10	19.23	<0.001*
	Interpersonal (mean ± SD)	2.68 ± 3.07	11.21 ± 6.65	15.12 ± 6.78	30.15	<0.001*
	Desorganization (mean ± SD)	0.92 ± 1.51	3.96 ± 3.77	5.88 ± 4.34	14.54	<0.001*
	Total	5.05 ± 6.16	23.63± 15.10	30.81 ± 18.92	27.71	<0.001*
6 Factors	Associability (mean ± SD)	1.50 ± 2.11	5.67 ± 4.62	8.04 ± 4.82	15.87	<0.001*
	Anomalous Experiences (mean ± SD)	0.95 ± 1.49	4.08 ± 4.07	5.88 ± 4.89	11.55	<0.001*
	Paranoid Ideation (mean ± SD)	0.61 ± 1.17	3.96 ± 3.71	6.12 ± 4.07	18.04	<0.001*
	Social Anxiety (mean ± SD)	1.26 ± 1.33	3.25 ±2.36	4.40 ± 2.55	13.2	<0.001*
	Odd Speech (mean ± SD)	0.74 ± 1.03	2.25 ± 1.85	2.72 ± 1.90	9.41	<0.001*
	Eccentricity (mean ± SD)	0.34 ± 0.91	1.83 ± 2.35	2.88 ± 2.79	9.13	<0.001*

In respect of the SPQ 6 Factors, in the Table 6.3, is shown that in Asociality and Anomalous Experiences, there is a significant difference between healthy controls vs patients or unaffected relatives, but there is no significant difference between patients and unaffected relatives. In the case of Paranoid Ideation, there is significant difference between the three groups: patient vs healthy controls, unaffected relatives vs healthy controls, and unaffected relatives vs patients. In the other Factors (Social Anxiety, Odd Speech, and Eccentricity), there is significant difference between patients vs healthy controls, and

unaffected relatives vs healthy controls. Also, in the Total SPQ 6 factors, there is a significant difference between all groups: patients vs healthy controls, unaffected relatives vs healthy controls, and unaffected relatives vs patients

On the other hand, about SPQ 3 Factors, the Table 6.3 shows that in the Cognitive Perceptual factor, there is significant difference only between patients vs healthy controls and unaffected relatives vs healthy controls. In the Disorganization factor, the years of education do play a role in the differences, thus there is significant difference between patients and healthy controls, and unaffected relatives and healthy controls, after considering the effect of years of education. Also, in the Interpersonal factor and in the Total SPQ 3, there is significant difference between all groups: patient vs healthy controls, unaffected relatives vs healthy controls, and unaffected relatives vs patients.

6.1.3 Neurological soft signs

Table 6.4 NES scores in healthy controls, unaffected relatives and patients with schizophrenia

Neurological Soft Sign scores	Healthy Controls	Unaffected Relatives	Patients	F	P
	n=38	n=24	n=29		
Motor Coordination (mean ± SD)	1.16 ± 1.05	2.54 ± 2.55	3.83 ± 2.22	15.87	<0.001*
Sensory Integration (mean ± SD)	1.18 ± 0.93	1.67 ± 0.92	3.03 ± 2.28	13.27	<0.001*
Sequencing of complex Motor Acts (mean ± SD)	0.84 ± 1.22	4.29 ± 1.55	4.31 ± 1.81	60.87	<0.001*
Others (mean ± SD)	1.50 ± 1.66	2.42 ± 2.00	5.79 ± 6.44	38.79	<0.001*
Total NES(mean ± SD)	4.68 ± 3.35	10.92 ± 3.87	16.97 ± 6.44	56.51	<0.001*

Significant differences between groups were observed for the total NSS scores [F(2,89) =16.97, p<0.001]. A subsequent post-hoc analysis revealed significantly higher NSS scores in both unaffected relatives and patients, compared with the control subjects. In addition, patients showed higher total NSS scores than unaffected relatives (Fig. 6.4). Scores obtained in each NSS domain for the three groups are shown in Table 6.4. Significant differences between groups were observed for each of the NSS sub-scores. Post-hoc analyses revealed significantly higher scores in Motor Coordination, Sensory Integration in patients and relatives, as compared with the controls. In addition, patients showed higher scores than relatives in both of these NES sub-scores. With respect to Sequencing of Complex Motor Acts, patients and relatives also showed higher scores than control subjects, while no significant differences were observed between patients and relatives. For Sensory Integration, higher scores were observed only in patients compared with the control group.

Figure 6.3: Neurological Soft Signs Scores

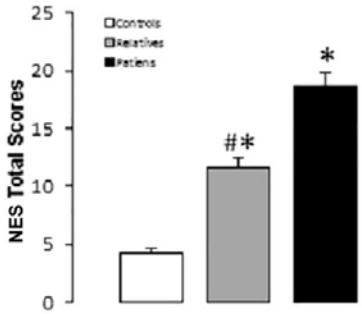


Figure 6.3. Total neurological soft signs (NSS) scores in controls, unaffected relatives and patients with schizophrenia. The data are represented as mean + SD. * p<0.05 vs controls; # p<0.05 vs relatives.

6.1.4 Association between personality and neurological soft signs

Table 6.5 shows the Pearson coefficients obtained for correlations between NES scores and temperament and character scores for the entire population studied. In terms of temperament, total NES scores were positively correlated with harm avoidance, while a negative correlation was observed between total NES, novelty seeking and persistence scores. When each temperament dimension was analyzed separately, harm avoidance scores correlated significantly with Sensory Integration, Motor Coordination and Sequencing of Complex Motor Acts scores. For persistence, significant negative correlations were observed with Motor Coordination, Sensory Integration, Sequencing of Complex Motor Acts and involuntary movements. Finally, a positive correlation was observed between reward dependence and involuntary movements. Novelty seeking scores were negatively correlated with Sensory Integration. With regards to character, total NES scores were negatively correlated with self-directedness and cooperativeness. For the individual character domains, self-directedness was negatively correlated with Motor Coordination and Sequencing of Complex Motor Acts scores, while cooperativeness was negatively correlated with Sensory Integration, Sequencing of Complex Motor Acts and Motor Coordination scores. No significant correlations were observed between self-transcendence and total NES scores, although a positive correlation was present with Motor Coordination.

Table 6.5: Pearson correlation between Temperament and NES

	Harm Avoidance		Dependence Reward		Novelty Seeking		Persistence	
	cc	p	cc	p	cc	p	cc	p
Sensory Integration	0.26	<0.01	-0.12	0.22	-0.14	0.19	-0.25	<0.01
Motor Coordination	0.39	<0.001	-0.24	<0.05	-0.20	<0.05	-0.22	<0.05
Sequencing of complex Motor Acts	0.33	<0.001	-0.17	0.09	-0.11	0.27	-0.27	<0.01
Others	0.21	<0.05	-0.09	0.37	-0.16	0.11	-0.14	0.18
Total NSS	0.38	<0.001	-0.20	<0.05	-0.20	<0.05	-0.27	0.27

cc: Pearson's Correlation coefficient

A positive correlation was found between Harm Avoidance, all subscores and total score of the NES. Specifically, Motor Coordination, Sequencing of complex Motor Acts and Total scores, show a higher correlation. Figure 6.4 shows how this correlation is maintained when covariating it with years of education. This figure also shows each subject and its group of origin (patients, unaffected relatives, healthy controls) in a differentiated way.

Figure 6.4: Correlation between Harm Avoidance and NES covariated with years of education

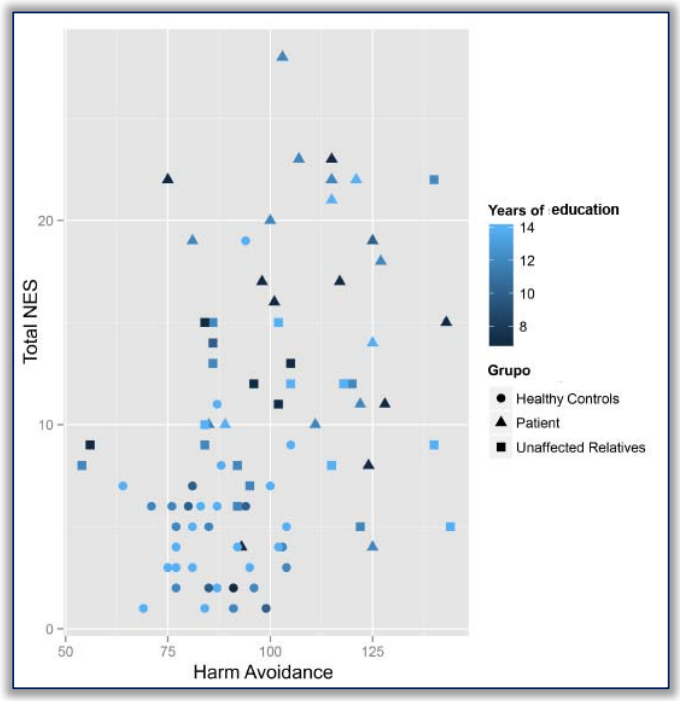
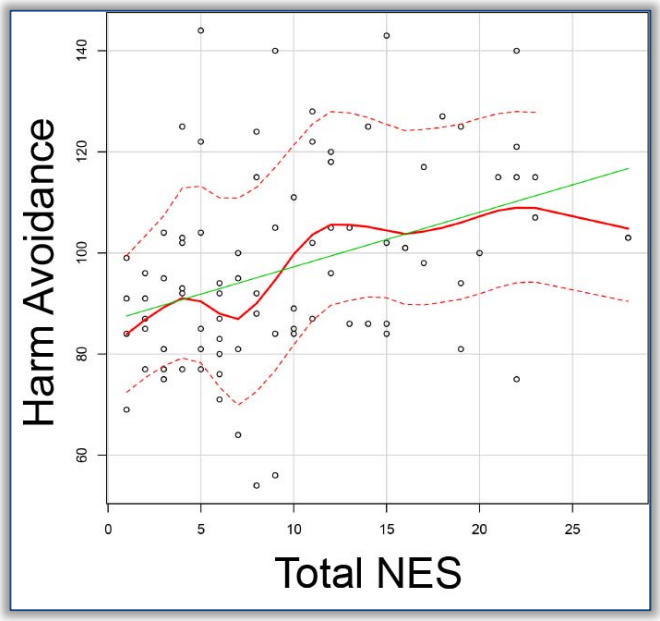


Figure 6.5: Correlation between Harm Avoidance and NES



A weak negative correlation was found between Persistence and the subscores of Sensory Integration, Motor Coordination and Sequencing of Complex Motor Acts.

Table 6.6: Pearson correlation between Character and NES

	Self-Directedness		Cooperativeness		Self-Transcendence	
	cc	p	cc	p	cc	P
Sensory Integration	-0.10	>0.05	-0.17	>0.05	-0.08	>0.05
Motor Coordination	-0.35	<0.001	0.32	<0.001	0.07	>0.05
Sequencing of Complex Motor Acts	-0.27	<0.05	-0.22	<0.05	0.06	>0.05
Others	-0.12	>0.05	-0.24	<0.05	-0.00	>0.05
Total NES	-0.27	<0.05	-0.31	<0.01	0.02	>0.05

cc: Pearson's Correlation coefficient

Table 6.6 shows that there is a negative correlation between Self-Directedness and Motor Coordination. In addition, there is a negative mid-low correlation with Sequencing of Complex Motor Acts and Total NES. Figure 6.6 showed that this correlation is maintained when

covariating it with years of education. It is also observed each subject and his group of origin.

However, there is no correlation between Self-Transcendence and any of the NES subscores. In addition, the subscore of Sensory Integration doesn't present correlation with any of the dimensions of the Character.

Figure 6.6: Correlation between Self-Directedness and NES, covariated with years of education

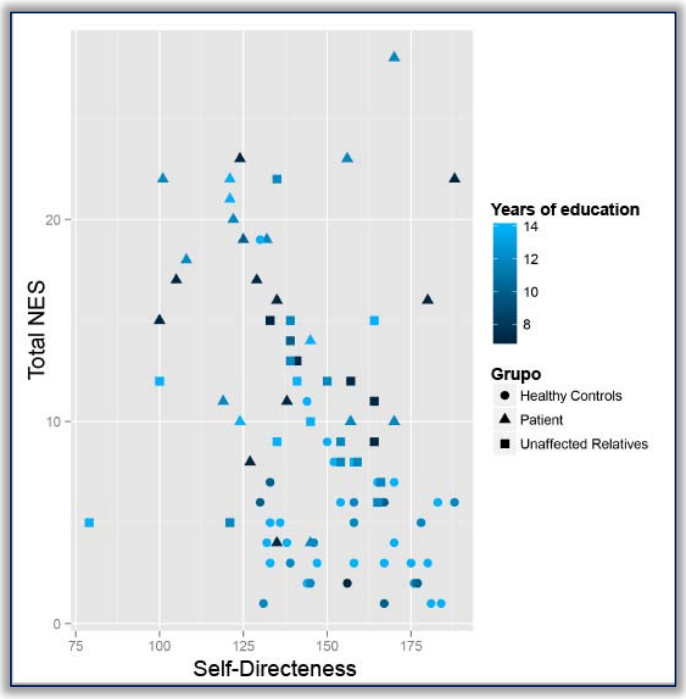


Figure 6.7: Correlation between Self-Directedness and NES

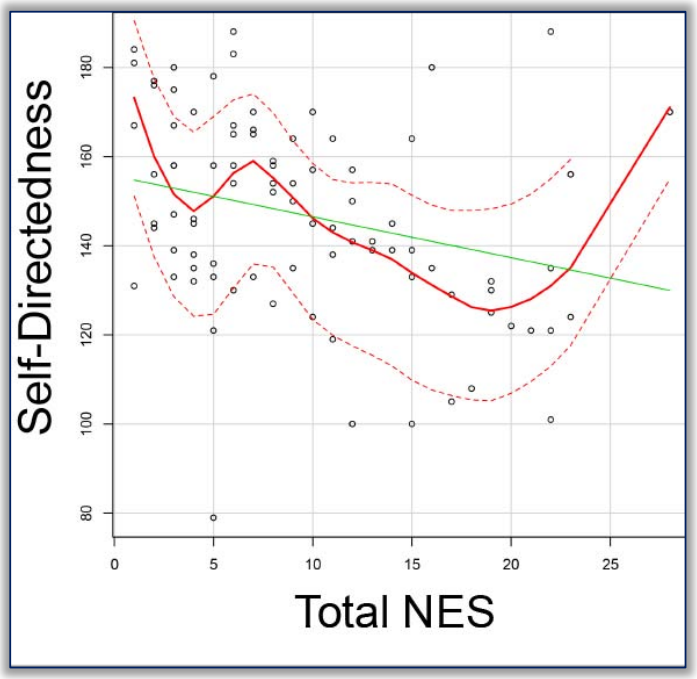


Table 6.6 also shows that there is a positive correlation between Cooperativeness and Motor Coordination, and a negative correlation between Cooperativeness and Total NES, as well as a negative mid-low correlation with the subscores of Sequencing of Complex Motor Acts and Others.

Table 6.7. Pearson Correlations between NES and SPQ 3 Factors

	Cognitive-Perceptual		Interpersonal		Desorganization		Total SPQ	
	cc	p	cc	p	cc	P	cc	p
Sensory Integration	0.32	<0.01	0.39	<0.001	0.37	<0.001	0.38	<0.001
Motor Coordination	0.36	<0.001	0.39	<0.001	0.33	<0.001	0.39	<0.001
Sequencing of complex Motor Acts	0.40	<0.001	0.42	<0.001	0.25	<0.05	0.37	<0.001
Others	0.45	<0.001	0.42	<0.001	0.42	<0.001	0.47	<0.001
Total NES	0.48	<0.001	0.53	<0.001	0.44	<0.001	0.53	<0.001

cc: Pearson's Correlation coefficient

In respect of SPQ 3 Factors, a positive correlation between the total scores and subscores and the NES scores and subscores. As Table 6.7 shows in the 3 Factors (Cognitive-Perceptual, Interpersonal, Disorganization), as well as in the Total SPQ, a moderately strong correlation with the Total scores and subscores of the NES.

Figure 6.8 shows how this positive correlation is maintained by covariating it with years of education. Each subject and their group of origin is also shown.

Figure 6.8: Correlation between Total SPQ 3 Factors and NES, covariated with years of education

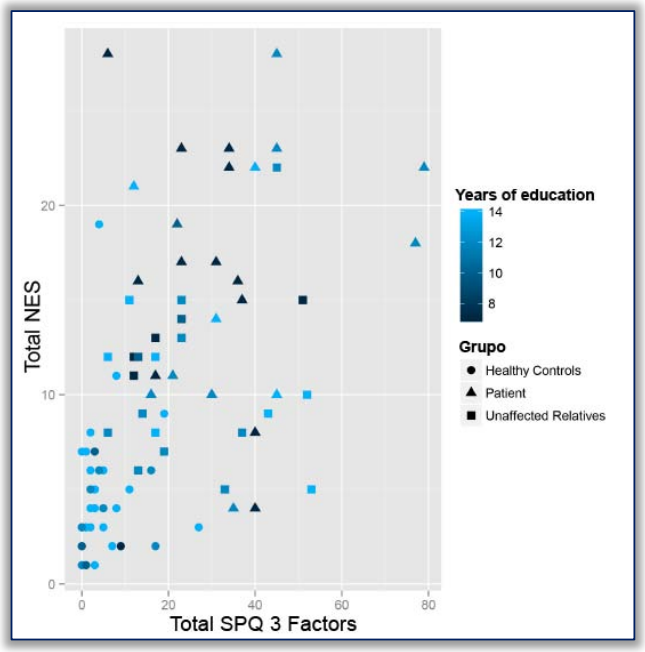


Figure 6.9: Correlation between Total SPQ 3 Factors and NES

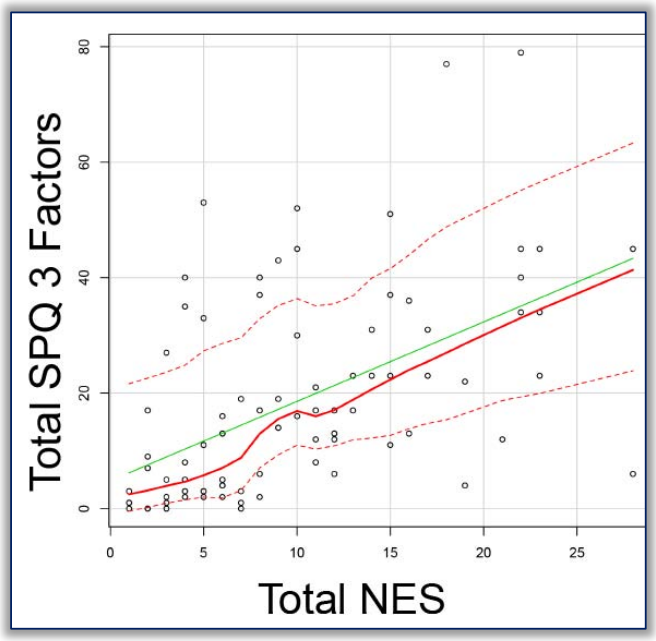


Table 6.8. Pearson Correlations between NES and SPQ 6 Factors

	Sensory Integration		Motor Coordination		Sequencing of complex Motor Acts		Others		**Total NES**	
	cc	p	cc	p	cc	P	cc	p	cc	p
Associability	0.36	<0.001	0.42	<0.001	0.32	<0.01	0.67	<0.001	0.40	<0.001
Anomalous Experiences	0.35	<0.001	0.32	<0.01	0.25	<0.05	0.47	<0.001	0.45	<0.001
Paranoid Ideation	0.29	<0.01	0.38	<0.001	0.27	<0.05	0.48	<0.001	0.47	<0.001
Social Anxiety	0.43	<0.001	0.38	<0.001	0.29	<0.01	0.36	<0.001	0.46	<0.001
Odd Speech	0.25	<0.01	0.34	<0.001	0.21	<0.05	0.36	<0.001	0.38	<0.001
Eccentricity	0.33	<0.01	0.36	<0.001	0.17	<0.05	0.39	<0.001	0.41	<0.001
Total SPQ 6 factors	0.40	<0.001	0.43	<0.001	0.30	<0.01	0.50	<0.001	0.53	<0.001

cc: Pearson's Correlation coefficient

As shown in Table 6.8, there is a positive correlation between all 6 SPQ Factors and NES subscores. The subscore of Sensory Integration presents a higher correlation with the Factors of Social Anxiety and Total SPQ. The subscore of Motor Coordination has a higher correlation with the Factor of Associability and Total SPQ. In the case of Sequencing of Complex Motor Coordination, there is a moderately low correlation with the 6 Factors of SPQ, with a higher correlation to Associability and Total SPQ. The subscore of Others is the one with

the highest correlation to Factors, being higher with the Associability and Total SPQ. For the Total NES, the strongest correlations are with the Total SPQ, and with the Factors of Paranoid Ideation, Social Anxiety and Anomalous Experiences.

As shown in Figure 6.10, the correlation between Total NES and Total SPQ is maintained by covariating it with the years of education.

Figure 6.10: Correlation between Total SPQ 6 Factors and NES, covariated with years of education

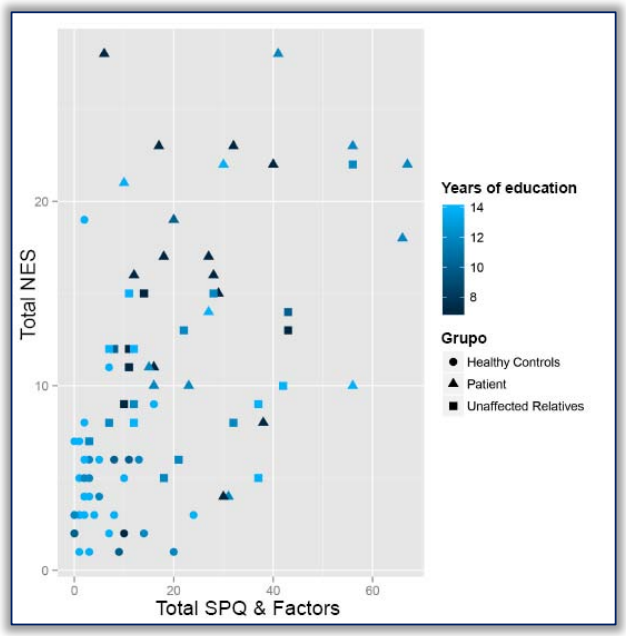
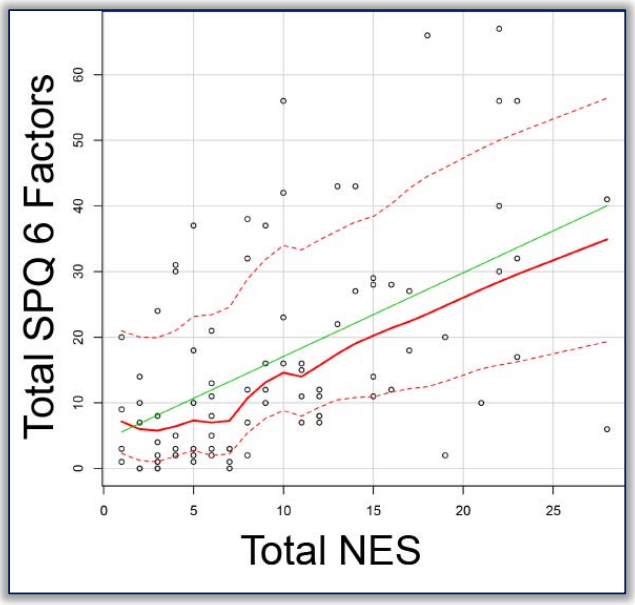


Figure 6.11: Correlation between Total SPQ 6 Factors and NES


Total SPQ 6 Factors
0
10
20
30
40
50
60
0
5
10
15
20
25
Total NES

6.2 Neuroimaging Analysis

6.2.1 Region-of-interest analysis

Table 6.9. ROIS Analysis of the Default Mode Network

Seed	3 Groups	Patients ¥	Relatives ¥	Patients £	Peak coordinates (MNI)		
					X	Y	Z
Medial Prefrontal Cortex R	si	si	si	0	9	56	31
Posterior Cingulate Cortex	si	si	si	0			
Precuneus L	si	si	si	0	-15	-59	33
Cortex Cingulado Anterior R	si	0	si	si			
Cortex Cingulado Anterior L	si	0	0	si			
Angular Gyri L	0	si	si	0			
Inferior Parietal Lobe R	si	si	si	0	-48	-64	43
Dorso Lateral Prefrontal Cortex	si	si	si	0			
Angular Gyri R	0	si	0	si			

¥: vs Controls £: vs Unaffected Relatives

Table 6.9. ROIS Analysis of the Default Mode Network

Seed	3 Groups	Patients ¥	Relatives ¥	Patients £	Peak coordinates (MNI)		
					X	Y	Z
Medial Prefrontal Cortex R	si	si	si	0	9	56	31
Posterior Cingulate Cortex	si	si	si	0			
Precuneus L	si	si	si	0	-15	-59	33
Cortex Cingulado Anterior R	si	0	si	si			
Cortex Cingulado Anterior L	si	0	0	si			
Angular Gyri L	0	si	si	0			
Inferior Parietal Lobe R	si	si	si	0	-48	-64	43
Angular Gyri R	0	si	0	si			

¥: vs Controls £: vs Unaffected Relatives

In Table 6.9 we observed the different ROIS that were used to do SI voxel analysis in the DMN. It was found that in the case of the Medial Prefrontal Cortex R, the Posterior Cingulate Cortex, the Precuneus L and the Lower Parietal Lobe R, there are significant differences between the 3 groups, between patients and healthy controls, and

between unaffected relatives and healthy controls. No significant differences were found between patients and unaffected relatives.

Table 6.10. Differences of connectivity of precuneus (voxels covering)

	3 Groups	Patients ¥	Relatives ¥	Patients £
Left fusiform gyrus	239	357	–	–
Left dorsal posterior cingulate	53	–	50	–
Left somatosensorial association	138	66	33	–
Left–right supramarginal gyrus	62	60	20	–

¥: vs Controls £: vs Unaffected Relatives
Red: Hyperconnectivity

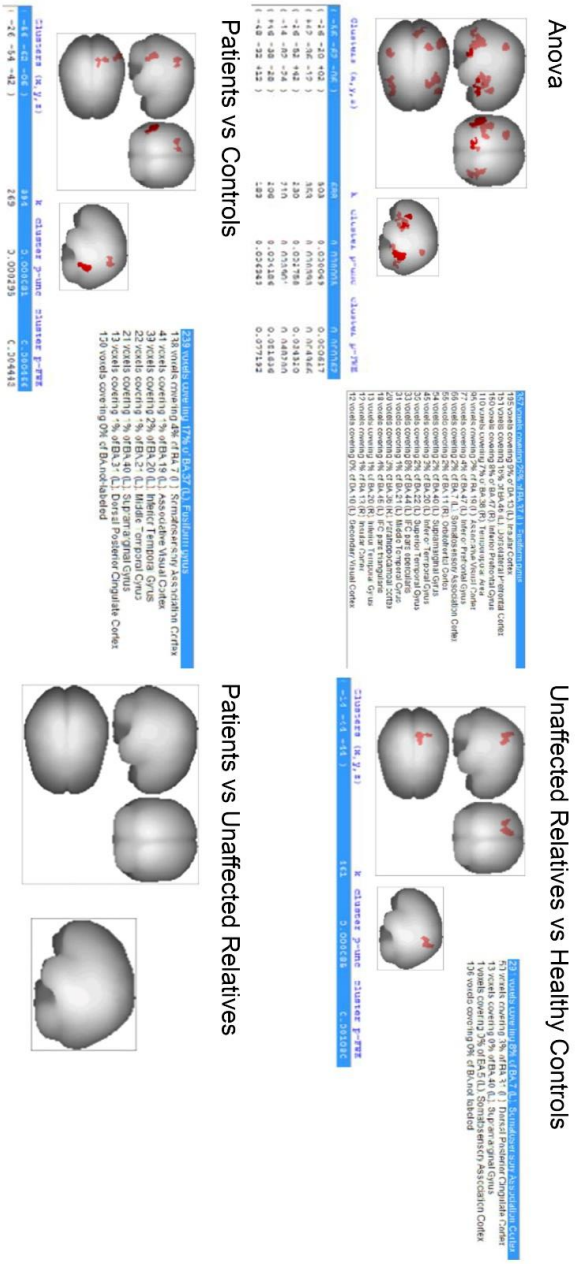


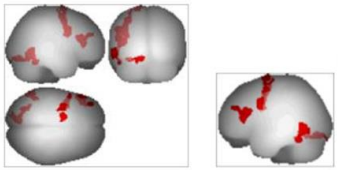
Figure 6.12. Connectivity of the Precuneus

In the Precuneus ROIS, we found that in the Left Somatosensory Association and the Left-Right Supramarginal Gyrus, there are

differences in connectivity between the 3 groups, and when doing a subgroup analysis, they present differences between patients and healthy controls and between unaffected relatives and healthy controls, but not in unaffected relatives and patients. In turn we found in the Left Fusiform Gyrus and the Left Dorsal Posterior Cingulate there are differences in connectivity between the 3 groups, in the Left Fusiform Gyrus there is greater connectivity between patients and healthy controls.

Figure 6.13. Connectivity of the Medial Prefrontal Cortex

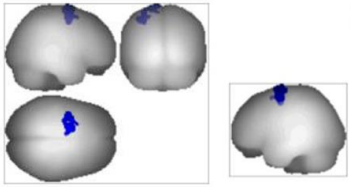
Anova



437 voxels covering 7% of BA 6 (L). Premotor Cortex
369 voxels covering 40% of BA 46 (L). Dorsolateral Prefrontal Cortex
220 voxels covering 7% of BA 9 (L). Dorsolateral Prefrontal Cortex
211 voxels covering 15% of BA 37 (L). Fusiform gyrus
98 voxels covering 3% of BA 18 (L). Secondary Visual Cortex
60 voxels covering 2% of BA 19 (L). Associative Visual Cortex
54 voxels covering 2% of BA 8 (L). Dorsal Frontal Cortex
38 voxels covering 2% of BA 20 (L). Inferior Temporal Gyrus
37 voxels covering 6% of BA 45 (L). IFG pars triangularis
33 voxels covering 2% of BA 21 (L). Middle Temporal Gyrus
28 voxels covering 1% of BA 10 (L). Anterior Prefrontal Cortex
5 voxels covering 1% of BA 17 (L). Primary Visual Cortex
1 voxels covering 0% of BA 36 (L). Parahippocampal cortex
630 voxels covering 0% of BA not labeled

Clusters (x,y,z)	k	cluster p-unc	cluster p-FWE
(-36 +00 +52)	728	0.000000	0.000004
(-50 +28 +20)	585	0.000001	0.000021
(-56 -58 -02)	403	0.000022	0.000344
(-10 -86 -16)	366	0.000042	0.000650
(-18 -04 +74)	139	0.004567	0.068348

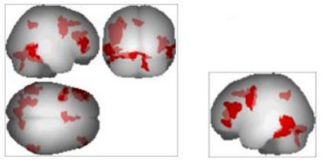
Unaffected Relatives vs Healthy Controls



336 voxels covering 0% of BA 6 (L). Premotor Cortex
338 voxels covering 0% of BA not-labeled

Clusters (x,y,z)	k	cluster p-unc	cluster p-FWE
(-32 -04 +56)	734	0.000001	0.000010

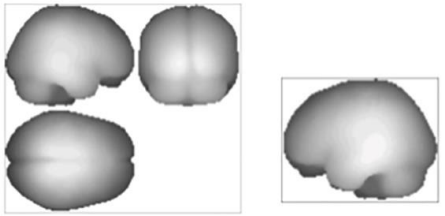
Patients vs Controls



686 voxels covering 10% of BA 6 (L). Premotor Cortex
554 voxels covering 60% of BA 46 (L). Dorsolateral Prefrontal Cortex
388 voxels covering 27% of BA 37 (L). Fusiform gyrus
334 voxels covering 11% of BA 9 (L). Dorsolateral Prefrontal Cortex
253 voxels covering 25% of BA 46 (R). Dorsolateral Prefrontal Cortex
207 voxels covering 15% of BA 37 (R). Fusiform gyrus
168 voxels covering 4% of BA 10 (L). Anterior Prefrontal Cortex
168 voxels covering 4% of BA 19 (L). Associative Visual Cortex
137 voxels covering 5% of BA 8 (L). Dorsal Frontal Cortex
111 voxels covering 3% of BA 18 (L). Secondary Visual Cortex
95 voxels covering 2% of BA 10 (R). Anterior Prefrontal Cortex
87 voxels covering 2% of BA 7 (L). Somatosensory Association Cortex
75 voxels covering 4% of BA 21 (L). Middle Temporal Gyrus
73 voxels covering 4% of BA 20 (R). Inferior Temporal Gyrus
64 voxels covering 13% of BA 44 (L). IFC pars triangularis
62 voxels covering 3% of BA 20 (L). Inferior Temporal Gyrus
57 voxels covering 4% of BA 32 (R). Dorsal anterior Cingulate Cortex
52 voxels covering 3% of BA 32 (L). Dorsal anterior Cingulate Cortex
51 voxels covering 2% of BA 8 (R). Dorsal Frontal Cortex

Clusters (x,y,z)	k	cluster p-unc	cluster p-FWE
(-10 -86 -16)	1002	0.000000	0.000001
(-50 +28 +20)	967	0.000000	0.000002
(-36 +00 +52)	931	0.000000	0.000003
(-56 -58 -02)	871	0.000000	0.000006
(+52 +48 +10)	483	0.000053	0.000692
(+58 -56 -12)	398	0.000175	0.002277
(+00 +18 +46)	373	0.000253	0.003282
(-26 -56 +42)	246	0.001883	0.024159
(-42 +42 -10)	218	0.003060	0.038967

Patients vs Unaffected Relatives



In the ROI of the Medial Prefrontal Cortex we found an increase in connectivity between the 3 groups with the Left Premotor Cortex, and there was also an increase in connectivity between patients and healthy controls. There is a decrease in connectivity between unaffected relatives and healthy controls.

For the other areas, there are only changes in connectivity between the 3 groups and also between patients and controls.

6.2.3 Independent component analysis

Two components with a fronto-parietal spatial scope were identified as the DMN following ICA.

One component was anterior and the other posterior. The anterior component encompassed regions of the medial prefrontal cortex and the posterior cingulate/precuneus, and the posterior DMN included the precuneus, bilateral inferior parietal cortex, left temporal cortex (including insula and medial temporal regions), subcortical structures (left thalamus).

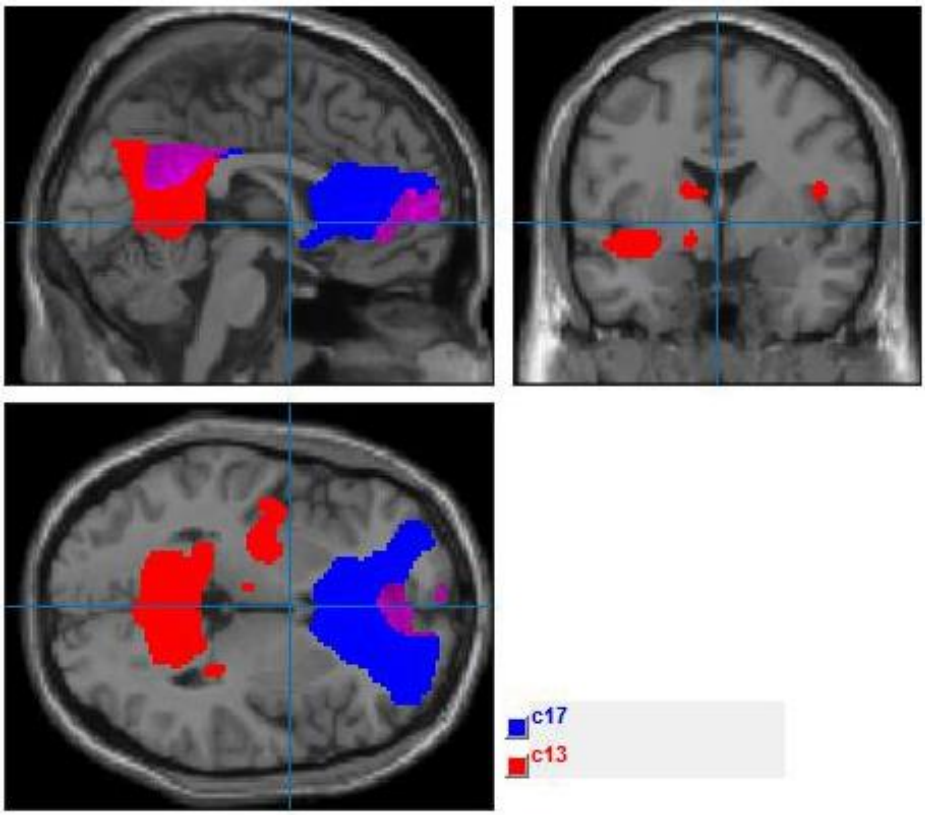


Figure 6.14 depicts the spatial maps for both the anterior and posterior DMN components for the whole sample.

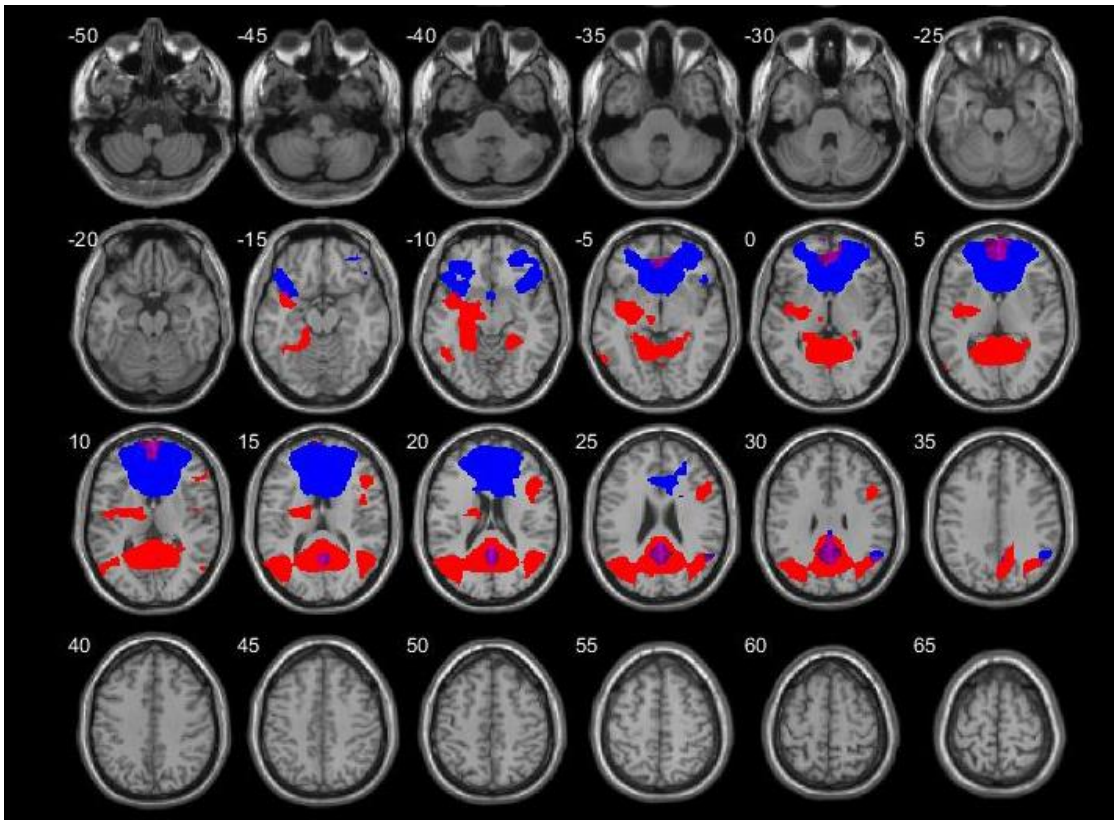


Figure 6.15 Transversal view the spatial maps for both the anterior and posterior DMN components for the whole sample.

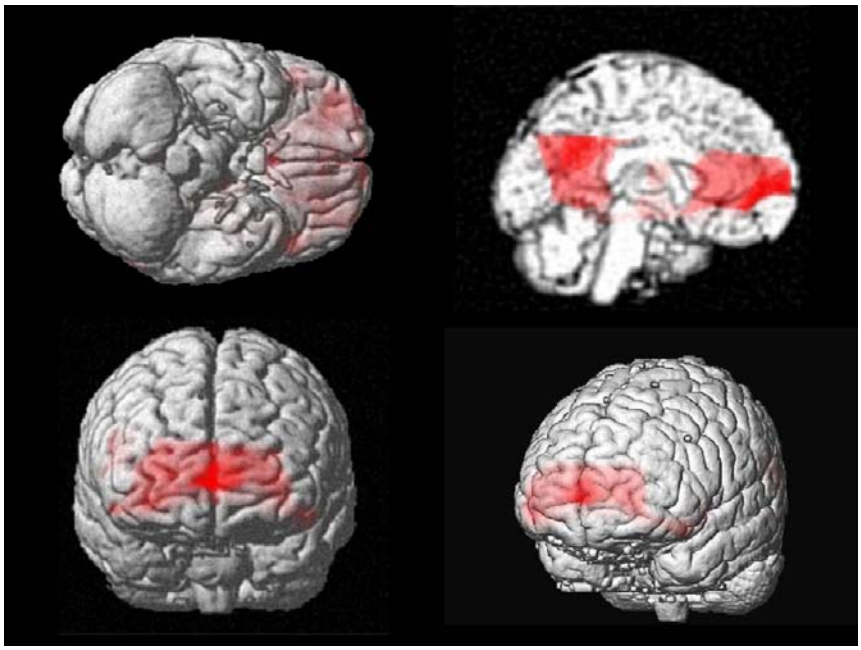


Figure 6.16 Tridimensional reconstructions of the anterior and posterior DMN components for the whole sample.

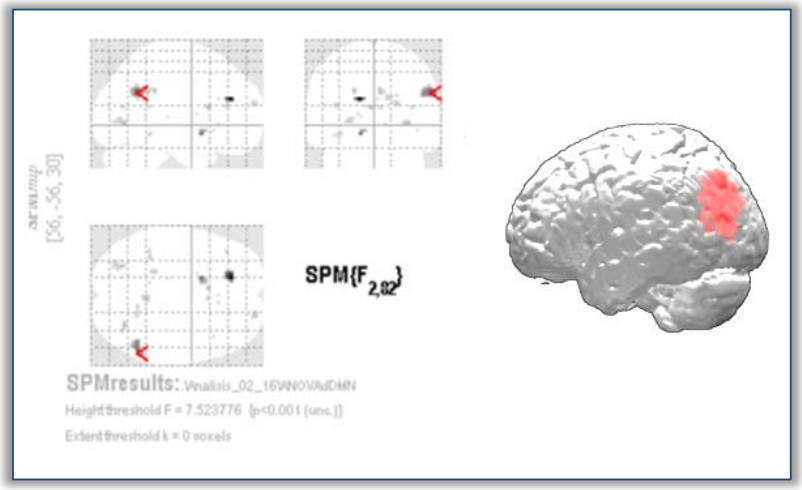


Figure 6.17 Left Parietal Cortex [56,-54,30]

A group effect was observed in a cluster in the lateral parietal cortex, part of the default mode network and related with the language network (F = 12.42, pFWE = 0.002, cluster size (k) = 88 voxels, Montreal Neurological Institute (MNI) spatial coordinates [56,-54,30], see Fig. (6.17). This corresponds to the parietal cortex, Brodmann area 39.

Pairwise comparisons showed an increase iFC within this region in patients and unaffected relatives in comparison to healthy controls (t = 5.30, p < 0.0001, k = 120, MNI [56,-54,30].

7. Discussion

7.1 Principal Findings

The clinical major finding in this study was that patients with schizophrenia and non-psychotic relatives display a unique profile of temperament and character that correlates with alterations in NSS.

Our most important findings are that patients with schizophrenia and the unaffected relatives present abnormalities in the connectivity of the Default Mode Network, specifically in the Precuneus and Medial Prefrontal Cortex, but also the connectivity with areas of the Fronto-Parietal Network. Specifically we found abnormalities in the Parietal Inferior Cortex that correlates with the Neurological Softs Signs in the whole sample. Also by a ROI analysis we found a hyper connectivity in the Dorso-Lateral Prefrontal Cortex in patients and in unaffected relatives, in comparison to healthy controls. The findings show how different functions such as motor coordination andsensory integrations are related to the personality traits involved with many different emotional and cognitive functions. The theory of Cognitive Dysmetria in schizophrenia could explain the diversity of symptoms associated with the illness.

7.2 Discussion of the principal clinical results

With respect to temperament and character, comparing personality traits and NSS between groups, both patients with schizophrenia and unaffected relatives obtained significantly higher scores on harm avoidance than controls, and patients showed significantly higher scores than relatives. Also patients and unaffected relatives had lower persistence, self-directedness, and cooperativeness scores than controls. In addition, no significant differences were observed in self-directedness or cooperativeness scores between patients and relatives. Finally, significantly higher self-transcendence scores were observed in patients with schizophrenia, compared to controls.

Studies in unaffected relatives have been essential to uncover new vulnerability biomarkers of schizophrenia. In this sense, several studies have provided evidence showing that particular personality features could be considered as possible schizophrenia-related endophenotypes (Smith, Cloninger, Harms, & Csernansky, 2009). In the current study it was found that unaffected relatives had significantly higher harm avoidance scores compared with the controls, but lower scores than patients with schizophrenia. In agreement with our data, Smith et al. (2009) found higher harm avoidance scores in siblings of patients with schizophrenia than in controls subjects, and another study reported that siblings are positioned between controls and patients with schizophrenia, in terms of temperament profile (Calvó de Padilla et al., 2006). In contrast, Bora and Veznedaroglu (2007) did not find differences in temperament between relatives of schizophrenic patients and the controls, although they did observe differences in harm avoidance between controls and relatives with high schizotypy. Together, these studies support the idea that high levels of harm avoidance may be associated with genetic vulnerability to schizophrenia, which, in turn, will interact with environmental and neurobiological influences to determine the expression of the disease.

According to Kim et al. (2011) and Hansenne et al. (2003), harm avoidance has been associated with D2/3 receptor availability in the associative and sensorimotor subdivisions of the striatum, high Mismatch Negativity and hypervigilant fear perception, suggesting abnormal sensory gating of aversive stimuli as a vulnerability variable in schizophrenia. Furthermore, a locus on chromosome 8p21 associated to schizophrenia showed a linkage to harm avoidance (Zohar et al., 2003).

With regards to character it was found that, similar to patients; unaffected relatives had significantly lower self-directedness and cooperativeness scores when compared to controls. Other studies have reported lower levels of self-directedness and cooperativeness in siblings with high schizotypy as compared to controls, and high levels were observed in siblings with low schizotypy (Bora & Veznedaroglu, 2007). One important aspect of the data in this study is that even though the unaffected relatives that participated in this study did not have familial ties to the patients with schizophrenia, they showed similar low levels of self-directedness and cooperativeness. It is well known that character is influenced more by environmental factors than temperament (Josefsson, Jokela, Cloninger, et al., 2013; Josefsson, Jokela, Hintsanen, et al., 2013). However, the data in this study agrees with other studies, such as Gillespie et al. 2003 and Josefsson et al. 2013, showing that character may also have a genetic component. Self-transcendence was higher in patients than in the control subjects, but not in relatives. These results are in agreement with other studies reporting elevated self-transcendence in patients (Glatt 2006; Smith et al., 2009). In contrast, Calvo de Padilla et al. (2006) found lower self-transcendence and cooperativeness in the relatives of patients with schizophrenia with respect to the controls. The discrepancies between studies could be due to the fact that the population used in the Calvo and Padilla study was an indigenous community living in a rural environment and not in an urban environment.

In accordance with previous studies, we found lower levels of persistence and reward dependence only in patients with schizophrenia as compared to controls. These findings endorse the hypothesis stating that high harm avoidance, low persistence and low reward dependence constitutes a temperament profile leading to social detachment, perseveration and schizotypy, when combined with a disorganized character profile that impairs emotional regulation (Smith et al. 2009; Bora & Veznedaroglu 2007).

Finally, several limitations of the study are acknowledged. The first is the small sample size used, even though the TCI-R scores and NSS scores were similar to those reported in larger samples in the literature (Smith et al. 2009; Mechri et al. 2010). The second limitation is the use of an estimate of IQ values as a selection criterion, but not as a covariate in the analysis. This issue may have been a potential confounding factor, since IQ has been previously associated with personality and with NSS.

In respect of schizotypy our results support the main findings. First, patients with schizophrenia did have higher scores than healthy siblings, both on the SPQ total scale score and on the three subscales (Cognitive, Perceptual, Interpersonal, and Disorganization), as we hypothesized at the outset. This was an expected finding which could only be related to the fact that schizotypal symptoms may represent attenuated expressions of the psychotic symptoms. These results are in agreement with previous research that has shown that the construct of SPD is genetically related to schizophrenia (Bolinskey et al., 2015) and therefore individuals who have high scores for SPD features have a higher risk of developing the illness (Webb & Levinson, 1993).

Some cognitive deficits and personality traits have been suggested as markers of disease vulnerability (Keshavan et al., 2010; Siever et al.,

2002). There is evidence that genetic predisposition to schizophrenia is present among the unaffected relatives of patients with schizophrenia and can produce traits "schizophrenia-like" observables in these families, even in the absence of frank psychosis (Bolinskey et al., 2015, 2017).

Studies in non-psychotic siblings are essential to find the genetic vulnerability markers. A high SPQ score is considered a vulnerability marker for possible development of schizophrenia. Several studies consistently found high rates of schizotypal traits among the biological relatives of schizophrenia patients(Barrantes-Vidal, Grant, & Kwapil, 2015; Webb & Levinson, 1993). In our study, both SPQ total score and subscales were significantly higher in unaffected siblings of patients with schizophrenia than in controls.

The addition of NSS in patients with schizotypal increases the predictive power of disease risk. Few studies have examined this relationship both in controls and in relatives of patients with schizophrenia, with controversial results. Bollini et al., 2007 examined these associations in first-degree relatives of patients with schizophrenia, and found that interpersonal and disorganized schizotypal dimensions were related to the overall NSS score and the sequencing of complex tasks engine sub-score in controls. Mechri et al., 2010 showed that the overall NSS score was correlated with the total SPQ score in both unaffected siblings and healthy controls and with the SPQ disorganization sub-score only in unaffected siblings of patients with schizophrenia. The lack of consistency between studies may be explained in part on the different ways to measure schizotypy different studies. It could also be influenced by the samples used. In our study, the NSS total score was correlated with the SPQ total score in both.

Searching for NSS in subjects having higher scores on measures of schizotypy can identify vulnerable subjects at a high riskof developing

schizophrenia. NSS excess in siblings of patients with schizophrenia compared with healthy controls and their associations with schizotypal dimension support the vulnerability model described by Meehl.

As reported previously in patients with schizophrenia (Bombin et al. 2003; Chen et al. 2005; Aksoy-Poyraz et al. 2011) and in unaffected relatives (Gourion, Goldberger, Olie, Lôo, & Krebs, 2004; Mechri et al., 2010), we found higher NSS in both groups as compared with the controls, confirming the hypothesis that NSS is a vulnerability marker for schizophrenia. In addition, these results agree with the idea that NSS segregate with the illness and may be a valid and useful endophenotype (Chan, Xu, Heinrichs, Yu, & Wang, 2010).

The association between personality characteristics and NSS has been studied separately in siblings, or in patients with schizophrenia, but there are no prior studies correlating NSS with personality traits in patients with schizophrenia, unaffected relatives and controls. Our correlational analysis, including all three groups, showed that subjects with higher NSS scores exhibited higher harm-avoidance and persistence scores, while they exhibited lower self-directness and cooperativeness. Two related studies have evaluated the association between NSS and schizotypal personality traits with contradictory results. Thus, Mechri et al. (2010), using the Schizotypal Personality Questionnaire (SPQ), showed that the overall NSS score was correlated with the presence of schizotypal traits in both non-psychotic siblings and controls, while no association was found between NSS and schizotypal dimensions in relatives of patients with schizophrenia, when the SPQ test was used (Bollini et al. 2007). The differences observed between these two studies, as well as the present work, could be due to the fact that they used a personality assessment tool based on outdated DSM III criteria. In this respect, one of the strengths

of this study is the use of the TCI-R scale, which is a comprehensive personality questionnaire that has been extensively validated in clinical practice and research (Fassino, Amianto, Sobrero, & Abbate Daga, 2013; Fresán et al., 2015). One of the advantages of the TCI-R is that it explores normal and pathological personalities in subjects with mental disorders and also in the general population (Cloninger et al. 2012; Josefsson et al. 2011; De Fruyt et al. 2006). Another advantage is that temperament and character domains have been associated with structural and functional changes in the brain (Laricchiuta et al., 2014; Lei et al., 2014; L Tuominen et al., 2013; Lauri Tuominen et al., 2012) and have been related to specific chromosomal regions (Serretti et al., 2008; Zohar et al., 2003) supporting the neurobiological substrate for this personality model (Yang et al., 2015). Another strength of the study is that the relatives of patients with schizophrenia had no familial ties to the patients used, thus decreasing the possibility that similar rearing would confound the results.

Our results reveal an association between these hypothesized vulnerability markers, as temperament (especially harm avoidance, reward dependence and persistence) and character (especially self-directedness and cooperativeness) correlated with the presence of NSS in the entire sample.

7.3 Theory of Cognitive Dysmetria in schizophrenia

Our most important findings are that patients with schizophrenia and the unaffected relatives presents abnormalities in the connectivity of the Default Mode Network, specifically in the Precuneus and Medial Prefrontral Cortex, but also the connectivity with areas of the Fronto-Parietal Network. Specifically we found abnormalities in the Parietal Inferior Cortex that correlates with the Neurological Soft Signs in the whole sample. Using ROI analysis we found hyperconnectivity in the Dorso Lateral Prefrontal Cortex in patients and in unaffected relatives, in comparison with healthy controls.

The current thinking regarding the etiopathogenesis of schizophrenia is that it may be a "progressive neurodevelopmental disorder" with a developmental predisposition for early degeneration(Barrantes-Vidal et al., 2003; Khandaker, Barnett, White, & Jones, 2011). This view postulates a disruption in functional circuits involving heteromodal association areas rather than abnormality in a single brain region (Shinn, Baker, Lewandowski, Öngür, & Cohen, 2015). These are among the brain regions that mature the latest. These regions include the frontal lobes, corpus callosum, basal ganglia, and recently, the cerebellum have been extensively studied in patients with schizophrenia. Studies have pointed to a possible dysfunction in the Cortical-Thalamic-Cerebellar-Cortical Circuit (CCTCC), causing a "cognitive dysmetria" which could explain the diversity of the disturbances in schizophrenia(Varambally, Venkatasubramanian, & Gangadhar, 2012).

Figure 7.1
Cortico-Cerebellar-Thalamic-Cortico Circuit (CCTCC)

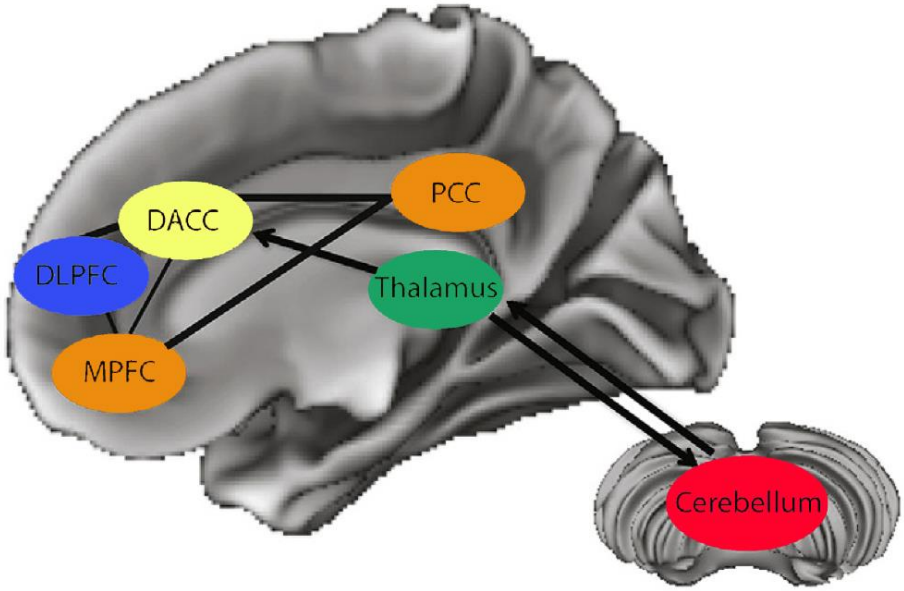


Figure based on Sheffield, J. M., & Barch, D. M. (2016). Neuroscience and Biobehavioral Reviews, 61, 108–120.
DLPFC, dorsolateral prefrontal cortex; DACC, dorsal anterior cingulate cortex; MPFC, medial prefrontal cortex; PCC, posteriorcingulate cortex

Default Mode Network
Cingulo-Opercular Network
Fronto-Parietal Network
Sub-Cortical Network
Cerebellar Network

Several studies revealed that healthy controls activated prefrontal, thalamic, and cerebellar areas during memory retrieval, but that patients with schizophrenia had significantly reduced cerebral blood flow in this circuit (Andreasen et al., 1996). Based on these findings, Andreasen theorized that schizophrenia is a disorder characterized by “cognitive dysmetria” as a result of inappropriate connections within

this key circuit in the brain. The cognitive dysmetria theory states that cognitive abilities, similar to motor functions, are supported by a fluid coordination of activity between the prefrontal cortex, cerebellum, and thalamus (cortico-cerebellar-thalamic-cortico circuit; CCTCC) (Sheffield & Barch, 2016).

This CCTCC feedback loop is thought to monitor and control the mental activity that is involved in many cognitive abilities. This feedback loop is disrupted patients with schizophrenia. In recent years by abnormalities in the CCTCC in task activation(Callicott et al., 2003; Heckers et al.,2000) and connectivity (Minzenberg et al., 2009; Zhou et al., 2007) of the prefrontal cortex in schizophrenia were reported.
More recently, studies on thalamic connectivity have provided some specificity to the relationship between thalamic nuclei and the PFC. Zhang and colleagues (2008) identified robust patterns of functional connectivity between non-overlapping voxels of the thalamus and different cortical regions, including between the medio dorsal nucleus of the thalamus and the PFC, in healthy controls (Zhanget al., 2010).

This pattern of functional connectivity has been shown to be abnormal in schizophrenia in a number of studies (Woodwardet al., 2012; Anticevic et al., 2013; Zhou et al., 2007; Welsh et al., 2010; Klingner et al., 2014), and reduced thalamic functional connectivity was found to be associated with multiple cognitive deficits in this review (Tu et al., 2013; Argyelan et al., 2013), providing support for dysregulation of this portion of the CCTCC in schizophrenia.

Our finding show how different functions such as motor coordination andsensory integrations are related to the personality traits involved with many different emotional and cognitive functions. The theory of

Cognitive Dysmetria in schizophrenia could explain the diversity of symptoms in schizophrenia.

7.4 Discussion neuroimaging results

Altered functional connectivity in the Precuneus region has been correlated in schizophrenia with dysfunctions in the sense of self and self – control, such as the volitional deficits (disturbances in self – initiation, maintenance and control of one's speech, thoughts, movements and behavior). Moreover, other general symptoms (including the general subtotal score of the PANSS) and several negative symptoms of schizophrenia have been associated with abnormal precuneus functional activity, but not with positive symptoms of disease.

Besides, it seems that these functional deficits in PCUN area are not only critical in the pathophysiology of schizophrenia, but also are possibly resistant to current neuroleptic drugs. This hypothesis supports the fact that current pharmacological treatment for schizophrenia are efficient at treating positive symptoms but may have less efficacy for the negative and cognitive symptoms of the disease. This point could be a clue for new pharmacological agents to target the negative symptoms and cognitive deficits in schizophrenia patients.

Hence, the role of the precuneus in schizophrenia has only recently become a focus of research, and it is yet unclear how this brain structure might link to negative symptoms. Above aberrant precuneus activation in patients with schizophrenia, it has been shown an increase of precuneus grey matter in unaffected biological relatives of schizophrenia patients, who are elevated risk to develop psychosis. Otherwise, high-risk groups for schizophrenia also show altered precuneus activation during a working memory task, which is associated with the expression of negative symptoms.

In studies of neuroimaging the amygdala, the anterior cingulate cortex, and the medial orbitofrontal cortex had been found to contribute significantly to Harm Avoidance) in several previous studies (Buckholtz et al., 2008; Iidaka et al., 2006; Pezawas et al., 2005; Pujol et al., 2002; Yamasue et al., 2008a; Yang et al., 2009). Recent studies also found that HA was associated with local structural integrity indexed by fractional anisotropy as well as mean and radial diffusivity within most main white matter fibres in the brain (Kim and Whalen, 2009; Westlye et al., 2011). There appears to be a widely distributed, interconnected neural network of HA, including the limbic system and the higher-function cortical regions (Lei et al. 2014).

In high HA scores there was observed stronger right amygdala connectivity with the MPFC, which is implicated in negative affect regulation (Baeken et al. 2014). For the higher HA scorers bilateral amygdala rsFC-HA correlations extended from the MPFC to the basal ganglia. (Baeken et al. 2014). In general, the neural activity in the prefrontal cortex was found to be higher in the high HA participants. These findings indicate that these participants had to make more efforts to regulate the induced emotional responses during explicit processing of the affective stimuli (Van Schuerbeek et al. 2014).

In addition, Novelty Seeking was positively correlated with fibre connections from the OFC and amygdala to the striatum, and HA was positively associated with the fibre connectivity from the PFC to the striatum (Lei et al., 2014). Several neurofunctional studies have reported that the HA score was correlated with the connectivity between the PFC and the insula (Markett et al., 2013), and between centromedial Amygdala subregions and frontal cortices associated with emotional processes (Li et al., 2012).

Important brain regions for the neural correlates underlying the temperaments are the Prefrontal cortex, limbic structure, and basal ganglia territories. This result indicates that the different patterns of

network associations constitute the neural substrates of personality that makes the two contrasting temperament groups different (Kyeong, Kim, Park, & Hwang, 2014).

Emotions involve brain networks including prefrontal cortical and limbic areas (Lindquist et al. 2012). Finally, a previous study reported that HA was positively associated with activation of the dorsal medial prefrontal cortex and posterior cingulate cortex during self-referential processing (Lemogne et al., 2011, Lei et al. 2014).

As a reflection of functional integration, we also found differences in the cerebral connectivity in set of brain regions that are involved in cognitive processing, such as the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobe. Most of these regions are activated together with nodes of the frontal cortex during a variety of cognitive tasks, such as the MPFC in prospecting the future, self-referential and envisaging the perspectives of others (Zhou et al., 2015).

Studies have also revealed that the brain regions commonly engaged by episodic memory and episodic future thinking are the DMN (Buckner, Andrews-Hanna, & Schacter, 2008; De Brigard, Nathan Spreng, Mitchell, & Schacter, 2015). The fact that this functional coupling occurred for familiar similar as opposed to self-based counterfactual simulations is consistent with recent evidence from Rabin and Rosenbaum (2012) showing involvement in the areas during theory of mind tasks involving familiar characters relative to autobiographical recollection. Perry et al. (2011) also showed functional coupling between hippocampus and MPFC during autobiographical and theory-of-mind processes involving familiar others. These findings have been interpreted as suggesting that episodic memory details are recruited during simulations involving

close similar others to a greater extent than simulations involving those we do not know or with whom we do not share personality traits (De Brigard et al., 2015).

7.5 Limitations

Several methodological limitations in the study should be mentioned. Examiners for the neurological assessment were not blind to group status. So it is not possible to predict the impact of the examiners in the assessment of the participants and their performance in each of the tasks. On occasion the expectation of "doing well" a specific task or the frustration of committing errors can consequently worsen outcomes.

As a relevant limitation in the use of this measure in the study, part B of the Rhythm Tapping Test was not carried out. In most versions of evaluation of NSS this item was not estimated.

A major problem was the composition of the different neurological scales and subscales as many different evaluations of the NSS exist. In our study we used the Neurological Evaluation Scale (NES), but the Cambridge Neurological Inventory or the Heidelberg Scale are also well established. The NES, which has been used by the largest number of studies, is a 30-item scale with ratings from 0 to 2 for each item, including Annett's handedness questionnaire. The Brief Motor Scale (BMS) is a recently developed scale which offers faster assessment with good sensitivity and specificity.

Other methodological limitations concern the reliability and validity of SPQ dimensions. We used two versions, with three factors (cognitive-perceptual, interpersonal, and disorganized). Fortunately, we had the opportunity to perform the test with the 6-factor model, which proposes a more precise and specific assessment of schizotypy.

Also for both personality measures, the detection of individuals at risk for schizophrenia is based solely on the use of self-reported measures, and this both restricts a participant's capacity to report about their own experiences and behaviors, and facilitates the possibility of distorting the answers given in the questionnaires.

Sample size is appropriate for a neuroimaging study, however not for particular clinical studies. The total number of participants is too small to be able to analyze subgroups of correlations and to understand if personality and NSS are directly correlated or if their association is due to group of origin.

As the study was composed of a clinical part and a neuroimaging part, not all participants were able to complete both examinations. Being able to make the comparisons without the exact same sample and with discrete variations in sample size may affect the results.

For temporal filtering, all data were high-pass filtered (128 s) to remove low-frequency noise. One of the most important limitations was that in the pre-processing of the image the application of a temporary filter could have an impact on masking or lowering the power of the results of the GIFT software analysis.

This however, caused problems when determining components following ICA since applying a filter prior to ICA is not recommended when using the GIFT software as it removes information required by ICA to separate components (Calhoun; Group ICA fMRI Toolbox forum, http://sourceforge.net/p/icatb/mailman/icatb-discuss/?viewmonth=201311).

Furthermore, the study of BOLD signal fluctuations with band-pass filtering is more widely used in seed-based approaches than in group ICA (McHugo, Rogers, Talati, Woodward, & Heckers, 2015) . For future analysis, the pre-processing of images will be performed again, avoiding this filter.

8. CONCLUSIONS

8.1 General conclusions in relation with the objectives and hypothesis

At the beginning of the study, a series of hypotheses and objectives were proposed, both through the clinical study of personality and the Neurological Soft Signs, and through the study of neuroimaging. We will review each objective according to the results obtained:

8.1.1 General Objective

General Objective

Explore the abnormalities in the functional connectivity of the default mode network related to the association between neurological soft signs and personality in schizophrenia.

The most important findings of the study are that patients with schizophrenia and the unaffected relatives presents abnormalities in the connectivity of the Default Mode Network, specifically in the Precuneus and Medial Prefrontral Cortex, but also the connectivity with areas of the Fronto- Parietal Network. Specifically, we found abnormalities in the Parietal Inferior Cortex that correlates with the Neurological Softs Signs in the whole sample. Also by a ROI analysis we found a hyper connectivity in the Dorso Lateral Prefrontal Cortex in patients and in unaffected relatives, in comparison to healthy controls. Our finding showed how differents functions as motor coordination, sensory integrations are related with the personality traits with involved many different emotional and cognitive functions. The theory of Cognitive Dysmetria in schizophrenia could explain the diversity of symptoms in schizophrenia

Objective 1: To explore the association between neurological soft signs and personality traits in schizophrenia.

In conclusion, these results showed that patients with schizophrenia were more asocial (higher harm avoidance and lower reward dependence), more persistent (higher persistence) and more schizotypal (lower self-directedness and cooperativeness, higher self-transcendence). In the group analysis we found significant changes in personality traits for relatives of patients with schizophrenia. Indeed, non-psychotic relatives showed higher harm avoidance, lower self-directness and lower cooperativeness when compared to control subjects. Interestingly, all three items were correlated with total NSS scores. Thus, a positive correlation was observed between higher harm avoidance and total NSS, and negative correlations were found between lower self-directedness and lower cooperativeness with total NSS. These findings lend support to the idea that such personality traits could be potential vulnerability markers for schizophrenia. These vulnerability markers are likely to be useful tools in the prospective studies of high-risk populations.

Objective 2: To explore the association between cerebral connectivity changes in the default mode network with the presence of neurological soft signs in schizophrenia.

Changes in connectivity were found mainly in Precuneus, in Medial Prefrontal Cortex, as well as other main nodes of the Default Mode Network. Also, to do a differential analysis between groups difference was found mainly with the inferior parietal cortex. These alterations have been related to already demonstrated functional alterations associated with the Neurological Soft Signs in schizophrenia.

8.1.2 Neurological soft signs and personality in schizophrenia

Objective 3: To determine the association of neurological soft signs and the temperament and character in patients with schizophrenia and their non-affected relatives in comparison to healthy controls.

According to the results, regarding temperament, we see that the Harm Avoidance was positively correlated with Total NES, and specifically, scores correlated significantly with Sensory Integration, Motor Coordination and Sequencing of Complex Motor Acts scores. However, a negative correlation was observed between total NES, Novelty Seeking and Persistence scores. For Persistence, significant negative correlations were observed with Motor Coordination, Sensory Integration, Sequencing of Complex Motor Acts and Involuntary Movements. Finally, a positive correlation was observed between Reward Dependence and Involuntary Movements.

With regards to character, total NES scores were negatively correlated with self-directedness and cooperativeness. For the individual character domains, self-directedness was negatively correlated with Motor Coordination and Sequencing of Complex Motor Acts scores, while cooperativeness was negatively correlated with Sensory Integration, Sequencing of Complex Motor Acts and Motor Coordination scores. No significant correlations were observed between self-transcendence and total NES scores, although a positive correlation was present with Motor Coordination

Objective 4: To determine the association between neurological soft signs and the schizotypal personality traits in patients with schizophrenia and their non-affected relatives in comparison to healthy controls.

The results show that there are differences between the three groups of participants. Specifically, in the SPQ 6 Factors in Associability and Anomalous Experiences, there is a significant difference between healthy controls vs patients or unaffected relatives, but there is no significant difference between patients and unaffected relatives. In the case of Paranoid Ideation, there are significant differences between the three groups: patient vs healthy controls, unaffected relatives vs healthy controls, and unaffected relatives vs patients. In the other Factors (Social Anxiety, Odd Speech, and Eccentricity), there are significant differences for patients vs healthy controls, and unaffected relatives vs healthy controls. Also, in the Total SPQ 6 factors, there are significant differences between all groups: patients vs healthy controls, unaffected relatives vs healthy controls, and unaffected relatives vs patients

Also, SPQ 3 Factors show that in the Cognitive Perceptual factor, there is significant difference only between patients vs healthy controls and unaffected relatives vs healthy controls. In the Disorganization factor, the years of education do play a role in the differences, thus there is significant difference between patients and healthy controls, and unaffected relatives and healthy controls after considering the effect of years of education. Also, in the Interpersonal factor and in the Total SPQ 3, there are significant differences between all groups: patient vs healthy controls, unaffected relatives vs healthy controls, and unaffected relatives vs patients.

8.1.3 Functional Neuroimaging

Objective 5: To explore the abnormalities in the connectivity of the default mode network by functional magnetic resonance imaging (fMRI) during resting state and the association between neurological soft signs and personality traits in the three groups of subjects.

The Neuroimaging results show that there are significant differences in the DMN between the 3 groups, between patients and healthy controls, and between unaffected relatives and healthy controls, but there are not significant differences found between patients and unaffected relatives. Specifically, those differences were found in Medial Prefrontal Cortex R, the Posterior Cingulate Cortex, the Precuneus L and the Lower Parietal Lobe R.

On the other hand the Precuneus ROIS results show that there are differences in connectivity in the Left Somatosensory Association and in the Left-Right Supramarginal Gyrus between the 3 groups, and when doing a subgroup analysis they present differences between patients and healthy controls, and between unaffected relatives and healthy controls, but not in unaffected relatives and patients.

In turn, in the Medial Prefrontal Cortex ROIS it was found that the Left Premotor Cortex displays an increase in connectivity between the 3 groups, and in between patients and healthy controls. But most relevantly, there is also a decrease in connectivity between unaffected relatives and healthy controls.

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Appendix A

Galindo, L., Pastoriza, F., Bergé, D., Mané, A., Picado, M., Bulbena, A., Pérez- Sola, A. Vilarroya-Olive, O. Cloninger, C. R. (2016).

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Association between neurological soft signs, temperament and character in patients with schizophrenia and non-psychotic relatives

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ABSTRACT

The heritability of schizophrenia and most personality traits has been well established, but the role of personality in susceptibility to schizophrenia remains uncertain. The aim of this study was to test for an association between personality traits and Neurological Soft Signs (NSS), a well-known biological marker of schizophrenia, in non-psychotic relatives of patients with schizophrenia. For this purpose, we evaluated the NSS scale and personality measured by the Temperament and Character inventory (TCI-R) in three groups of subjects: 29 patients with schizophrenia, 24 unaffected relatives and 37 controls. The results showed that patients with schizophrenia were more asocial (higher harm avoidance and lower reward dependence), more perseverative (higher persistence), and more schizotypal (lower self-directedness and cooperativeness, higher self-transcendence). The unaffected relatives showed higher harm avoidance, lower self-directedness and cooperativeness than the healthy controls. Higher NSS scores and sub-scores were found in patients and non-psychotic relatives compared with the controls. Among all the patients, total NSS scores were positively correlated with harm avoidance but negatively correlated with novelty seeking and persistence. Total NSS were also correlated with low scores on self-directedness and cooperativeness, which are indicators of personality disorder. Our results show that susceptibility to NSS and to schizophrenia are both related to individual differences in the temperament and character features in non-psychotic relatives of patients with schizophrenia. High harm avoidance, low persistence, low self-directedness and low cooperativeness contribute to both the risk of NSS and schizophrenia. These findings highlight the value of using both assessments to study high risk populations.

Subjects Psychiatry and Psychology

Keywords Schizophrenia, Neurological Soft Signs, Temperament and character, Vulnerability markers, Personality

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INTRODUCTION

Although the etiology of schizophrenia is still largely unknown, the genetic basis of this disorder has been well established (*Singh et al., 2014*). The expression of susceptibility to schizophrenia is incomplete and variable, as shown by the non-psychotic status of most monozygotic co-twins of patients with schizophrenia, and the complex relationships of different sets of genes with distinct sets of clinical features (*Arnedo et al., 2014*). Fortunately, more subtle expressions of susceptibility to schizophrenia can be evaluated by studying neuropsychological markers of susceptibility, such as personality traits and neurological soft signs in the non-psychotic relatives of patients with schizophrenia (*Smith et al., 2008*).

Several studies have shown an association between schizophrenia and certain personality traits; however, the nature of this relationship is not clarified (*Silberschmidt & Sponheim, 2008*; *Smith et al., 2008*). Among the different models for studying personality, Cloninger's model is the one with the most explicit neurobiological basis (*Cloninger, Svrakic & Przybeck, 1993*). This model suggests that a person's temperament is heritable and regulated by neurotransmitters and brain circuits, which are involved in the pathophysiology of schizophrenia. Both temperament and character traits are equally heritable (*Gillespie et al., 2003*), but character is more shaped by sociocultural influences as it develops across a lifespan (*Josefsson et al., 2013a*; *Josefsson et al., 2013b*). Temperament consists of individual differences in behavioral conditioning of habits and skills, whereas character comprises of individual differences based on goals and values, which involve higher cognitive processes of semantic and autobiographical learning and memory (*Silberschmidt & Sponheim, 2008*; *Van Schuerbeek et al., 2014*). Environmental factors do impact on both temperament and character traits, however, these factors are more critical for the development of character than temperament. By using this model, patients with schizophrenia have shown a temperament and character profile that is distinct from the general population (*Bora & Veznedaroglu, 2007*; *Glatt et al., 2006*; *Kurs, Farkas & Ritsner, 2005*; *Ritsner & Susser, 2004*). Specifically, people with schizophrenia and their non-psychotic relatives are higher in the temperament of harm avoidance (i.e., more anxious and shy) and lower in the temperament of reward dependence (i.e., more detached and cold emotionally), so that they are more socially distant than controls. More recently, evidence has emerged showing that the dimensions of character are heritable and may also influence the risk of schizotypy (*Silberschmidt & Sponheim, 2008*). Specifically, people with schizophrenia and their non-psychotic relatives have the schizotypal character profile of low self-directedness (i.e., aimless and tending to blame others for their problems), low cooperativeness (i.e., suspicious and lacking in empathy), and high self-transcendence (i.e., prone to fantasy and magical thinking). Thus, Cloninger's TCI provides a reliable way to quantify personality traits related to susceptibility to the schizophrenia spectrum.

The association between personality and schizophrenia has been reinforced by several studies that relate these personality traits with other abnormalities in schizophrenia. For example, the correlation between some dimensions of temperament and changes in monoaminergic activity has been postulated as the biological basis of schizophrenia (*Ebstein, 2006*; *Mitsuyasu et al., 2001*). In addition, an interaction has been observed

between polymorphisms of these two systems that predicts the scores on harm avoidance (*Benjamin et al., 2000*).

Furthermore, several studies of schizophrenia have suggested an association between personality traits and other candidate markers of vulnerability. Specifically, the presence of schizotypal personality traits correlates with the presence of neurological soft signs (NSS) in relatives of patients with schizophrenia (*Mechri et al., 2009*; *Mechri et al., 2010*). Traditionally, NSS are defined as minor neurological abnormalities without a definite localization in the brain, including several clinical manifestations related to simple motor coordination, complex motor sequencing, sensory integration and disinhibition signs (*Chan & Gottesman, 2008*). Alterations in motor coordination and integration of stimuli are positively correlated with both the total scores and with the cognitive perceptive component of scales measuring schizotypy (*Chan et al., 2010*; *Kaczorowski, Barrantes-Vidal & Kwapil, 2009*). Thus, NSS have been suggested as markers of disease vulnerability, which are present prior to the start of treatment and are independent of illness state (as well as type of antipsychotic treatment) (*Chan et al., 2010*; *Bombin, Arango & Buchanan, 2003*), and NSS are correlated with structural and functional brain abnormalities related to schizophrenia (*Mouchet-Mages et al., 2011*; *Zhao et al., 2014*).

Interestingly, temperament and character features and NSS have been shown to aggregate in the relatives of schizophrenia patients (*Krebs et al., 2000*; *Andreasen et al., 2005*), supporting the view that both are likely to reflect genetic liability to schizophrenia. In addition, the distribution of NSS in schizophrenia, and in first-degree relatives, is consistent with the endophenotype criterion of familial association (*Zhao et al., 2014*). However, belonging to the same family could act as a confounding factor because it includes environmental influence and common genetic factors unrelated to the illness. In this respect, no studies are available comparing both NSS and personality in patients with schizophrenia and non-psychotic relatives.

The aim of this study was to investigate the association between personality traits, neurological soft signs and vulnerability to schizophrenia. Firstly, to determine whether personality traits could be vulnerability markers of schizophrenia, or if they are simply associated with the disease, we compared personality traits and neurological soft signs between patients, relatives and controls. Secondly, to establish whether those domains that showed differences between groups were significantly associated with known markers of disease vulnerability, correlations between personality traits and NSS were calculated for the entire population.

MATERIALS AND METHODS

Subjects

A cross-sectional study was conducted on 29 patients with schizophrenia, 24 unaffected relatives of patients and 37 controls. This study was conducted at the Neuropsychiatry and Addictions Institute of the Parc de Salut Mar of Barcelona. The patients and the non-psychotic relatives were recruited from outpatient services of the same institution. Control subjects were recruited by announcements in the University and the Hospital. All

participants lived in Spain for more than five years and were fluent Spanish speakers. The non-psychotic relatives were not from the same families of the patients included in the study, in order to avoid the effects of similar rearing that could induce potential similarities in temperament and character between patients and siblings. Considering that the total population was organized into three categories (patients, unaffected relatives and healthy controls), the participants were matched by gender and age.

The exclusion criteria included the presence of a substance dependence disorder (with the exception of nicotine dependence) according to DSM IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), the presence any other psychiatric disorder of axis I or II of DSM IV-TR as well as the personal history of severe somatic or neurological disorders. All subjects were between 25 and 50 years old and had an estimated IQ >80 measured by WAIS subscales (Digit, cubes, vocabulary, arithmetic, symbol search). The patients were diagnosed with schizophrenia from the medical record and confirmed by the Structured Clinical Interview for DSM Disorders. Unaffected relatives and healthy controls were evaluated as well. All the patients had a disease duration between 5 and 15 years, were treated with atypical antipsychotics, had never received electroconvulsive therapy and had been clinically stable for the last six months (all positive items of the PANSS positive subscale scoring 4 or lower). The non-psychotic relatives were from the same mother and father of a patient with a diagnosis of schizophrenia, according to DSM IV-TR. Control subjects and their first and second degree relatives had to be free of any axis I disorders. The study was approved by the ethics committee of the CEIC-Parc de Salut Mar Hospital (2011/4141/I). All subjects gave informed written consent and were assured of the confidentiality of the data being collected.

Experimental procedure

Basic socio-biographical data were collected from the medical history. This data included years of education, socio-economic level, psychiatric and medical history, years from disease onset, administered treatment and psychiatric history of first degree relatives. Patients were clinically assessed using the Positive and Negative Syndrome Scale (PANSS) (*Peralta & Cuesta, 1994*) and the overall functioning of the subjects was assessed using the Global Adaptive Functioning (GAF) (*Jones et al., 1995*).

All subjects were assessed with the Spanish version of the Temperament and Character Inventory (TCI-R) (*Gutiérrez-Zotes et al., 0000*) and the Neurological Soft Signs Scale (*Krebs et al., 2000*). Temperament is comprised of novelty seeking (i.e., impulsive, exploratory), harm avoidance (i.e., anxious, shy), reward dependence (i.e., sentimental, approval-seeking) and persistence (i.e., determined, ambitious). Character is comprised of self-directedness (i.e., responsible, purposeful), cooperativeness (i.e., helpful, empathic) and self-transcendence (i.e., imaginative, self-forgetful). The TCI-R sub-scores for each of the seven dimensions were calculated.

The NSS scale is composed of 23 items, rated from 0 to 3, and regrouped in five consistent factors: Motor coordination (hand dysrhythmia, finger opposition, fist edge–palm, foot dysrhythmia, alternative movements: foot speed, alternative movements: hand speed,

Table 1 Demographic characteristics in controls, non-psychotic relatives and patients with schizophrenia.

	Controls	Non-psychotic relatives	Patients	*p*
	n = 37	*n* = 24	*n* = 29	
Mean Age (years) ± SD	36.78 ± 7.61	40.92 ± 10.32	37.97 ± 7.13	0.165
Gender (M/F)	17/20	11/13	16/13	0.713
Mean years of education (years) ± SD	12.89 ± 1.76	11.50 ± 2.65	10.00 ± 2.80	<0.05*

standing heel-to-toe), Motor integration (Romberg, apraxia, tandem walk, finger-to-nose, gait, tongue protrusion), Sensory integration (stereognosia, hand–face, constructive apraxia, graphesthesia, right-left recognition), Quality of lateralization (right-left confusion, lateral preference, right-left asymmetry) and Involuntary movements (abnormal movement and posture, mirror movements).

The NSS total score and sub-scores for each of the factors were calculated. Two assessors (LG and FP) were trained to perform the neurological assessment. The inter-rater reliability of the assessment of NSS was established by the two assessors and jointly examined 20 independent subjects. The intra-class correlation coefficient (SPSS: two way Mixed Effect Model, confidence interval = 95%) was 0.90 [0.77–0.95].

Statistical analysis

First, univariate analyses of the sociodemographic data were performed. Differences in age and years of education were determined with the Analysis of Variance (ANOVA), and the *chi* square test was applied for gender differences. As there were statistical differences in years of education, it was added as a covariate in the rest of the analyses.

Temperament, character and NSS scores were analyzed with the Levene test. Then, to study differences between groups, and depending on the results on Levene tests, the analysis was performed with ANOVAs followed by the Bonferroni post-hoc test or a Kruskall–Wallis test followed by Mann–Whitney U test, adding years of education as a covariate. Pearson correlations were performed using the entire population between the total NSS scores and sub-scores for each temperament and character domains, adding years of education as a covariate. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 23 subjects are necessary in every group to recognize as statistically significant a difference greater than or equal to 1 unit. The common standard deviation is assumed to be 1.2. It has been anticipated a drop-out rate of 0%.

RESULTS

Demographic characteristics

No significant differences between groups were observed in terms of age or gender; although patients with schizophrenia and non-psychotic relatives showed significantly less years of education than controls (Table 1).

Table 2 Temperament and character scores in controls, non-psychotic relatives and patients with schizophrenia.

		Controls	Non-psychotic relatives	Patients	*F*	*p*
		n = 37	*n* = 24	*n* = 29		
Temperament	Harm avoidance (mean ± SEM)	86.18 ± 1.85	99.38 ± 4.49	109.21 ± 2.97	13.10	<0.01*
	Reward dependence (mean ± SEM)	109.36 ± 2.03	101.38 ± 3.13	99.79 ± 3.66	3.15	<0.05*
	Novelty seeking (mean ± SEM)	102.39 ± 1.55	102.81 ± 2.88	97.7 ± 2.43	1.29	0.27
	Persistence (mean ± SEM)	113.91 ± 2.63	103.14 ± 4.75	100.58 ± 3.50	3.83	<0.05*
Character	Self-directedness (mean ± SEM)	159.62 ± 2.87	141.14 ± 4.64	134.67 ± 4.40	10.11	<0.01*
	Cooperativeness (mean ± SEM)	147.17 ± 2.24	137.05 ± 2.57	133.12 ± 3.86	5.59	<0.05∗
	Self-Transcendence (mean ± SEM)	54.30 ± 2.56	58.76 ± 2.82	66.25 ± 3.99	3.63	<0.05*

Temperament scores (TCI-R)

Table 2 shows the scores obtained for each temperament dimension in controls, non-psychotic relatives and patients. Harm Avoidance scores were significantly different between the groups ($F(2,88) = 13.10$, $p < 0.001$) (Fig. 1). Subsequent post-hoc analysis revealed that patients with schizophrenia and non-psychotic relatives obtained significantly higher scores on harm avoidance than controls, and patients showed significantly higher scores than relatives (Fig. 1). In addition, significant differences between the groups were observed in reward dependence ($F(2,88) = 3.15$, $p < 0.05$) and persistence ($F(2,88) = 3.83$, $p < 0.05$) scores. The post-hoc test revealed that patients obtained significantly lower reward dependence scores than controls and both patients and non-psychotic relatives had lower persistence scores than controls. No significant differences between groups were observed for novelty seeking scores (Fig. 1).

Character scores (TCI-R)

Table 2 shows the scores obtained for each character dimension in controls, non-psychotic relatives and patients. Significant differences between groups were observed in self-directedness, cooperativeness and self-transcendence scores. A subsequent subgroups analysis revealed that both patients and relatives obtained significantly lower scores on self-directedness and cooperativeness than the controls (Fig. 2). In addition, no significant differences were observed in self-directedness or cooperativeness scores between patients and relatives. Finally, significantly higher self-transcendence scores were observed in patients with schizophrenia than in the controls (Fig. 2).

Neurological soft signs scores

Significant differences between groups were observed for the total NSS scores ($F(2,88) = 41.98$, $p < 0.01$). A subsequent post-hoc analysis revealed significantly higher NSS scores in both non-psychotic relatives and patients, compared with the control subjects.

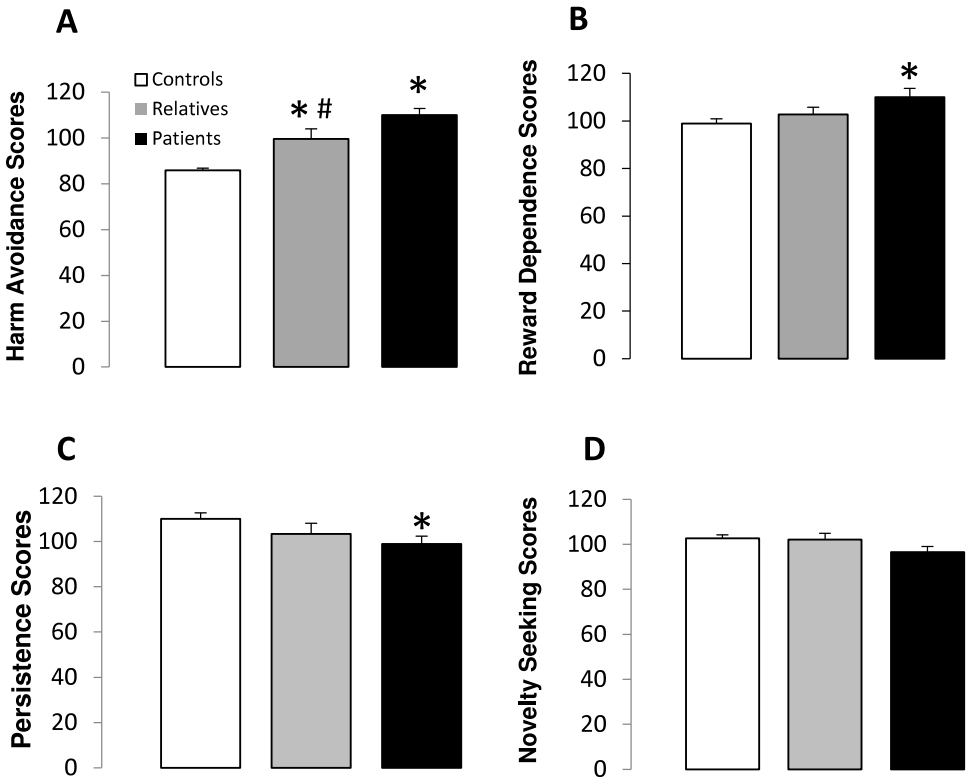

Figure 1 Temperament scores in controls, non-psychotic relatives and patients with schizophrenia. Harm avoidance (A), reward dependence (B), persistence (C) and novelty seeking (D) scores. The data are represented as mean + SD. $^{*}p < 0.05$ vs. controls; $\#p < 0.05$ vs. relatives.

In addition, patients showed higher total NSS scores than non-psychotic relatives (Fig. 3). Scores obtained in each NSS domain for the three groups are shown in Table 3. Significant differences between groups were observed for each of the NSS sub-scores. Post-hoc analyses revealed significantly higher scores in motor coordination and involuntary movements in patients and relatives, as compared with the controls. In addition, patients showed higher scores than relatives in both of these NSS sub-scores. With respect to motor integration and quality of lateralization, patients and relatives also showed higher scores than control subjects, while no significant differences were observed between patients and relatives. For sensory integration, higher scores were observed only in patients compared with the control group (Fig. 3).

Correlations between NSS and TCI-R scores

Table 4 shows the Pearson coefficients obtained for correlations between NSS scores and temperament and character scores for the entire population studied. In terms of temperament, total NSS scores were positively correlated with harm avoidance, while a negative correlation was observed between total NSS, novelty seeking and persistence scores. When each temperament dimension was analyzed separately, harm

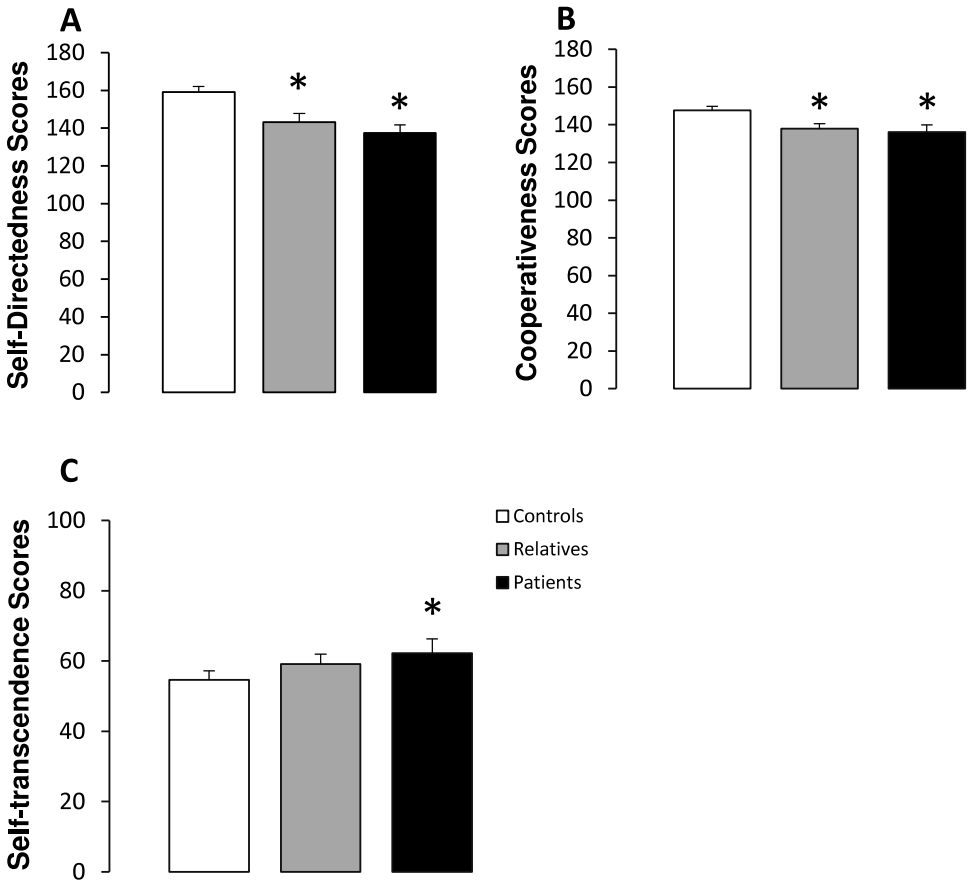

Figure 2 Character scores in controls, non-psychotic relatives and patients with schizophrenia. Self-directedness (A), cooperativeness (B) and self-transcendence (C) scores. The data are represented as mean + SD. $^{*}p < 0.05$ vs. controls.

Table 3 NSS scores in controls, non-psychotic relatives and patients with schizophrenia.

Neurological soft sign scores	Controls	Non-psychotic relatives	Patients	*F*	*P*
	n = 37	*n* = 24	*n* = 29		
Motor coordination (mean ± SEM)	0.71 ± 0.18	1.65 ± 0.34	3.13 ± 0.37	15.32	<0.001*
Sensory integration (mean ± SEM)	1.13 ± 0.15	1.65 ± 0.18	2.57 ± 0.38	6.31	<0.001*
Motor integration (mean ± SEM)	1.32 ± 0.11	4.85 ± 0.33	4.52 ± 0.33	36.29	<0.001*
Quality of lateralization (mean ± SEM)	0.29 ± 0.09	0.95 ± 0.34	0.73 ± 0.17	4.20	<0.01*
Involuntary movement (mean ± SEM)	0.94 ± 0.15	1.25 ± 0.18	2.78 ± 0.40	13.03	<0.001*

avoidance scores correlated significantly with sensory integration, motor coordination and motor integration scores. For persistence, significant negative correlations were observed with motor coordination, sensory integration, motor integration and involuntary movements. Finally, a positive correlation was observed between reward dependence and involuntary movements. Novelty seeking scores were negatively correlated with

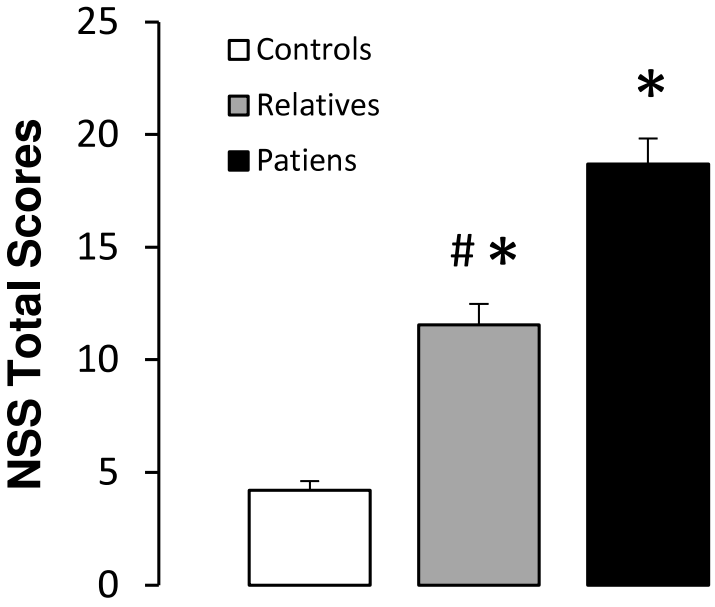

Figure 3 Total neurological soft signs (NSS) scores in controls, non-psychotic relatives and patients with schizophrenia. The data are represented as mean + SD. $^{*}p < 0.05$ vs. controls; $\#p < 0.05$ vs. relatives.

Table 4 Correlations coefficients between NSS and temperament features and between NSS and character traits in controls, non-psychotic relatives and patients with schizophrenia.

	Total NSS	Sensory integration	Motor coordination	Motor integration	Quality lateralization	Involuntary movement
Harm avoidance	0.95*	0.38*	0.35**	0.48*	0.03	0.16
Reward dependence	−0.12	−0.12	−0.16	−0.15	0.10	0.25*
Novelty seeking	−0.40*	−0.84*	−0.22	−0.15	−0.29*	−0.15
Persistence	−0.95*	−0.43*	0.29*	−0.43*	−0.08	−0.40*
Self-directedness	−0.80*	−0.18	−0.39*	−0.40*	0.03	−0.08
Cooperativeness	−0.55*	−0.22*	−0.32*	−0.23*	−0.01	−0.13
Self-transcendence	0.19	0.07	0.27*	0.20	−0.01	−0.01

sensory integration. With regards to character, total NSS scores were negatively correlated with self-directedness and cooperativeness. For the individual character domains, self-directedness was negatively correlated with motor coordination and motor integration scores, while cooperativeness was negatively correlated with sensory integration, motor integration and motor coordination scores. No significant correlations were observed between self-transcendence and total NSS scores, although a positive correlation was present with motor coordination.

DISCUSSION

The major finding in this study was that patients with schizophrenia and non-psychotic relatives display a unique profile of temperament and character that correlates with

alterations in NSS. Comparing personality traits and NSS between groups, both patients with schizophrenia and non-psychotic relatives obtained significantly higher scores on harm avoidance than controls, and patients showed significantly higher scores than relatives. Also, patients and non-psychotic relatives had lower persistence, self-directedness, and cooperativeness scores than controls. In addition, no significant differences were observed in self-directedness or cooperativeness scores between patients and relatives. Finally, significantly higher self-transcendence scores were observed in patients with schizophrenia, compared to controls.

Our results reveal an association between these hypothesized vulnerability markers, as temperament (especially harm avoidance, reward dependence and persistence) and character (especially self-directedness and cooperativeness) correlated with the presence of NSS in the entire sample.

Studies in non-psychotic relatives have been essential to uncover new vulnerability biomarkers of schizophrenia. In this sense, several studies have provided evidence showing that particular personality features could be considered as possible schizophrenia-related endophenotypes (*Smith et al., 2008*). In this study, it was found that non-psychotic relatives had significantly higher harm avoidance scores compared with the controls, but lower scores than patients with schizophrenia. In agreement with our data, *Smith et al. (2008)* found higher harm avoidance scores in siblings of patients with schizophrenia than in controls subjects, and another study reported that siblings are positioned between controls and patients with schizophrenia, in terms of temperament profile (*Calvó de Padilla et al., 2006*). In contrast, *Bora & Veznedaroglu (2007)* did not find differences in temperament between relatives of schizophrenic patients and the controls, although they did observe differences in harm avoidance between controls and relatives with high schizotypy. Together, these studies support the idea that high levels of harm avoidance may be associated with genetic vulnerability to schizophrenia, which, in turn, will interact with environmental and neurobiological influences to determine the expression of the disease. According to *Kim et al. (2011)* and *Hansenne et al. (2003)*, harm avoidance has been associated with D2/3 receptor availability in the associative and sensorimotor subdivisions of the striatum and high Mismatch Negativity and hypervigilant fear perception, suggesting abnormal sensory gating of aversive stimuli as a vulnerability variable in schizophrenia. Furthermore, a locus on chromosome 8p21 associated to schizophrenia showed a linkage to harm avoidance (*Zohar et al., 2003*).

With regards to character, it was found that, similar to patients; non-psychotic relatives had significantly lower self-directedness and cooperativeness scores when compared to controls. Other studies have reported lower levels of self-directedness and cooperativeness in siblings with high schizotypy as compared to controls, and high levels were observed in siblings with low schizotypy (*Bora & Veznedaroglu, 2007*). One important aspect of the data in this study is that even though the non-psychotic relatives that participated in this study did not have familial ties to the patients with schizophrenia, they showed similar low levels of self-directedness and cooperativeness. It is well known that character is influenced more by environmental factors than temperament (*Josefsson et al., 2013a*; *Josefsson et al., 2013b*). However, the data in this study agrees with other studies, such as *Gillespie et al., (2003)*;

Josefsson et al., (2013a); *Josefsson et al., (2013b)*, showing that character may also have a genetic component. Self-transcendence was higher in patients than in the controls subject, but not in relatives. These results are in agreement with other studies reporting elevated self-transcendence in patients (*Glatt et al., 2006*; *Smith et al., 2008*). In contrast, *Calvó de Padilla et al. (2006)* found lower self-transcendence and cooperativeness in the relatives of patients with schizophrenia with respect to the controls. The discrepancies between studies could be due to the fact that the population used in the Calvo and Padilla study was an indigenous community living in a rural environment and not in an urban environment.

In accordance with previous studies, we found lower levels of persistence and reward dependence only in patients with schizophrenia as compared to controls. These findings endorse the hypothesis stating that high harm avoidance, low persistence and low reward dependence constitutes a temperament profile leading to social detachment, perseveration and schizotypy, when combined with a disorganized character profile that impairs emotional regulation (*Smith et al., 2008*; *Bora & Veznedaroglu, 2007*).

As reported previously in patients with schizophrenia (*Bombin, Arango & Buchanan, 2003*; *Chen et al., 2005*; *Aksoy-Poyraz et al., 2011*) and in non-psychotic relatives (*Gourion et al., 2004*; *Mechri et al., 2010*), we found higher NSS in both groups as compared with the controls, confirming the hypothesis that NSS is a vulnerability marker for schizophrenia. In addition, these results agree with the idea that NSS segregate with the illness and may be a valid and useful endophenotype (*Chan et al., 2010*). The association between personality characteristics and NSS has been studied separately in siblings, or in patients with schizophrenia, but there are no prior studies correlating NSS with personality traits in patients with schizophrenia, non-psychotic relatives and controls. Our correlational analysis, including all three groups, showed that subjects with higher NSS scores exhibited higher harm-avoidance and persistence scores, while they exhibited lower self-directness and cooperativeness. Two related studies have evaluated the association between NSS and schizotypal personality traits with contradictory results. Thus, *Mechri et al. (2010)*, using the Schizotypal Personality Questionnaire (SPQ), showed that the overall NSS score was correlated with the presence of schizotypal traits in both non-psychotic siblings and controls, while no association was found between NSS and schizotypal dimensions in relatives of patients with schizophrenia, when the SPQ test was used (*Bollini et al., 2007*). The differences observed between these two studies, as well as the present work, could be due to the fact that they used a personality assessment tool based on outdated DSM III criteria. In this respect, one of the strengths of this study is the use of the TCI-R scale, which is a comprehensive personality questionnaire that has been extensively validated in clinical practice and research (*Fassino et al., 2013*; *Fresán et al., 2015*). One of the advantages of the TCI-R is that it explores normal and pathological personalities in subjects with mental disorders and also in the general population (*Cloninger et al., 2012*; *Josefsson et al., 2011*; *De Fruyt et al., 2006*). Another advantage is that temperament and character domains have been associated with structural and functional changes in the brain (*Laricchiuta et al., 2014*; *Lei et al., 2014*; *Tuominen et al., 2013*), and have been related to specific chromosomal regions (*Serretti et al., 2008*; *Zohar et al., 2003*) supporting the neurobiological substrate for this personality model (*Yang et al., 2015*). Another strength of the study is that the relatives

of patients with schizophrenia had no familial ties to the patients used, thus decreasing the possibility that similar rearing would confound the results.

Finally, several limitations of the study are acknowledged. The first is the small sample size used, even though the TCI-R scores and NSS scores were similar to those reported in larger samples in the literature (*Smith et al., 2008*; *Mechri et al., 2010*). The second limitation is the use of an estimate of IQ values as a selection criterion, but not as a covariate in the analysis. This issue may have been a potential confounding factor, since IQ has been previously associated with personality and with NSS.

In conclusion, these results showed that patients with schizophrenia were more asocial (higher harm avoidance and lower reward dependence), more perseverative (higher persistence) and more schizotypal (lower self-directedness and cooperativeness, higher self-transcendence). In the group analysis, we found significant changes in personality traits in relatives of patients with schizophrenia. Indeed, non-psychotic relatives showed higher harm avoidance, lower self-directness and lower cooperativeness when compared to control subjects. Interestingly, all three items were correlated with total NSS scores. Thus, a positive correlation was observed between higher harm avoidance and total NSS, and negative correlations were found between lower self-directedness and lower cooperativeness with total NSS. These findings lend support to the idea that such personality traits could be potential vulnerability markers for schizophrenia. These vulnerability markers are likely to be useful tools in the prospective studies of high-risk populations.

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Author Contributions

- Liliana Galindo conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, wrote the paper, prepared figures and/or tables, reviewed drafts of the paper.
- Francisco Pastoriza performed the experiments, wrote the paper, reviewed drafts of the paper.
- Daniel Bergé, Anna Mané and Claude Robert Cloninger conceived and designed the experiments, analyzed the data, wrote the paper, reviewed drafts of the paper.
- Marisol Picado, Antonio Bulbena and Victor Pérez contributed reagents/materials/analysis tools, reviewed drafts of the paper.
- Patricia Robledo analyzed the data, contributed reagents/materials/analysis tools, wrote the paper, prepared figures and/or tables, reviewed drafts of the paper.
- Oscar Vilarroya conceived and designed the experiments, contributed reagents/materials/analysis tools, reviewed drafts of the paper.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

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Data Availability

The following information was supplied regarding data availability:

The raw data has been supplied as Data S1.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.1651#supplemental-information.

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Appendix B

A.1 Schizophrenia

Diagnostic Criteria, according to DSM-IV-TR

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

    1. Delusions.

    2. Hallucinations.

    3. Disorganized speech (e.g., frequent derailment or incoherence).

    4. Grossly disorganized or catatonic behavior.

    5.Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more

symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Specify if:

The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria.

First episode, currently in acute episode: First manifestation of the disorder meeting the defining diagnostic symptom and time criteria. An *acute episode* is a time period in which the symptom criteria are fulfilled.

First episode, currently in partial remission: *Partial remission* is a period of time during which an improvement after

a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled.

First episode, currently in full remission: *Full remission* is a period of time after a previous episode during which no disorder-specific symptoms are present.

Multiple episodes, currently in acute episode: Multiple episodes may be determined after a minimum of two episodes (i.e., after a first episode, a remission and a minimum of one relapse).

Multiple episodes, currently in partial remission

Multiple episodes, currently in full remission

Continuous: Symptoms fulfilling the diagnostic symptom criteria of the disorder are remaining for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course.

Unspecified

Specify if:

With catatonia

Coding note: Use additional code 293.89 (F06.1) catatonia associated with

schizophrenia to indicate the presence of the comorbid catatonia.

Specify current severity:

Severity is rated by a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe). (See Clinician-Rated Dimensions of Psychosis Symptom Severity in the chapter “Assessment Measures.”)

Note: Diagnosis of schizophrenia can be made without using this severity specifier

Appendix C

A.3 Null Hypothesis

A.3.1 General Hypothesis

There is no association between higher presence of neurological soft signs, and temperament with higher harm avoidance, low reward dependence, low novelty seeking, low persistence (according to Cloninger's personality model), schizotypy and functional brain alterations in areas of the default mode network in patients with schizophrenia and their non-affected relatives.

A.3.2 Specific Hypothesis

A.3.2.1 Neurological soft signs and personality in schizophrenia

c) A temperament with higher harm avoidance, low reward dependence, low novelty seeking and low persistence traits will not show any correlation with the neurological soft signs across the three groups of subjects.

d) Higher scores in schizotypal personality traits will not show any correlation with the neurological soft signs, across the three groups of subjects.

A.3.2.2 Functional Neuroimaging

d) There is no set of abnormalities in functional connectivity in the default mode network and personality traits, so abnormalities won't be present in patients with schizophrenia and their non-affected relatives with higher neurological soft sign scores.

e) This set of alterations in functional connectivity in the default mode network and neurological soft signs will not be present in the control subjects or in the unaffected relatives who do not have high scores for the afore mentioned personality traits.

f) Subjects with higher neurological soft sign scores will not show a significant correlation with changes in functional connectivity patterns in regions involved in reward dependence (ventral striatum), harm avoidance (medial and dorsolateral prefrontal cortex), persistence (inferior frontal cortex) and novelty seeking.

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