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

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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.

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27 **Abstract**

28

29 The heritability of schizophrenia and most personality traits has been well established,

30 but the role of personality in susceptibility to schizophrenia remains uncertain. The aim

31 of this study was to test for an association between personality traits and Neurological

32 Soft Signs (NSS), a well-known biological marker of schizophrenia, in non-psychotic

33 relatives of patients with schizophrenia. For this purpose, we evaluated the NSS scale

34 and personality measured by the Temperament and Character inventory (TCI-R) in three

35 groups of subjects: 29 patients with schizophrenia, 24 unaffected relatives and 37

36 controls. The results showed that patients with schizophrenia were more asocial (higher

37 harm avoidance and lower reward dependence), more perseverative (higher

38 persistence), and more schizotypal (lower self-directedness and cooperativeness, higher

39 self-transcendence). The unaffected relatives showed higher harm avoidance, lower self-

40 directedness and cooperativeness than the healthy controls. Higher NSS scores and sub-

41 scores were found in patients and non-psychotic relatives compared with the controls.

42 Among all the patients, total NSS scores were positively correlated with harm avoidance

43 but negatively correlated with novelty seeking and persistence. Total NSS were also

44 correlated with low scores on self-directedness and cooperativeness, which are indicators

45 of personality disorder. Our results show that susceptibility to NSS and to schizophrenia

46 are both related to individual differences in the temperament and character features in

47 non-psychotic relatives of patients with schizophrenia. High harm avoidance, low

48 persistence, low self-directedness and low cooperativeness contribute to both the risk of

49 NSS and schizophrenia. These findings highlight the value of using both assessments to

50 study high risk populations.

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1. 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 et al. 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, Jokela, Cloninger, et al. 2013; Josefsson, Jokela, Hintsanen, et al. 2013). 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).

77 Environmental factors do impact on both temperament and character traits, however,

78 these factors are more critical for the development of character than temperament. By

79 using this model, patients with schizophrenia have shown a temperament and character

80 profile that is distinct from the general population (Bora & Veznedaroglu 2007; Glatt et al.

81 2006; Kurs et al. 2005; Ritsner & Susser 2004). Specifically, people with schizophrenia

82 and their non-psychotic relatives are higher in the temperament of harm avoidance (i.e.,

83 more anxious and shy) and lower in the temperament of reward dependence (i.e., more

84 detached and cold emotionally), so that they are more socially distant than controls. More

85 recently, evidence has emerged showing that the dimensions of character are heritable

86 and may also influence the risk of schizotypy (Silberschmidt & Sponheim 2008).

87 Specifically, people with schizophrenia and their non-psychotic relatives have the

88 schizotypal character profile of low self-directedness (i.e., aimless and tending to blame

89 others for their problems), low cooperativeness (i.e., suspicious and lacking in empathy),

90 and high self-transcendence (i.e., prone to fantasy and magical thinking).   Thus

91 Cloninger's TCI provides a reliable way to quantify personality traits related to

92 susceptibility to the schizophrenia spectrum.

93 The association between personality and schizophrenia has been reinforced by several

94 studies that relate these personality traits with other abnormalities in schizophrenia. For

95 example, the correlation between some dimensions of temperament and changes in

96 monoaminergic activity has been postulated as the biological basis of schizophrenia

97 (Ebstein 2006; Mitsuyasu et al. 2001). In addition, an interaction has been observed

98 between polymorphisms of these two systems that predicts the scores on harm avoidance

99 (Benjamin et al. 2000).

100 Furthermore, several studies of schizophrenia have suggested an association between

101 personality traits and other candidate markers of vulnerability. Specifically, the presence

102 of schizotypal personality traits correlates with the presence of neurological soft signs

103 (NSS) in relatives of patients with schizophrenia (Mechri et al. 2009; Mechri et al. 2010).

104 Traditionally, NSS are defined as minor neurological abnormalities without a definite

105 localization in the brain, including several clinical manifestations related to simple motor

106 coordination, complex motor sequencing, sensory integration and disinhibition signs

107 (Chan & Gottesman 2008). Alterations in motor coordination and integration of stimuli are

108 positively correlated with both the total scores and with the cognitive perceptive

109 component of scales measuring schizotypy (Chan et al. 2010; Kaczorowski et al. 2009).

110 Thus, NSS have been suggested as markers of disease vulnerability, which are present

111 prior to the start of treatment and are independent of illness state (as well as type of

112 antipsychotic treatment) (Chan et al. 2010; Bombin et al. 2003), and NSS are correlated

113 with structural and functional brain abnormalities related to schizophrenia (Mouchet-

114 Mages et al. 2011; Zhao et al. 2014).

115 Interestingly, temperament and character features and NSS have been shown to

116 aggregate in the relatives of schizophrenia patients (Krebs et al. 2000; Andreasen et al.

117 2005), supporting the view that both are likely to reflect genetic liability to schizophrenia.

118 In addition, the distribution of NSS in schizophrenia, and in first-degree relatives, is

119 consistent with the endophenotype criterion of familial association (Zhao et al. 2014).

120 However, belonging to the same family could act as a confounding factor because it

121 includes environmental influence and common genetic factors unrelated to the illness. In

122   this respect, no studies are available comparing both NSS and personality in patients with

123   schizophrenia and non-psychotic relatives.

124   The aim of this study was to investigate the association between personality traits,

125   neurological soft signs and vulnerability to schizophrenia. Firstly, to determine whether

126   personality traits could be vulnerability markers of schizophrenia, or if they are simply

127   associated with the disease, we compared personality traits and neurological soft signs

128   between patients, relatives and controls. Secondly, to establish whether those domains

129   that showed differences between groups were significantly associated with known

130   markers of disease vulnerability, correlations between personality traits and NSS were

131   calculated for the entire population.

132

133

2. Materials and methods

2.1. 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 5 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 3 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

157 received electroconvulsive therapy and had been clinically stable for the last 6 months

158 (all positive items of the PANSS positive subscale scoring 4 or lower). The non-psychotic

159 relatives were from the same mother and father of a patient with a diagnosis of

160 schizophrenia, according to DSM IV-TR. Control subjects and their first and second

161 degree relatives had to be free of any axis I disorders. The study was approved by the

162 ethics committee of the CEIC-Parc de Salut Mar Hospital (2011/4141/I). All subjects gave

163 informed written consent and were assured of the confidentiality of the data being

164 collected.

165 *2.2. Experimental Procedure*

166 Basic socio-biographical data were collected from the medical history. This data included

167 years of education, socio-economic level, psychiatric and medical history, years from

168 disease onset, administered treatment and psychiatric history of first degree relatives.

169 Patients were clinically assessed using the Positive and Negative Syndrome Scale

170 (PANSS) (Peralta & Cuesta 1994) and the overall functioning of the subjects was

171 assessed using the Global Adaptive Functioning (GAF) (Jones et al. 1995).

172 All subjects were assessed with the Spanish version of the Temperament and Character

173 Inventory (TCI-R) (Gutiérrez-Zotes et al.) and the Neurological Soft Signs Scale (Krebs

174 et al. 2000). Temperament is comprised of novelty seeking (i.e., impulsive, exploratory),

175 harm avoidance (i.e., anxious, shy), reward dependence (i.e., sentimental, approval-

176 seeking) and persistence (i.e., determined, ambitious). Character is comprised of self-

177 directedness (i.e., responsible, purposeful), cooperativeness (i.e., helpful, empathic) and

178 self-transcendence (i.e., imaginative, self-forgetful). The TCI-R sub-scores for each of the

179 seven dimensions were calculated.

180   The NSS scale is composed of 23 items, rated from 0 to 3, and regrouped in five

181   consistent factors: Motor coordination (hand dysrhythmia, finger opposition, fist edge–

182   palm, foot dysrhythmia, alternative movements: foot speed, alternative movements: hand

183   speed, standing heel-to-toe), Motor integration (Romberg, apraxia, tandem walk, finger-

184   to-nose, gait, tongue protrusion), Sensory integration (stereognosia, hand–face,

185   constructive apraxia, graphesthesia, right-left recognition), Quality of lateralization (right-

186   left confusion, lateral preference, right-left asymmetry) and Involuntary movements

187   (abnormal movement and posture, mirror movements).

188   The NSS total score and sub-scores for each of the factors were calculated. Two

189   assessors (LG and FP) were trained to perform the neurological assessment. The inter-

190   rater reliability of the assessment of NSS was established by the two assessors and jointly

191   examined 20 independent subjects. The intra-class correlation coefficient (SPSS: two

192   way Mixed Effect Model, confidence interval=95%) was 0.90 [0.77–0.95].

193

194   *2.3. Statistical analysis*

195   First, univariate analyses of the sociodemographic data were performed. Differences in

196   age and years of education were determined with the Analysis of Variance (ANOVA), and

197   the *chi* square test was applied for gender differences. As there were statistical

198   differences in years of education, it was added as a covariate in the rest of the analyses.

199   Temperament, character and NSS scores were analyzed with the Levene test. Then, to

200   study differences between groups, and depending on the results on Levene tests, the

201   analysis was performed with ANOVAs followed by the Bonferroni post-hoc test or a

202   Kruskall-Wallis test followed by Mann-Whitney U test, adding years of education as a

203 covariate. Pearson correlations were performed using the entire population between the

204 total NSS scores and sub-scores for each temperament and character domains, adding

205 years of education as a covariate. Accepting an alpha risk of 0.05 and a beta risk of 0.2

206 in a two-sided test, 23 subjects are necessary in every group to recognize as statistically

207 significant a difference greater than or equal to 1 unit. The common standard deviation is

208 assumed to be 1.2. It has been anticipated a drop-out rate of 0%.

209

210

211   **3. Results**

212   *3.1. Demographic characteristics*

213   No significant differences between groups were observed in terms of age or gender;

214   although patients with schizophrenia and non-psychotic relatives showed significantly

215   less years of education than controls (Table 1).

216

217   *3.2. Temperament scores (TCI-R)*

218   Table 2 shows the scores obtained for each temperament dimension in controls, non-

219   psychotic relatives and patients. Harm Avoidance scores were significantly different

220   between the groups [$F(2,88) = 13.10$, $p<0.001$] (Fig. 1). Subsequent post-hoc analysis

221   revealed that patients with schizophrenia and non-psychotic relatives obtained

222   significantly higher scores on harm avoidance than controls, and patients showed

223   significantly higher scores than relatives (Fig. 1). In addition, significant differences

224   between the groups were observed in reward dependence [$F(2,88) = 3.15$, $p<0.05$] and

225   persistence [$F(2,88) = 3.83$, $p<0.05$] scores. The post-hoc test revealed that patients

226   obtained significantly lower reward dependence scores than controls and both patients

227   and non-psychotic relatives had lower persistence scores than controls. No significant

228   differences between groups were observed for novelty seeking scores (Fig. 1).

229

230   *3.3. Character scores (TCI-R)*

231   Table 2 shows the scores obtained for each character dimension in controls, non-

232   psychotic relatives and patients. Significant differences between groups were observed

233   in self-directedness, cooperativeness and self-transcendence scores. A subsequent

234   subgroups analysis revealed that both patients and relatives obtained significantly lower

235   scores on self-directedness and cooperativeness than the controls (Fig. 2). In addition,

236   no significant differences were observed in self-directedness or cooperativeness scores

237   between patients and relatives. Finally, significantly higher self-transcendence scores

238   were observed in patients with schizophrenia than in the controls (Fig. 2).

239

240   *3.4. Neurological Soft Signs Scores*

241   Significant differences between groups were observed for the total NSS scores [F(2,88)

242   =41.98, p<0.01]. A subsequent post-hoc analysis revealed significantly higher NSS

243   scores in both non-psychotic relatives and patients, compared with the control subjects.

244   In addition, patients showed higher total NSS scores than non-psychotic relatives (Fig.

245   3). Scores obtained in each NSS domain for the three groups are shown in Table 3.

246   Significant differences between groups were observed for each of the NSS sub-scores.

247   Post-hoc analyses revealed significantly higher scores in motor coordination and

248   involuntary movements in patients and relatives, as compared with the controls. In

249   addition, patients showed higher scores than relatives in both of these NSS sub-scores.

250   With respect to motor integration and quality of lateralization, patients and relatives also

251   showed higher scores than control subjects, while no significant differences were

252 observed between patients and relatives. For sensory integration, higher scores were

253 observed only in patients compared with the control group (Fig 3).

254

255 *3.5 Correlations between NSS and TCI-R scores*

256   Table 4 shows the Pearson coefficients obtained for correlations between NSS scores

257 and temperament and character scores for the entire population studied. In terms of

258 temperament, total NSS scores were positively correlated with harm avoidance, while a

259 negative correlation was observed between total NSS, novelty seeking and persistence

260 scores. When each temperament dimension was analyzed separately, harm avoidance

261 scores correlated significantly with sensory integration, motor coordination and motor

262 integration scores. For persistence, significant negative correlations were observed with

263 motor coordination, sensory integration, motor integration and involuntary movements.

264 Finally, a positive correlation was observed between reward dependence and involuntary

265 movements. Novelty seeking scores were negatively correlated with sensory integration.

266 With regards to character, total NSS scores were negatively correlated with self-

267 directedness and cooperativeness. For the individual character domains, self-

268 directedness was negatively correlated with motor coordination and motor integration

269 scores, while cooperativeness was negatively correlated with sensory integration, motor

270 integration and motor coordination scores. No significant correlations were observed

271 between self-transcendence and total NSS scores, although a positive correlation was

272 present with motor coordination.

273

275 **4. Discussion**

276 The major finding in this study was that patients with schizophrenia and non-psychotic

277 relatives display a unique profile of temperament and character that correlates with

278 alterations in NSS. Comparing personality traits and NSS between groups, both patients

279 with schizophrenia and non-psychotic relatives obtained significantly higher scores on

280 harm avoidance than controls, and patients showed significantly higher scores than

281 relatives.   Also patients and non-psychotic relatives had lower persistence, self-

282 directedness, and cooperativeness scores than controls. In addition, no significant

283 differences were observed in self-directedness or cooperativeness scores between

284 patients and relatives. Finally, significantly higher self-transcendence scores were

285 observed in patients with schizophrenia, compared to controls.

286 Our results reveal an association between these hypothesized vulnerability markers, as

287 temperament (especially harm avoidance, reward dependence and persistence) and

288 character (especially self-directedness and cooperativeness) correlated with the

289 presence of NSS in the entire sample.

290 Studies in non-psychotic relatives have been essential to uncover new vulnerability

291 biomarkers of schizophrenia. In this sense, several studies have provided evidence

292 showing that particular personality features could be considered as possible

293 schizophrenia-related endophenotypes (Smith et al. 2008). In this study, it was found that

294 non-psychotic relatives had significantly higher harm avoidance scores compared with

295 the controls, but lower scores than patients with schizophrenia. In agreement with our

296 data, Smith et al. (2008) found higher harm avoidance scores in siblings of patients with

297 schizophrenia than in controls subjects, and another study reported that siblings are

298　positioned between controls and patients with schizophrenia, in terms of temperament

299　profile (Calvó de Padilla et al. 2006). In contrast, Bora and Veznedaroglu (2007) did not

300　find differences in temperament between relatives of schizophrenic patients and the

301　controls, although they did observe differences in harm avoidance between controls and

302　relatives with high schizotypy. Together, these studies support the idea that high levels

303　of harm avoidance may be associated with genetic vulnerability to schizophrenia, which,

304　in turn, will interact with environmental and neurobiological influences to determine the

305　expression of the disease. According to Kim et al. (2011) and Hansenne et al. (2003),

306　harm avoidance has been associated with D2/3 receptor availability in the associative

307　and sensorimotor subdivisions of the striatum and high Mismatch Negativity and

308　hypervigilant fear perception, suggesting abnormal sensory gating of aversive stimuli as

309　a vulnerability variable in schizophrenia. Furthermore, a locus on chromosome 8p21

310　associated to schizophrenia showed a linkage to harm avoidance (Zohar et al. 2003)

311　With regards to character, it was found that, similar to patients; non-psychotic relatives

312　had significantly lower self-directedness and cooperativeness scores when compared to

313　controls. Other studies have reported lower levels of self-directedness and

314　cooperativeness in siblings with high schizotypy as compared to controls, and high levels

315　were observed in siblings with low schizotypy (Bora & Veznedaroglu 2007). One

316　important aspect of the data in this study is that even though the non-psychotic relatives

317　that participated in this study did not have familial ties to the patients with schizophrenia,

318　they showed similar low levels of self-directedness and cooperativeness. It is well known

319　that character is influenced more by environmental factors than temperament (Josefsson,

320　Jokela, Cloninger, et al. 2013; Josefsson, Jokela, Hintsanen, et al. 2013). However, the

321 data in this study agrees with other studies, such as Gillespie et al. 2003; Josefsson et

322 al. 2013, showing that character may also have a genetic component. Self-transcendence

323 was higher in patients than in the controls subject, but not in relatives. These results are

324 in agreement with other studies reporting elevated self-transcendence in patients (Glatt

325 et al. 2006; Smith et al. 2008). In contrast, Calvo de Padilla et al. (2006) found lower self-

326 transcendence and cooperativeness in the relatives of patients with schizophrenia with

327 respect to the controls. The discrepancies between studies could be due to the fact that

328 the population used in the Calvo and Padilla study was an indigenous community living

329 in a rural environment and not in an urban environment.

330 In accordance with previous studies, we found lower levels of persistence and reward

331 dependence only in patients with schizophrenia as compared to controls. These findings

332 endorse the hypothesis stating that high harm avoidance, low persistence and low reward

333 dependence constitutes a temperament profile leading to social detachment,

334 perseveration and schizotypy, when combined with a disorganized character profile that

335 impairs emotional regulation (Smith et al. 2008; Bora & Veznedaroglu 2007).

336 As reported previously in patients with schizophrenia (Bombin et al. 2003; Chen et al.

337 2005; Aksoy-Poyraz et al. 2011) and in non-psychotic relatives (Gourion et al. 2004;

338 Mechri et al. 2010), we found higher NSS in both groups as compared with the controls,

339 confirming the hypothesis that NSS is a vulnerability marker for schizophrenia. In addition,

340 these results agree with the idea that NSS segregate with the illness and may be a valid

341 and useful endophenotype (Chan et al. 2010). The association between personality

342 characteristics and NSS has been studied separately in siblings, or in patients with

343 schizophrenia, but there are no prior studies correlating NSS with personality traits in

344 patients with schizophrenia, non-psychotic relatives and controls. Our correlational

345 analysis, including all three groups, showed that subjects with higher NSS scores

346 exhibited higher harm-avoidance and persistence scores, while they exhibited lower self-

347 directness and cooperativeness. Two related studies have evaluated the association

348 between NSS and schizotypal personality traits with contradictory results. Thus, Mechri

349 et al. (2010), using the Schizotypal Personality Questionnaire (SPQ), showed that the

350 overall NSS score was correlated with the presence of schizotypal traits in both non-

351 psychotic siblings and controls, while no association was found between NSS and

352 schizotypal dimensions in relatives of patients with schizophrenia, when the SPQ test was

353 used (Bollini et al. 2007). The differences observed between these two studies, as well

354 as the present work, could be due to the fact that they used a personality assessment

355 tool based on outdated DSM III criteria. In this respect, one of the strengths of this study

356 is the use of the TCI-R scale, which is a comprehensive personality questionnaire that

357 has been extensively validated in clinical practice and research (Fassino et al. 2013;

358 Fresán et al. 2015). One of the advantages of the TCI-R is that it explores normal and

359 pathological personalities in subjects with mental disorders and also in the general

360 population (Cloninger et al. 2012; Josefsson et al. 2011; De Fruyt et al. 2006). Another

361 advantage is that temperament and character domains have been associated with

362 structural and functional changes in the brain (Laricchiuta et al. 2014; Lei et al. 2014;

363 Tuominen et al. 2013)), and have been related to specific chromosomal regions (Serretti

364 et al. 2008; Zohar et al. 2003) supporting the neurobiological substrate for this personality

365 model (Yang et al. 2015). Another strength of the study is that the relatives of patients

366   with schizophrenia had no familial ties to the patients used, thus decreasing the possibility

367   that similar rearing would confound the results.

368   Finally, several limitations of the study are acknowledged. The first is the small sample

369   size used, even though the TCI-R scores and NSS scores were similar to those reported

370   in larger samples in the literature (Smith et al. 2008; Mechri et al. 2010). The second

371   limitation is the use of an estimate of IQ values as a selection criterion, but not as a

372   covariate in the analysis. This issue may have been a potential confounding factor, since

373   IQ has been previously associated with personality and with NSS.

374   In conclusion, these results showed that patients with schizophrenia were more asocial

375   (higher harm avoidance and lower reward dependence), more perseverative (higher

376   persistence) and more schizotypal (lower self-directedness and cooperativeness, higher

377   self-transcendence). In the group analysis we found significant changes in personality

378   traits in relatives of patients with schizophrenia. Indeed, non-psychotic relatives showed

379   higher harm avoidance, lower self-directness and lower cooperativeness when compared

380   to control subjects. Interestingly, all three items were correlated with total NSS scores.

381   Thus, a positive correlation was observed between higher harm avoidance and total NSS,

382   and negative correlations were found between lower self-directedness and lower

383   cooperativeness with total NSS. These findings lend support to the idea that such

384   personality traits could be potential vulnerability markers for schizophrenia. These

385   vulnerability markers are likely to be useful tools in the prospective studies of high-risk

386   populations.

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390

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Figure 1(on next page)

Figure 1

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.

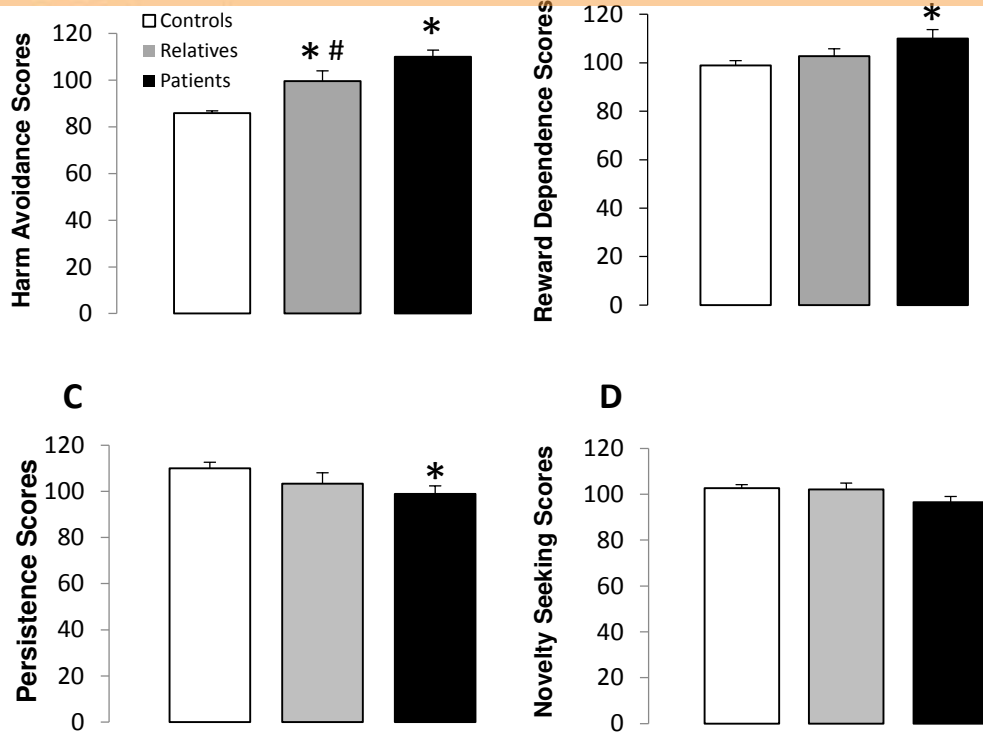**Figure 2**(on next page)

Figure 2

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.
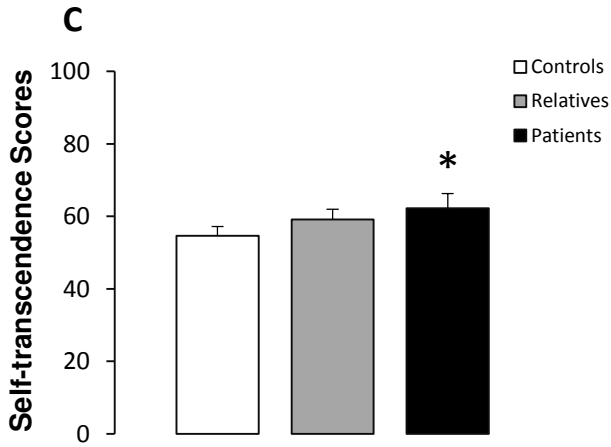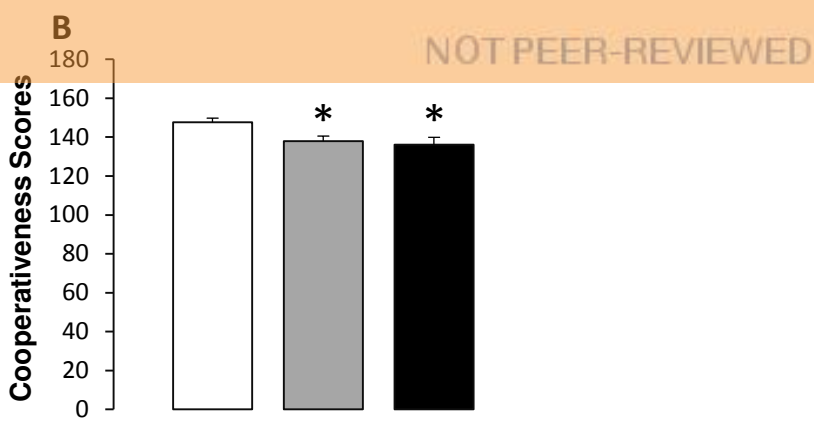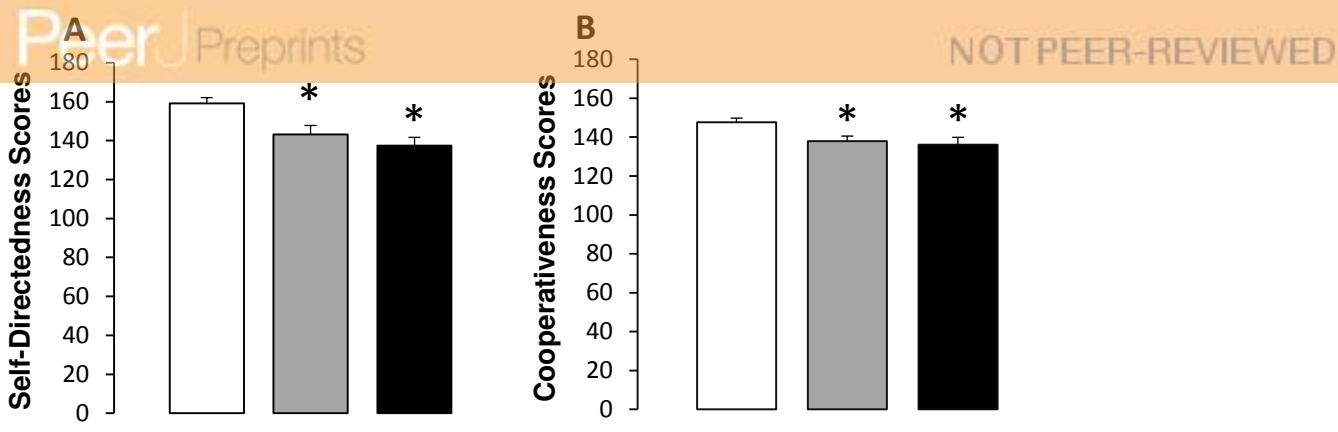
A

B

C

☐ Controls
◼ Relatives
■ Patients

Figure 3(on next page)

Figure 3

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.
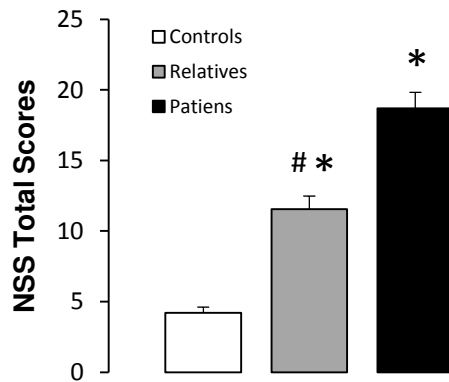
Table 1(on next page)

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

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

1
2   **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*

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Table 2(on next page)

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

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

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*

Table 3 (on next page)

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

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

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*

Table 4 (on next page)

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

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

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