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Schizotypal traits, neurocognition, and paternal age in unaffected first degree relatives of patients with familial or sporadic schizophrenia☆

Chrysoula Zouraraki[a,*], Leda Karagiannopoulou[a], Penny Karamaouna[a], Eleftherios G. Pallis[b], Stella G. Giakoumaki[a]

[a] Department of Psychology, Faculty of Social Sciences, University of Crete, Rethymno 74100, Crete, Greece
[b] Department of Medicine, School of Health Sciences, National and Kapodistrian University of Athens, Athens 11527, Greece

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ABSTRACT

Studies comparing cognitive processes between familial and sporadic schizophrenia have yielded inconsistent findings. In this study we examined differences in neurocognition and schizotypal traits in unaffected relatives of schizophrenia-spectrum patients with either the familial (multiplex) or the sporadic (simplex) subtype of the disorder, taking paternal age at birth into consideration. Simplex (n = 65; SR), multiplex (n = 35; MR) relatives and controls (n = 114) were compared on several cognitive functions and schizotypal traits; between-group differences were evaluated with and without including paternal age in the analyses. SR and MR had higher negative and paranoid traits compared with controls, but paternal age abolished the differences between the SR and control groups. When taking into account schizotypal traits and participants' age, controls outperformed MR in strategy formation and set-shifting and SR in psychomotor speed, set-shifting and executive working memory. After including paternal age in the analyses, controls outperformed MR in strategy formation, working memory and executive working memory and both groups in psychomotor speed and set-shifting. These findings suggest that multiplex relatives present with a "riskier" personality and cognitive profile when considering the effects of paternal age. Nevertheless, simplex relatives are impaired in fundamental cognitive processes, thus highlighting the detrimental effects of paternal age on neurocognition.

1. Introduction

Schizophrenia is a heterogeneous psychiatric disorder, characterized by a complex genetic and environmental etiology (Tsuang et al., 2001). One way to elucidate the risk factors implicated, is to sub-divide schizophrenia into a familial (or multiplex) and a sporadic (or simplex) subtype, according to the presence or absence of family history (Murray et al., 1985), respectively. The familial subtype is more genetically-determined compared with the sporadic, while the latter has been widely attributed to environmental insults or with genetic alterations caused by environmental factors (Kranz et al., 2016; Maziade & Paccalet, 2013; Schwab & Wildenaue, 2013). Advanced paternal age is one of the non-genetic factors implicated in sporadic schizophrenia (see Malaspina et al., 2015), although it has also been associated with increased susceptibility and earlier onset of the disease in familial cases (Wang et al., 2015). The classification into multiplex and sporadic simplex forms of schizophrenia, has revealed that multiplex patients exhibit more severe positive and negative symptoms (Arajärvi et al., 2006), persistent and higher emotional distress (Ritsner et al., 2007), greater neurocognitive impairment (Erol et al., 2012; Liang et al., 2016) and neuroanatomical abnormalities (Lui et al., 2009) compared with simplex patients.

A promising approach to investigate the vulnerability to schizophrenia, avoiding the confounding effects of the illness, is through the study of endophenotypic markers, in unaffected first-degree relatives of patients. Previous studies have shown that multiplex relatives express increased schizotypal traits (Appels et al., 2004; Lien et al., 2010) and also present with deficits on several neurocognitive functions, such as cognitive flexibility (Aydin et al., 2017; Erol et al., 2012; Liang et al., 2016; Lin et al., 2011; Quinones et al., 2009), sustained (Tsuang et al., 2006) and selective (Erol et al., 2012) attention as well as verbal fluency (Birkett et al., 2008; Liang et al., 2016) compared with "simplex" relatives and/or control individuals. Findings on the neurocognitive performance of simplex unaffected relatives are not consistent. As the higher familial genetic loading for schizophrenia is suggested to be accompanied by worse neurocognitive performance, simplex relatives

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* Corresponding author.
E-mail address: psyp172@psy.soc.uoc.gr (C. Zouraraki).

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are expected to present with an intermediate performance between multiplex relatives and controls (Birkett et al., 2008; Erol et al., 2012; Gur et al., 2007; Tsuang et al., 2006). The latter has been confirmed, as simplex relatives have indeed more pronounced neuropsychological deficits (Aydin et al., 2017; Birkett et al., 2008; Erol et al., 2012) and neuro-motor abnormalities (Lencer et al., 2003; Petrovsky et al., 2009) compared with controls. However, (a) Warnick & Allen (2005) reported that simplex relatives (with high schizotypy) showed greater deficits in verbal working memory than multiplex relatives and (b) McDonald (2008) in the Maudsley family study of psychosis reported that simplex relatives had impairments in verbal episodic memory, strategy formation and planning, which were not identified in multiplex relatives.

Although advanced paternal age has been clearly associated with the incidence of schizophrenia (for a review see de Kluiver et al., 2017), little is known on its effects/associations with markers of the disease, such as cognitive abilities and schizotypal traits. Thus, so far there is one report of advanced paternal age being associated with poorer non-verbal intelligence in schizophrenia patients (Lee et al., 2011) and a second one describing that advanced paternal age predicts higher positive schizotypal traits in a healthy sample (Grattan et al., 2015). In order to further investigate the topic, the present study aimed to examine whether there are any differences between unaffected first-degree multiplex and simplex relatives of schizophrenia-spectrum patients and control individuals in schizotypal traits and neurocognitive performance, taking paternal age into consideration. We hypothesized that multiplex relatives would show higher schizotypal traits along with reduced neurocognitive performance compared with simplex relatives and controls and that simplex relatives would be intermediate. Given the lack of literature on the effects of paternal age on schizotypal traits and neurocognition, we could not formulate any further hypotheses involving this factor.

2. Methods

2.1. Participants

The initial sample consisted of 123 unaffected first-degree relatives (offspring and siblings) of patients with a diagnosis of schizophrenia-spectrum disorders (only one relative of each patient was included). They were recruited via the local psychiatric services (i.e. public and private psychiatric clinics and day centres offering psychiatric treatment) and advertisements briefly describing the study in local media. They were assessed by an experienced psychiatrist (E.G.P.) or psychologist (C.Z.) with the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and had to meet the following criteria: (i) no personal history of head trauma, medical/neurological conditions, (ii) no current use of prescribed/recreational drugs and (iii) no personal history of DSM-IV Axis I disorders. Nineteen subjects did not fulfil the criteria for participation (7 were excluded due to Axis I pathology, 5 reported personal history of head trauma, medical/neurological conditions, 6 were excluded due to self-reported current use of recreational/prescribed drugs) and another 5 participants dropped-out; therefore, the final sample consisted of 100 unaffected first-degree relatives. The group of relatives was split into two sub-groups according to their “familiality loading.” All relatives in the multiplex group (n = 35) had more than one member in their family diagnosed with a schizophrenia spectrum disorder, whereas relatives in the simplex group (n = 65) had only one first-degree relative diagnosed with a schizophrenia spectrum disorder (the information on the family history of the relatives was collected by themselves during the psychiatric evaluation). One-hundred and fourteen community participants, recruited via advertisements briefly describing the study in the local media, also participated in the study as the control group. This group also underwent psychiatric evaluation using the MINI (Sheehan et al., 1998) and had identical exclusion criteria with the relatives, with the additional exclusion criterion of family (up to second-degree) history of DSM-IV Axis I disorders.

2.2. Procedure

The present study was part of the Prefrontally-Mediated Endophenotypes in the Schizophrenia Spectrum (PreMES) study. The study was approved by the Research Ethics Committee of the University of Crete and the Bureau for the Protection of Personal Data of the Greek State. All participants, after detailed presentation of the study's aims and procedures and prior to their inclusion in the study, gave written informed consent; they were also informed both orally and in written that they could withdraw their consent for participation at any time without any cost. The study took place between January 2014 and October 2015, all participants were allowed to choose their preferred time during the day for the assessment, they were tested in configured testing rooms in the University of Crete and each individual assessment lasted approximately 2.5 hours in total. After completion of the assessment, participants had the opportunity to discuss with the research team any additional questions arising from the testing procedure.

2.3. Instruments and variables

2.3.1. Assessment of schizotypy

All participants were administered the Greek version of the Schizotypal Personality Questionnaire (SPQ; Tsaousis et al., 2015). The SPQ is a self-report, 74-item questionnaire with a dichotomous response format (Raine, 1991). The item scores provide nine subscales that are analysed into four schizotypal factors, namely Negative (NegS; comprising of excessive social anxiety, lack of close friends, constricted affect and suspiciousness) Paranoid (ParS; including ideas of reference, excessive social anxiety and suspiciousness), Cognitive-Perceptual (CPS; consisting of odd beliefs/magical thinking and unusual perceptual experiences) and Disorganized (DiS; including eccentric/odd behaviour and odd speech) schizotypal factors.

2.3.2. Neuropsychological assessment

Neurocognitive abilities were assessed with an extensive battery of tasks that either have not been widely employed in schizotypy research or have yielded discrepant findings. Specifically, we administered the

(1) Iowa Gambling Task (IGT; Bechara et al., 1994), for emotional decision making.
(2) Stroop color-word test (Golden, 1978) for control inhibition.
(3) Wisconsin Card Sorting test (WCST; Nelson, 1976) for set-shifting.
(4) Letter–Number Sequencing (LNS; Wechsler, 2008) for executive working memory.
(5) Trail-Making Test (TMT; Tombaugh, 2004; Zalonis et al., 2008) for processing speed/set-shifting.
(6) Verbal Fluency test (VF; Kosmidis et al., 2004) for phonemic/semantic fluency.
(7) Raven's Progressive Matrices (Raven et al., 2003) for abstract reasoning
(8) Stockings of Cambridge (SoC) of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Robbins et al., 1998) for planning/complex problem solving (Owen et al., 1990).
(9) Spatial Working Memory (SWM) of the CANTAB for spatial working memory/strategy formation (Owen et al., 1990).
(10) Stop Signal Task (SST) of the CANTAB for response inhibition (Cambridge Cognition, 2012).
(11) Action Program Test of the Behavioral Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996) for practical problem solving.
(12) Key Search Test of the BADS for strategy formation (Wilson et al., 1996).

A detailed description of the neuropsychological tasks and outcome measures is provided in Supplementary Material.[1]

2.3.3. Subjective ratings of mood and feelings

Upon their arrival at the testing site participants were assessed for their subjective mood and feelings, with a set of visual analogue scales (VAS; Bond & Lader, 1974). VAS is a set of 16-item 10-cm scales examining anxiety, discontentment and alertness. We administered the scales, in order to control for between-group differences in mood/feelings on the day of testing, which might bias our findings. A detailed description is provided in Supplementary material.

2.3.4. Sociodemographic variables

Participants were asked for additional details regarding their age, years of education, smoking habits, paternal age at birth, the month of their birth (to determine season of birth) and whether there were any complications at their birth or during their fetal life (none reported). We collected these data to control for between-group differences in variables that could potentially bias our findings.

2.4. Statistical analyses

Demographic and VAS data were compared between the 3 groups using either parametric or non-parametric tests, according to normality of the distribution. Thus, between-group differences in age, years of education, cigarettes smoked/day, paternal age at birth and VAS anxiety were examined with non-parametric Kruskall–Wallis comparisons due to lack of normality in the distribution of these variables while VAS discontentment and alertness scores were analyzed with one-way analysis of variance (ANOVA). Differences in sex, season of birth and relationship with the patient were examined with Pearson's χ^2. Between-group differences in SPQ scores were examined with a series of analyses of covariance (ANCOVAs) with either only age of the participants or both age of the participants and paternal age at birth as covariates and sex and group (i.e., simplex relatives, multiplex relatives and controls) as grouping factors. We included these covariates and sex in the models, because, as described below, we found significant between-group differences in these variables. In order to compare the 3 groups on their neurocognitive performance, we ran either ANCOVAs or multivariate analyses of covariance (MANCOVAs) for each neuropsychological task (dependent variables: all outcome variables of the neuropsychological tasks; described in detail in the Supplementary material). ANCOVAs were selected for the tasks that yielded only one outcome variable while MANCOVAs were selected for the tasks with multiple outcome variables. In these analyses, group and sex were the between-subjects' factors. The covariates were either age, ParS and NegS ("analysis one" in findings) or age along with ParS, NegS and paternal age ("analysis two" in findings). This time ParS and NegS were added in the covariates, because, as described below, we found significant between-group differences in these schizotypal factors. Significant between-group differences were followed-up with Bonferroni post-hoc comparisons. To correct for multiple testing and reduce the probability of type I error, p values were Bonferroni corrected [0.05/12 (12 neurocognitive measures) = 0.0042]. Therefore, we considered only p values ≤ 0.0042, as significant and p values < 0.01 as trends for significance.

3. Results

3.1. Group differences in demographic variables

There were significant between-group differences in age [$p < 0.05$; multiplex relatives were older than controls and simplex relatives (both p values < 0.05)], paternal age at birth [$p < 0.001$; simplex relatives had older fathers at the time of their birth compared with controls and "multiplex" relatives (both p values < 0.001)], sex [$p < 0.001$; the multiplex group comprised of fewer men compared with the simplex and control groups, whereas the simplex group included fewer women compared with the control group] and relationship with the patient [$p < 0.001$); the simplex group included more offspring compared with the multiplex group ($p < 0.001$)]. The three groups did not differ in any other demographic or VAS-rated variable (all p values > 0.078). A detailed description of the demographic characteristics of the three groups is presented in Supplementary Table 1.

3.2. Group differences in schizotypal traits

The results of the univariate ANCOVAs are presented in Supplementary Table 2. When only age of the participants was included as a covariate, both groups of relatives scored higher compared with the control group, in ParS and NegS (p values < 0.001). There were no significant differences in CPS and DiS (p values > 0.05). There was a significant sex x familiality interaction for CPS ($p < 0.05$) with multiplex males scoring intermediate between simplex and controls, whereas control females scored higher than multiplex and simplex females. We also found a significant sex main effect for ParS, NegS, and DiS, with males scoring higher compared with females (all p values < 0.05).

When we added paternal age in the analysis, the significant differences in ParS and NegS were retained (both p values < 0.005), but this time only the multiplex relatives scored higher than controls ($p < 0.005$). The sex main effect for ParS and NegS, with males scoring higher than females (all p values < 0.05) remained significant.

3.3. Group differences in neurocognitive performance

Table 1 details the scores (mean ± *SD*) of the three groups in the neurocognitive tasks and between-group significant differences (for the non-significant between-group differences, see Supplementary Table 3). We also describe below only the statistically significant findings as well as the findings with trend-level significances.

3.3.1. Spatial working memory

In analysis one, there was a significant multivariate main effect of familiality [Wilks' $\lambda = 0.892$, $F(8,404) = 2.981$, $p < 0.005$, partial $\eta^2 = 0.056$]. Follow-up ANOVAs revealed significant between-group differences in Strategy score [$F(2,205) = 7.775$, $p < 0.001$, partial $\eta^2 = 0.071$], with the control group outperforming multiplex relatives ($p < 0.001$). When we added paternal age as a covariate in the model, the significant multivariate main effect of familiality [Wilks' $\lambda = 0.864$, $F(8,368) = 3.497$, $p < 0.001$, partial $\eta^2 = 0.071$] remained. The ANOVAs revealed significant between-group differences in Strategy score [$F(2,187) = 8.119$, $p < 0.001$, partial $\eta^2 = 0.080$] and within errors [$F(2,187) = 5.646$, $p < 0.005$, partial $\eta^2 = 0.057$], with the control group outperforming multiplex relatives (both p values < 0.005).

3.3.2. Wisconsin card sorting test

In analysis one, there was a significant multivariate main effect of familiality [Wilks' $\lambda = 0.849$, $F(14,398) = 2.431$, $p < 0.005$, partial $\eta^2 = 0.079$]. Follow-up ANOVAs revealed a trend-level significance for Nelson-type perseverative errors [$F(2,205) = 5.124$, $p < 0.01$, partial $\eta^2 = 0.048$] with the control group tending to outperform multiplex relatives ($p = 0.005$). In analysis two, we also found a significant multivariate main effect of familiality [Wilks' $\lambda = 0.801$, $F(14,362) = 3.041$, $p < 0.001$, partial $\eta^2 = 0.105$]. The ANOVAs revealed significant between-group differences in Nelson-type perseverative errors [$F(2,187) = 8.178$, $p < 0.001$, partial $\eta^2 = 0.080$] but this time both the control group and simplex relatives outperformed

[1] Behavioural Assessment of the Dysexecutive Syndrome (BADS) Greek Research Edition. Copyright © (1996, 2016) by Barbara A Wilson et al. Adapted and used with permission by Pearson Education Ltd.

Table 1
Scores in neurocognitive measures [M(SD)] and significant between-group differences.

	Controls (n = 114)	Simplex group (n = 65)	Multiplex group (n = 35)	p value of familiality (considering participants' age, NegS, ParS)	p value of familiality (additionally considering paternal age)	Cohen's d
SWM total within errors	1.61 (1.87)	4.75 (10.37)	6.17 (11.54)	.039	**.004 C < MR (p = .003)**	C vs MR (d = 0.55) vs SR (d = 0.42)
SWM strategy score[a]	38.65 (5.58)	37.83 (6.99)	44.66 (6.92)	**.001 C < MR (p < .001)**	**.001 C < MR (p < .001)**	C vs MR (d = 0.96) C vs SR (d = 0.13)
WCST Nelson-type P.E.	1.96 (1.93)	2.68 (4.22)	4.66 (3.86)	.007C ≤ MR (p = .005)	**.001 C < MR (p < .001) SR < MR (p = .004)**	C vs MR (d = 0.88) C vs SR (d = 0.22)
BADS key search total score	11.08 (3.44)	9.85 (3.92)	8.37 (1.97)	**.004 C > MR (p = .004)**	.006 C ≥ MR (p = .006)	C vs MR (d = 0.97) C vs SR (d = 0.33)
TMT part A'	22.02 (6.34)	42.30 (27.02)	29.16 (12.71)	**.001 C < SR (p < .001)**	**.001 C < SR (p < .001) C < MR (p < .001)**	C vs MR (d = 0.71) C vs SR (d = 1.03)
TMT part B'	43.58 (13.60)	86.90 (62.70)	68.42 (42.01)	**.001 C < SR (p < .001) C < MR (p < .001)**	**.001 C < SR (p < .001) C < MR (p < .001)**	C vs MR (d = 0.80) C vs SR (d = 0.95)
LNS total score	11.54 (2.49)	8.95 (3.29)	9.46 (3.10)	**.001 C > SR (p < .001)** C ≥ MR (p = .009)	**.001 C > MR (p = .004)**	C vs MR (d = 0.74) C vs SR (d = 0.89)

Note: SWM = Spatial Working Memory; WCST = Wisconsin Card Sorting Test; BADS = Behavioural Dysexecutive Syndrome; TMT = Trail Making Test; LNS = Letter Number Sequencing Test; C = Control Group; MR = Multiplex Relatives Group; SR = Simplex Relatives Group; P.E. = Perseverative Errors; ParS = Paranoid Schizotypy Dimension; NegS = Negative Schizotypy Dimension.

[a] Higher scores indicate poorer performance.

multiplex relatives (both p values < 0.005).

3.3.3. Behavioral assessment of dysexecutive syndrome-Key search test

In analysis one, there was a significant multivariate main effect of familiality [Wilks' λ = 0.890, F(6,404) = 4.050, p < 0.001, partial η^2 = 0.057]. The ANOVAs revealed significant between-group differences in the total score [F(2,204) = 5.578, p < 0.005, partial η^2 = 0.052] with the control group scoring higher in comparison with multiplex relatives (p < 0.005). When we added paternal age as a covariate in the model, the significant multivariate main effect of familiality remained [Wilks' λ = 0.891, F(6,368) = 3.660, p < 0.005, partial η^2 = 0.056]. This time, the follow-up ANOVAs revealed a trend-level significant difference for total score [F(2,186) = 5.303, p < 0.010, partial η^2 = 0.054], with the control group tending to outperform multiplex relatives (p < 0.006).

3.3.4. Trail-making test

In analysis one, there was a significant multivariate main effect of familiality [Wilks' λ = 0.858, F(4,408) = 8.103, p < 0.001, partial η^2 = 0.074]. The ANOVAs revealed significant between-group differences in both Part A' [F(2,205) = 11.400, p < 0.001, partial η^2 = 0.100] and Part B' [F(2,205) = 13.994, p < 0.001, partial η^2 = 0.120]. The control group outperformed only simplex relatives in Part A and both groups of relatives in Part B (all p values < 0.001). In the analysis two, the multivariate main effect of familiality remained significant [Wilks' λ = 0.808, F(4,372) = 10.444, p < 0.001, partial η^2 = 0.101]. The ANOVAs revealed significant between-group differences in both Part A' [F(2,187) = 11.911, p < 0.001, partial η^2 = 0.113] and Part B' [F(2,187) = 21.553, p < 0.001, partial η^2 = 0.187]. This time, however, the control group outperformed both groups of relatives in both parts of the task (all p values < 0.001).

3.3.5. Letter-number sequencing

In analysis one, there was a significant main effect of familiality [F(2,205) = 9.484, p < 0.001, partial η^2 = 0.085] with the control group outperforming simplex relatives (p < 0.001). We also found that controls had higher total LNS score compared with multiplex relatives, but only at trend-level (p < 0.01). When paternal age was added in the analysis, the main effect of familiality remained significant [F(2,187) = 7.036, p < 0.001, partial η^2 = 0.070]. This time the control group outperformed multiplex relatives (p < 0.005).

4. Discussion

The aim of the study was to examine potential differences in schizotypal traits and cognitive functions in simplex and multiplex relatives of schizophrenia-spectrum patients, taking into consideration paternal age at birth. In brief, we found that (a) both simplex and multiplex relatives had higher NegS and ParS compared with controls but the inclusion of paternal age in our models abolished the differences between the simplex and the control groups and (b) paternal age differentially affects differences in cognition between simplex and multiplex relatives and controls. As regards the simplex group, simple and complex processing speed were impaired irrespective of paternal age while performance in the executive working memory task was poor only was when taking NegS and ParS into account. The multiplex group had impaired strategy formation and complex processing speed irrespective of paternal age; impairments in working memory, set-shifting, simple processing speed and executive working memory were evident only when paternal age at birth was included in the models.

4.1. Schizotypal traits

At first glance our finding that paternal age abolished the difference between simplex relatives and controls in NegS and ParS might seem counter-intuitive. Advanced paternal age has been quite consistently

associated with increased risk for schizophrenia (e.g., Sørensen et al., 2014), especially in its sporadic form (e.g., Malaspina et al., 2002; Sipos et al., 2004), while there is also one study reporting associations with positive schizotypy in a college sample (Grattan et al., 2015). A plausible explanation could be that the average paternal age of our simplex relatives did not reach the critical age of ≥ 50 years that seems to be most crucial for the development of schizophrenia in the offspring as revealed by both research studies (Byrne et al., 2003; Frans et al., 2011; Malaspina et al., 2001; Sipos et al., 2004) and meta-analyses (Torrey et al., 2009; Wohl & Gorwood, 2007). A second plausible explanation is related to the fact that NegS and ParS, which are actually the sub-clinical manifestations of negative and paranoid symptoms, seem to be more genetically than environmentally determined. The high genetic loading of paranoid symptoms was suggested quite early by Kendler & Davis (1981) who reported that paranoid psychosis breeds within families and in accordance with this view, multiplex relatives have been reported to score higher on ideas of reference and paranoid ideation (Yaralian et al., 2000). Negative symptoms have also been found to be highly heritable in families with multiple members affected by schizophrenia (McGrath et al., 2009), while there are also studies reporting that first degree multiplex relatives express higher negative symptoms compared to both simplex relatives and controls (Martin-Reyes et al., 2004, 2010). Our hypothesis that simplex relatives would express schizotypal traits at an intermediate level between multiplex relatives and controls was not confirmed. Actually, our simplex group scored higher compared with the multiplex group in all schizotypal dimensions, although the differences were not statistically significant. As Tarbox et al. (2012) note, however, there might be a response-bias in multiplex relatives due to their *"increased exposure"* (p. 403) to the illness and reluctance to acknowledge associated symptoms.

We also found significant sex differences with males scoring higher in ParS, NegS and DiS compared with females. This is in agreement with previous studies reporting similar findings for negative (Bora & Baysan-Arabaci, 2009; Ma et al., 2015) and disorganized traits (Barron et al., 2015; Bora & Baysan-Arabaci, 2009; Fossatti et al., 2003; Ma et al., 2010, 2015; Mata et al., 2005; Miller & Burns, 1995; Zhang & Brenner, 2017). Although to our knowledge there is currently no other study with the four-factor model of schizotypy reporting higher ParS in males compared with females, out finding is consistent with reports of a higher incidence of paranoid schizophrenia in male patients (Beratis et al., 1997; Petkari et al., 2017).

4.2. Neurocognitive performance

When taking the seemingly genetically mediated paranoid and negative schizotypal traits into consideration, the multiplex group had poorer strategy formation (as assessed with both SWM strategy formation and Key-search total scores) compared with control individuals irrespective of paternal age. The finding is consistent with the schizophrenia literature (Evans et al., 1997; Joyce et al., 2002; Pantelis et al., 1997; Vargas et al., 2009) and the high heritability rates of strategy formation (Need et al., 2009); it also indicates that the risk carried by paternal age at birth is not a strong enough risk-factor to alter the effects of combined genetic influences on strategy formation.

The multiplex group also had poorer working memory as indexed with more within-errors in the SWM task (within errors refer to memory lapses within the same search and can thus be considered as an index of working memory) compared with controls, but only after adjusting for paternal age. Working memory deficits are only partially mediated by genetic factors (Gur et al., 2007) and Need et al., (2009) reported low heritability rates for this specific measure further justifying our finding. Contrary to previous findings by the COGS group on the high heritability of executive working memory in schizophrenia (Greenwood et al., 2007), though, in the present study we found that control individuals scored higher in LNS compared only with the simplex group when we considered for the effects of ParS and NegS. The difference between the present study and the study by Greenwood et al. (2007) could be attributed to (a) differences in demographic variables between the two samples (e.g. COGS examined participants in a wider age range), (b) differences in the design of the study (e.g. the COGS study recruited more than one participants from the same family while in the present study we included only one member from each family) and (c) to the fact that in the present study we took into account the effects of ParS and NegS which has been shown to be associated with executive working memory (Zouraraki et al., 2017). Contrary to our expectations, when we added the effects of paternal age in our model, a different pattern emerged with controls outperforming multiplex relatives. Although highly speculative, we could hypothesize that the actual executive working memory capacity is revealed only when the effects of a number of risk factors both genetic (i.e. high familial loading and positive/negative schizotypal traits) and non-familial (i.e. paternal age) in nature are examined in combination. Thus, when co-examining the effects of all these factors, only the multiplex relatives present with poorer executive working memory while simplex relatives do not.

In Part A of TMT (which assesses "simple processing speed"), the controls outperformed only the simplex relatives when we considered ParS and NegS, but they outperformed both groups when we included paternal age in the analysis. In Part B (which assesses "complex processing speed" involving set-shifting and attentional processes) the control group outperformed both groups of relatives irrespective of paternal age. Models of human cognition propose a hierarchical organization with more complex processes occupying the higher levels of the hierarchy (Carroll, 1997). In a review paper, Goldberg-Hermo et al. (2014) reported that more complex functions are highly heritable, whereas simpler functions have low to moderate heritability estimates leaving space for environmental risk-factors to exert their effects. Thus, because of the low heritability of processes implicated in the simple processing speed sub-task, the simplex group has poor performance due to de novo genetic risk-factors that have been associated with sporadic schizophrenia (Xu et al., 2008) or epigenetic mechanisms as suggested by Quiñones et al. (2009); this effect is retained after including additional risk-factors, such as paternal age. For the multiplex group to perform poorly, though, additional non-familial risk-factors are required. As regards the complex processing speed sub-task, paternal age did not affect the difference between either group of relatives and controls, possibly because of the high genetic liability conferred in the processes involved in this part of the task and the significant effects of NegS and ParS.

In agreement with previous studies (Birkett et al., 2008; Lin et al., 2011), we found a linear increase in perseverative errors as familiality loading increased (i.e. multiplex relatives made more perseverative errors in comparison to both simplex and control groups) with the statistical significance reaching our criterion only when we included paternal age in the analysis. The findings on the heritability of WCST performance are conflicting (Anokhin et al., 2010; Kremen et al., 2007; Taylor, 2007) and small to moderate heritability estimates have been reported (Anokhin et al., 2003, 2010). Interestingly, though, perseverative errors have been suggested to be mediated by combined genetic and environmental risk factors in twin studies (Chou et al., 2010; Godinez et al., 2012). The present finding further confirms this view and indicates that paternal age is indeed a critical factor for the lack of set-shifting when the familiality loading for schizophrenia spectrum disorders is high and paranoid as well as negative schizotypal traits are taken into consideration.

4.3. Limitations of the study

Although this is the first report on the combined effects of schizotypal traits and paternal age on neurocognition, the study has several limitations. Specifically, the higher familiality loading of the multiplex group was deduced only by the higher incidence of schizophrenia-

spectrum disorders in their families. We also included an unequal number of offspring and siblings in the two relatives' groups, which was not controlled for in the statistical analyses and the group of multiplex relatives was rather small. Finally, we did not control for the effects of sex and the affected relatives were diagnosed with a schizophrenia-spectrum disorder and not schizophrenia per se.

4.4. Conclusions

To conclude, the present study suggests that both simplex and multiplex relatives express high NegS and ParS, but these traits do not depend on the age of father at birth in multiplex relatives possibly due to their higher familiality loading. As regards neurocognition, when taking negative and paranoid schizotypal traits into consideration, our findings indicate that (a) strategy formation is highly determined by familiality loading, (b) working memory is only partially mediated by familiality loading while executive working memory depends upon both familial and non-familial risk factors, (c) simple processing speed is not as determined by familiality loading as complex processing speed and (d) perseveration relates to both increased familiality loading and paternal age. These findings could put the basis for future research that will address the limitations of the present study. Equally important is the fact that there is increasing evidence in clinical practice indicating that (a) targeting cognitive deficits in individuals at risk for schizophrenia-spectrum disorders improves the efficacy of early-intervention programs (e.g. Kar & Jain, 2016) and (b) personalized treatment approaches are becoming crucial (Medalia et al., 2018). According to the present findings, the formulation of individualized intervention plans is essential for people having different degrees of familial loading: schizotypal traits, non-familial factors such as paternal age at birth and their concurrence seem to have different effects on cognition in these groups.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.142.

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