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Neurological soft signs in familial and sporadic schizophrenia

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ABSTRACT

Objective: Neurological soft signs (NSS) are a group of minor non-localizable neurological abnormalities found more often in patients with schizophrenia. The aim of the current study was investigate whether there is any difference in their manifestation in familial vs. sporadic schizophrenia.
Material and methods: The study sample included 120 patients suffering from schizophrenia according to DSM-5 (71 males and 49 females; aged 32.79 ± 11.11 years old) and 110 normal controls (57 males and 53 females; aged 33.38 ± 10.14 years old). The assessment included the Neurological Evaluation Scale (NES) and the detailed investigation family history. The statistical analysis included exploratory Analysis of Covariance.
Results: The results of the current study suggest that NSS are more frequent in familial cases of schizophrenia and are even more pronounced in cases with family history of psychosis in either first or second degree relatives.
Discussion: Overall the results suggest the presence of a spectrum of increasing severity from healthy controls to sporadic cases, to cases with non-psychotic family history and eventually to cases with psychotic family history, rather than a categorical distribution.

Significant outcomes:

1. Neurological softs signs are present in patients with schizophrenia irrespective of their family history for mental disorders.
2. NSS are more prevalent in cases with psychotic family history.
3. Presence of family history in first degree relatives is similar to the presence in second degree relatives in terms of NSS.
4. Patients with family history of non-psychotic mental disorder manifest fewer NSS.
5. There seems to be a spectrum of increasing severity from healthy controls to psychotic family history, rather than a categorical distribution.

Strengths and limitations:

1. It constitutes the first paper to report on the relationship of NSS with family history in schizophrenia.
2. IQ was established according to the clinical impression of the interviewer.
3. The control sample was not representative of the general population but it was rather a convenient study sample.
4. Family history was obtained solely on the basis of self-report by the subject and non-reporting could not be excluded.
5. All patients have been previously hospitalized which means they represent maybe a more severe form of schizophrenic illness.

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1. Introduction

Neurological soft signs (NSS) are a group of minor non-localizable neurological abnormalities. Mainly they include dysfunction in simple motor coordination, complex motor sequencing, and in integration, but also lateralization variability (Bombin et al., 2005; Heinrichs and Buchanan, 1988). While they are not 'psychomotor' per se, it is important to note that psychomotor abnormalities are highly prevalent phenomena in schizophrenia and have to be considered as a heterogeneous construct, often including or misidentifying NSS (Docx et al., 2012).

NSS are found more often in patients with schizophrenia in comparison to the normal population, even during the first episode (Buchanan and Heinrichs, 1989; Chen et al., 2005; Dazzan et al., 2004; Fountoulakis et al., 2018a; Janssen et al., 2009; Krebs et al., 2000; Mayoral et al., 2008; Panagiotidis et al., 2013; Zabala et al., 2006), while they are also present in relatives of patients and in general in individuals at risk to develop psychosis (Barkus et al., 2006; Chan et al., 2010a, 2016). Recently it has been shown that even normal healthy control subjects without being at any risk to develop a mental disorder could also manifest a significant degree of NSS (Fountoulakis et al., 2018b). This means they could be of value as endophenotypes (Chan and Gottesman, 2008; Chan et al., 2010b; Chan et al., 2010c). Medication of any type seem to have little or no impact at all (Boks et al., 2004; Buchanan et al., 1994; Chen et al., 2005; Dazzan et al., 2008; Prikryl et al., 2007; Scheffer, 2004). Whether they are specific to schizophrenia is a matter of debate (Dazzan et al., 2008; Goswami et al., 2006; Negash et al., 2004; Zhao et al., 2013).

The Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989) and the Cambridge Neurological Inventory (CNI) (Chen et al., 1995) are the two most frequently used measures for NSS in schizophrenia and other neuropsychiatric disorders but a number of other instruments also exist (Convit et al., 1994; Rossi et al., 1990; Schroder et al., 1992; Smith et al., 1999a; Smith et al., 1999b).

It should be noted that there are methodological issues resulting in inconsistencies in these studies comparing the prevalence of NSS in schizophrenia and other neuropsychiatric disorders. A major issue is that most of these studies have not controlled for confounding variables such as age, education, IQ and the presence of family history. It has been shown that education (Chen et al., 1995, 2005) is inversely associated, whereas age is positively associated (Chen et al., 2005, 2010b) with NSS in patients with schizophrenia and healthy controls. Moreover, the different assessment tools used to measure NSS might have confounded the results from the literature.

1.1. Aim of the study

The primary aim of the current study was to compare patients with schizophrenia with a family history of psychosis in first degree relatives with those with sporadic schizophrenia in terms of neurological soft signs. Additionally, secondary aims were to test the difference between those with family history of any mental disorders and also those with family history of psychosis in second degree relatives vs. sporadic cases.

2. Study sample

The study sample included 120 patients suffering from schizophrenia according to DSM-5 (71 males and 49 females; aged 32.79 ± 11.11 years old) and 110 normal controls (57 males and 53 females; aged 33.38 ± 10.14 years old). Control subjects did not have any first or second degree relative with any mental disorder.

Thirty three (27.5%) of patients were not under medication while the rest were receiving medication with an average dosage in haloperidol equivalents of 6.07 ± 6.12 mg/day (range 0–33). Some patients were also receiving benzodiazepines at the time of assessment.

In terms of education, patients with schizophrenia included 1 (0.83%) person who had no education at all, 23 (19.17%) with less than 6 years of education, 21 (17.50%) with 6–9 years, 47 (39.17%) with 9–12 years 26 (21.67%) with a university degree and 2 (1.67%) with post-graduate education. The respected numbers for controls were 0 (0.00%), 7 (6.36%), 12 (10.91%), 39 (35.45%), 46 (41.82%) and 6 (5.45%).

Patients were recruited from local hospitals and the diagnosis was made by two of the authors (KNF and PP) with the use of the MINI and after consensus. The exclusion criteria for the present study included (1) a history of neurological disorder (2) presence of any somatic disorder; (3) a lifetime prevalence of substance abuse; (4) an IQ estimate lower than 70. (5) age below 18 or above 65.

Controls came from the community and their exclusion criteria included (1) presence of any mental disorder (2) past history of any mental disorder (3) first or second-degree family member with any mental disorder and (4) age below 18 or above 65.

The study received ethical approval from the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki Greece. Written informed consent was obtained from all participants before the administration of NSS and related measures. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

3. Assessment tools

The NSS were assessed with the use of the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989) which includes four main subscales in addition to the total NES score: sensory integration, motor coordination, sequencing of complex motor acts and a fourth subscale with all other signs. Concerning the scoring of lateralizing items, some researchers used the mean score while others kept the highest side score (Keshavan et al., 2003; Malla et al., 1997; Sanders et al., 2000, 2005). We chose to use the sum of both (Compton et al., 2006). Two additional scores were used, the sum of all items concerning the left and the sum concerning the right side of the body.

4. Statistical analysis

4.1. Primary aim

The study sample was allocated to three groups: Group of patients with schizophrenia with a first degree relative with psychotic disorder (Sfam), patients with schizophrenia without a first degree relative with psychotic disorder (sporadic cases Ssp) and control subjects (C). The difference between these three groups was tested with Analysis of Covariance with age and gender as covariates and NES subscales and total score as dependent variables. A second ANCOVA was performed between Sfam and Ssp with the medication status as an additional covariate.

4.2. Secondary aims

Four more ANCOVAs similar to the previous but with different grouping of patients were performed. The first included the group of patients with any family history of mental disorder (Saf) vs. sporadic cases (Ssp) and vs controls (C). The second included patients with family history of psychosis in second degree relatives alone (Ssec) vs. sporadic cases (Ssp) and vs. controls (C). The third included patients with any family history of any non-psychotic mental disorder in first or second degree relatives alone (Soth) vs. sporadic cases (Ssp) and vs. controls (C). The fourth included patients with first degree psychotic relative (Sfam) vs. those with a second degree relative with psychosis (Ssec). Again the medication status was added in a second ANCOVA each time.

Table 1
Descriptive statistics of the study groups.

Group	N	Males N(%)	Age		Neurological Evaluation Scale (NES) scores Sensory integration		Motor integration		Complex motor acts		Others		Right		Left		NES-total	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	110	57 (51.8)	33.38	10.14	0.12	0.40	0.20	0.54	0.54	0.83	0.19	0.61	0.35	0.80	0.56	0.93	1.05	1.42
Patients	120	71 (59.2)	32.79	11.11	4.33	3.18	3.93	2.77	6.61	3.53	4.53	3.49	6.04	3.31	6.03	3.32	19.40	9.44
Saf	53	30 (56.6)	31.68	9.32	4.30	3.32	4.74	2.92	6.51	3.70	5.11	3.56	6.11	3.42	6.26	3.53	20.66	10.07
Sfam	15	9 (60.0)	34.93	10.63	3.87	3.80	4.87	2.95	6.80	3.71	3.80	2.91	5.00	2.73	5.60	2.92	19.33	10.80
Soth	33	21 (63.6)	33.82	9.13	4.24	3.50	4.64	3.01	6.58	3.63	4.73	3.26	6.42	3.63	6.39	3.49	20.18	10.00
Ssec	20	9 (45.0)	28.15	8.74	4.40	3.08	4.90	2.83	6.40	3.91	5.75	4.01	5.60	3.05	6.05	3.66	21.45	10.39
Ssp	67	41 (61.2)	33.67	12.34	4.34	3.10	3.30	2.49	6.69	3.42	4.07	3.39	5.99	3.25	5.84	3.17	18.40	8.86

Saf: patients with any family history of mental disorder
Sfam: patients with a first degree relative with psychotic disorder
Soth: patients with any family history of any non-psychotic mental disorder in first or second degree relatives alone
Ssec: patients with family history of psychosis in second degree relatives alone
Ssp: sporadic cases
Note: the above groups overlap

The Scheffe test was used as the post-hoc test.

5. Results

The descriptive statistics (means and standard deviations) for each variable in the various groups are shown in Table 1.

5.1. Primary aim

Concerning the primary aim, (Sfam vs. Ssp vs. C) the ANCOVA results suggested a significant effect for the groups but not for gender or age. The Scheffe test revealed a significant difference between controls and both patients groups ($p < 0.001$) concerning all NES subscales as well as total NES score and between the two patient groups concerning NES Motor integration ($p = 0.007$). When the medication status was added as a covariate and only the two patient groups were compared, the results were identical for the ANCOVA and the Scheffe test ($p = 0.038$).

The results of the analyses for the primary aim are shown in detail in Table 2 while the distribution of scores in the various groups are shown in Fig. 1.

5.2. Secondary aims

- The ANCOVA for the first secondary aim (Saf vs. Ssp vs. C) suggested a significant effect for the groups but not for gender or age. The Scheffe test revealed a significant difference between controls and both patients groups ($p < 0.001$) concerning all NES subscales as well as total NES score and between the two patient groups concerning NES Motor integration ($p < 0.001$). When the medication status was added as a covariate and only the two patient groups were compared, the results were identical concerning the ANCOVA and the Scheffe test was significant concerning NES-Motor integration ($p = 0.004$).
- The ANCOVA for the second secondary aim (Ssec vs. Ssp vs. C) was identical with the previous. The Scheffe test revealed that the control group differed in all NES subscales and total score ($p < 0.001$) but the two patient groups differed only in terms of NES-Motor integration ($p = 0.002$) and NES-Others ($p = 0.022$). When the medication status was added as a covariate and only the two patient groups were compared, the results suggested a significant effect for group and medication status. The Scheffe test revealed a difference between the two groups only in terms of NES-Motor integration ($p = 0.016$).
- The ANCOVA for the third secondary aim (Soth vs. Ssp vs. C) was identical with the previous. The Scheffe test revealed that the control group differed in all NES subscales and total score ($p < 0.001$) but the two patient groups differed only in terms of NES-Motor integration ($p = 0.004$). When the medication status was added as a covariate and only the two patient groups were compared, the

Table 2
ANCOVA results for the primary aim (Sfam vs. Ssp vs. C). Significant are p-values in bold italics underlined.

Primary aim variable	Wilks	F	effect df	Error df	p
Sfam vs. Ssp vs. C with gender and age as covariates					
Group	0.221	34.21	6	182	*≤0.001*
Gender	0.977	0.710	6	182	0.645
Age	0.963	1.180	6	182	0.320
Sfam vs. Ssp with gender, age and medication status as covariates					
Group	0.682	5.588	6	72	*≤0.001*
Gender	0.926	0.956	6	72	0.461
Age	0.896	1.388	6	72	0.231
Medication status	0.853	2.071	6	72	0.067

C: controls
Saf: patients with any family history of mental disorder
Sfam: patients with a first degree relative with psychotic disorder
Soth: patients with any family history of any non-psychotic mental disorder in first or second degree relatives alone
Ssec: patients with family history of psychosis in second degree relatives alone
Ssp: sporadic cases
Note: the above groups overlap

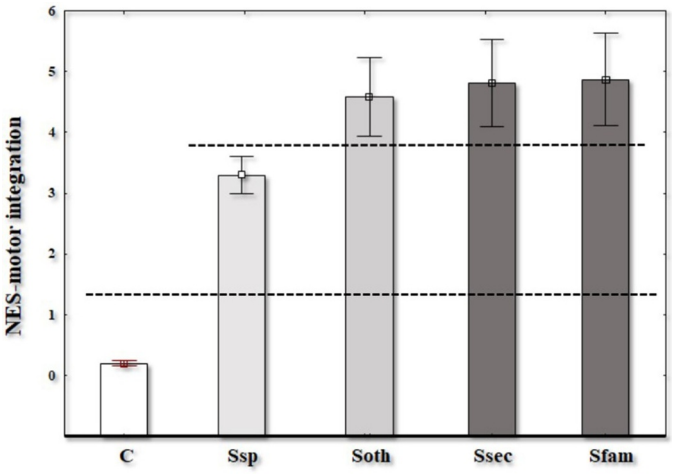

Fig. 1. Means and standard errors of NES-Motor integration scores in the diagnostic groups.
C: controls; **Sfam:** patients with a first degree relative with psychotic disorder; **Soth:** patients with any family history of any non-psychotic mental disorder in first or second degree relatives alone; **Ssec:** patients with family history of psychosis in second degree relatives alone; **Ssp:** sporadic cases
The dotted lines delinate the significant differences: Controls differ from all patient groups, Ssp differ from the other patients groups while the rest three groups (Soth, Ssec, Sfam) do not differ from each other.

results suggested no difference between the two groups.

- The ANCOVA for the fourth secondary aim (Sfam vs. Ssec) returned a significant effect for gender but not for the diagnostic group (0.414).

The results of all analyses for secondary aims are shown in detail in Table 3.

6. Discussion

6.1. Summary of main findings

The results of the current study suggest that all patient groups differed from controls in all NES scores. Additionally, patients with Schizophrenia with a first degree relative with psychotic disorder (Sfam), patients with a second degree relative with psychotic disorder (Ssec) and patients with any family history of mental disorder (Saf) differed from sporadic cases of Schizophrenia (Ssp) only in terms of NES Motor integration. On the contrary, patients with family history of other non-psychotic mental disorders (Soth) did not differ from sporadic cases of schizophrenia in any NES score. Also there was no difference in terms of NES scores between patients with a first degree psychotic relative (Sfam) and those with a second degree psychotic relative (Ssec).

What is very interesting in these results is that while all patient groups have significantly higher NES scores and thus manifest the presence of more in number and severe neurological soft signs (NSS), sporadic cases manifest lower Motor integration scores while patients with family history of non-psychotic mental disorder are positioned in the middle between psychotic family history and sporadic cases but much closer to psychotic family history than to sporadic cases (Fig. 1).

6.2. Relevance of the results of the current study to the existing literature, and implications for future research and clinical practice

While the age beyond which the finding of NSS is not considered to be 'normal' has not been firmly established, they are not expected to be present beyond the age of 7 (Larson et al., 2007). Many authors suggest that their presence beyond this age is indicative of some kind of maturational delay (Largo et al., 2001a; 2001b). They are often found in patients suffering from mental disorders (Dazzan et al., 2008; Fountoulakis et al., 2018a; Goswami et al., 2006; Negash et al., 2004; Panagiotidis et al., 2013; Zhao et al., 2013), and also in children with ADHD (Patankar et al., 2012) or other developmental disorders (Dickstein et al., 2005; Gottesman et al., 1984; Szatmari and Taylor, 1984; Vitiello et al., 1990). In adults they are most frequently related to schizophrenia (Buchanan and Heinrichs, 1989; Chen et al., 2005; Dazzan et al., 2004; Fountoulakis et al., 2018a; Janssen et al., 2009; Krebs et al., 2000; Mayoral et al., 2008; Panagiotidis et al., 2013; Zabala et al., 2006).

Previous studies suggested that NSS constitute an independent (from the rest of symptoms), core (present in the vast majority of patients) and trait (unrelated to age and probably to the stage of schizophrenia) symptom of schizophrenia which could be of value in the clinical assessment and research of schizophrenia (Gunasekaran et al., 2016; Janssen et al., 2009; Mayoral et al., 2012; Peralta et al., 2011; Thomann et al., 2009a; 2009b). The literature provides some support concerning their relationship with negative symptoms and cognitive ability. There seems to correlate with age and negative symptoms (Albayrak et al., 2015; Bachmann et al., 2014; Chan et al., 2016; Cvetic et al., 2009; Dazzan et al., 2008; Fountoulakis et al., 2018a; Gureje, 1988; Nasrallah et al., 1982; Peralta et al., 2014; Petruzzelli et al., 2015; Prikryl et al., 2012; Ruiz-Veguilla et al., 2008; Smit et al., 2012; Tripathi et al., 2015) while their usefulness for the staging of schizophrenia is controversial (Fountoulakis et al., 2018a; Prikryl et al., 2012; White et al., 2009).

To our knowledge this is the first study to investigate the effect of family history for mental disorders and especially concerning different levels of family history with the manifestation of NSS. It seems that sporadic differ from familial cases in terms of Motor integration, which includes problems with tandem walk, finger to nose, finger to thumb opposition and dysdiadochokinesis. This kind of dysfunction is very difficult to identify whether it corresponds to a maturation phase or not. The more frequently observed NSS in children under the age of 6 are overflow-type NSS and are considered to be normal (Denckla et al., 1985; Krain and Castellanos, 2006; Martins et al., 2008) reflecting and immature sensory integration, simple and complex motor coordination and sequencing, and also variability in lateralization (Bombin et al., 2005; Heinrichs and Buchanan, 1988). Thus the NSS probably constitute part of a neurodevelopmental problematic maturation and reflect deficits in sensory integration, motor coordination, and sequencing of complex motor acts (Bombin et al., 2005; Heinrichs and Buchanan, 1988; Manschreck and Ames, 1984; Schroder et al., 1991).

In case there is a brain development with problems in normal central nervous system maturation NSS persist through adulthood and often are accompanied by delayed psychological and neurological development (Golembo-Smith et al., 2012; Isohanni et al., 2001; Nicolson et al., 2000; Niemi et al., 2003; Remschmidt, 2002; Vyas et al., 2011). Since the understanding of the brain evolutionary trajectories is incomplete, currently it is not possible to distinguish between specific and non-specific or even benign neurological findings (Rapoport et al., 2012).

Concerning their presence in patients with schizophrenia, there is a widely accepted belief that they reflect both genetic and neurodevelopmental processes (Tsuang and Faraone, 1999; Tsuang et al., 1991) and most authors argue that they constitute a state marker of schizophrenia and they tend to attenuate with remission of clinical symptoms (Bachmann et al., 2005; Bottmer et al., 2005; Manschreck and Ames, 1984; Prikryl et al., 2007, 2012; Schroder et al., 1992, 1998; Schroder et al., 1996; Torrey, 1980)

The familiar appearance of NSS is supported by reports suggesting they are often found in relatives of patients and in individuals at risk to develop psychosis of any kind, but they are not related to parental age (Barkus et al., 2006; Chan et al., 2010a, 2016; Fountoulakis et al.,

Table 3
ANCOVA results for the Secondary aims. Significant are p-values in bold italics underlined.

Secondary aims Variable	Wilks	F	Effect df	Error df	p
First secondary aim: Saf vs. Ssp vs. C with gender and age as covariates					
Group	0.298	30.530	12	440	≤*0.001*
Gender	0.968	1.230	6	220	0.292
Age	0.954	1.750	6	220	0.110
Saf vs. Ssp with gender, age and medication status as covariates					
Group	0.860	2.986	6	110	*0.010*
Gender	0.942	1.135	6	110	0.227
Age	0.930	1.385	6	110	0.347
Medication status	0.888	2.304	6	110	*0.039*
Second secondary aim: Ssec vs. Ssp vs. C with gender and age as covariates					
Group	0.237	32.890	12	374	≤*0.001*
Gender	0.957	1.400	6	187	0.217
Age	0.944	1.840	6	187	0.094
Ssec vs. Ssp with gender, age and medication status as covariates					
Group	0.718	5.037	6	77	≤*0.001*
Gender	0.887	1.639	6	77	0.148
Age	0.865	2.001	6	77	0.076
Medication status	0.780	3.623	6	77	*0.003*
Third secondary aim: Soth vs. Ssp vs. C with gender and age as covariates					
Group	0.301	27.41	12	400	≤*0.001*
Gender	0.985	0.52	6	200	0.796
Age	0.958	1.47	6	200	0.191
Soth vs. Ssp with gender, age and medication status as covariates					
Group	0.908	1.523	6	90	0.180
Gender	0.969	0.481	6	90	0.821
Age	0.917	1.367	6	90	0.237
Medication status	0.889	1.865	6	90	0.096
Fourth secondary aim: Sfam vs. Ssec with gender, age and medication status as covariates					
Group	0.767	1.065	6	21	0.414
Gender	0.513	3.328	6	21	*0.018*
Age	0.601	2.325	6	21	0.070
Medication status	0.840	0.668	6	21	0.676

C: controls; **Saf:** patients with any family history of mental disorder; **Sfam:** patients with a first degree relative with psychotic disorder; **Soth:** patients with any family history of any non-psychotic mental disorder in first or second degree relatives alone; **Ssec:** patients with family history of psychosis in second degree relatives alone; **Ssp:** sporadic cases
Note: the above groups overlap

2018a, 2018b; Neelam et al., 2011; Niethammer et al., 2000; Rossi et al., 1990; Torrey et al., 1994), thus suggesting they could serve as endophenotypes (Chan and Gottesman, 2008; Chan et al., 2010b, 2010c), but the evidence concerning a familial co-localization with schizophrenia is inconsistent (Bollini et al., 2007; Compton et al., 2007; Egan et al., 2001; Gourion et al., 2004; Lawrie et al., 2001). Two systematic reviews failed to reply to the question whether there are differences between patients' relatives and controls (Bombin et al., 2005; Chan and Gottesman, 2008).

So far there is only one small old paper suggesting that 'hard' neurological signs are more frequent in patients with familial vs. sporadic schizophrenia. These authors suggest that there was a great variability concerning which signs were present while some of them fall into what today is defined as NSS (Woods et al., 1991). On the contrary previous studies suggested that patients with premorbid social dysfunction differed from the rest and familial load was inversely related with the presence of neurological signs (Quitkin et al., 1976, 1980). The results of the current study are in partial accord with the results by Woods et al. (1991) however a significant difference is that they suggest a spectrum rather than a categorical grouping of patients according to family history and NSS.

Attributing NSS to the core biological substrate of schizophrenia seems unlikely because NSS are present in all patients with only a quantitative difference between groups. They are also present in relatives of patients and in a significant number of healthy controls without any family history of mental disorder (Fountoulakis et al., 2018b). However there seems to be some kind of accumulation of genetic load which functions probably with multiple thresholds predisposing not only to schizophrenia but also to other surrounding and related brain dysfunction.

6.3. Conclusion

To summarize, the current study is the first to study NSS in relation to various types of family history. The results suggest that all patient groups manifested higher NES scores from controls, but sporadic cases manifest lower Motor integration scores in comparison to familiar cases. Patients with family history of non-psychotic mental disorder were positioned in the middle between psychotic family history and sporadic cases but much closer to psychotic family history than to sporadic cases. Patients with a first degree relative with psychosis did not differ from those with a second degree relative with psychosis.

Overall the results suggest the presence of a spectrum of increasing severity from healthy controls to sporadic cases, to cases with non-psychotic family history and eventually to cases with psychotic family history, rather than a categorical distribution.

6.4. Strengths and limitations of the present study

The advantages of the current study is that it constitutes the first paper to report detailed prevalence NSS data on a strictly selected sample of patients with different types of family history and healthy individuals without a family history of any mental disorders.

The limitations include the fact that the IQ was not established after formal testing but according to the clinical impression of the interviewer and that only two individuals were over 60 years of age. Additionally the control sample was not representative of the general population but it was rather a convenient study sample. A representative sample would have the same gender and age composition with the general population of the country and additionally several possible confounders would had been taken into account including economic status, education etc. Although the use of convenient instead of representative samples is not uncommon in research practice it includes the danger of potential bias in the selection of study sample towards an unknown direction.

Also although the authors went to significant extend and dedicated much effort to identify and exclude subjects with a family history of any mental disorder, this was made solely on the basis of self-report by the subject and non-reporting could not be excluded. Access to psychiatric family data was impossible at the time the study took place.

Additionally, all patients have been previously hospitalized which means they represent maybe a more severe form of schizophrenic illness.

Author contributions

KNF, IN, VK and XG conceived and designed the study. KNF and PP participated in involving the subjects. PP and VK participated in clinical assessment and data acquisition and management. KNF and XG participated in data analysis. KNF and XG wrote the first draft of the paper. All authors participated in interpreting the data and developing further stages of the paper.

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Statement of conflict of interest

None

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