Psychiatry Research 304 (2021) 114140

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

The neurocognitive and functional profile of schizophrenia in a genetically homogenous European sample

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ARTICLE INFO

Keywords:
Schizophrenia
Endophenotype
High-risk
Cognition
Social cognition
Impairment
Outcomes

ABSTRACT

Schizophrenia is a complex heritable brain disorder that entails significant social, neurocognitive, and functional deficits, and significant psychosocial challenges to affected and unaffected family members. In this cross-sectional study, we explore impairments in specific neurocognitive and social cognition processes in patients affected with schizophrenia, unaffected relatives, and in controls to provide a characterization of a genetically homogenous European sample from an endophenotypic and functional standpoint. A sample of 38 affected patients, 28 first-degree relatives, and 97 controls performed a series of computerized and skills-based assessments. Samples were compared across several neurocognitive, social, and functional domains. Significant impairments in episodic memory, executive function, social cognition, complex cognition, sensorimotor domains were found in patients and first-degree relatives. Findings also showed increased processing speed in memory and other complex cognitive processes relevant to autonomous living. A discriminant function analysis yielded 2 functions allowing 79% of correct group classifications based on social cognition and functional skills, neurocognition, and age. The study highlights the importance of resourcing to wide-ranging assessment methodologies, of developing research efforts to further understand the decline of social and neurocognitive processes, and the need for designing more targeted intervention strategies to be implemented both with affected patients and families.

Schizophrenia is a complex heritable brain disorder that entails a significant social, psychological, and financial burden to patients and families worldwide, despite its relatively low prevalence (American Psychological Association, 2013). Notwithstanding being one of the oldest subjects of study in psychiatry and psychopathology, traditional diagnostic systems have proven to be insufficient to foster progress in the understanding of the pathophysiology of schizophrenia in the recent decades (Gottesman and Gould, 2003; Jablensky, 2010). For this reason, current research trends have shifted the focus from 'fuzzy', heterogeneous phenotypic descriptions and classifications of observable symptoms of this disease to its endophenotypic aspects (Braff, 2015; Jablensky, 2009). This effort to study and systematize the underpinnings of schizophrenia with the aid of modern genetic and neurobiological methodologies, and neurobehavioral assessment methods, became a privileged venue to the understanding of the relationship between neurocognitive variables and their impact on the functional outcomes of patients (Halverson et al., 2019; Harvey and Rosenthal, 2018a; Ivleva et al., 2010; Pato et al., 2013). The resulting evidence has been allowing researchers to uncover a more homogenous profile of schizophrenia, further closing the existing knowledge gap between biology, brain structures and function, and psychology (Pato et al., 2013).

The use of neurobehavioral measures exposed a series of cognitive deficits with a significant impact on high-risk or affected individuals' functional outcomes (Halverson et al., 2019). Studies showed that patients diagnosed with schizophrenia present impairments in 7 neurocognitive domains–processing speed, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning, problem-solving and verbal comprehension–that greatly affect functional outcomes (Fett et al., 2011; Green et al., 2004; Halverson et al., 2019; Harvey and Rosenthal, 2018a; Muralidharan et al.,

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https://doi.org/10.1016/j.psychres.2021.114140
Received 11 February 2020; Received in revised form 22 July 2021; Accepted 24 July 2021
Available online 26 July 2021

2018; Nuechterlein et al., 2008). Salient impairments in the domains of social cognition have been systematically pointed out as another important domain significantly affected by the disease (e.g. Albacete et al., 2016; Eack et al., 2010; Lysaker et al., 2014; Martínez-Domínguez et al., 2015; Schmidt et al., 2011), increasing the interpersonal and social difficulties experienced by affected families. Sensory processing, in particular sensory and auditory processing, is another domain that has been gaining some traction over the past decade as more evidence shows that disruptions in lower-level neurophysiological processes may also underlie deficits in higher-order processes (Butler et al., 2008; Gold et al., 2012; Yeap et al., 2006; Zemon et al., 2021). In this regard, the introduction of more systematic studies focusing on those kinds of deficits in samples that included unaffected family members have allowed researchers to circumvent the confounding effects of clinical symptomatology, uncovering that those deficits were also present in patient's relatives, albeit in milder forms (Albacete et al., 2016; Eack et al., 2010; Galderisi et al., 2016). Those deficits in neurocognitive and social cognition processes were also found to be stable before and after the illness onset, across gender and age groups, in groups at high-risk of developing psychosis, and first and second-degree relatives of patients (Savage et al., 2012; Stone et al., 2011). For those reasons, impairments in cognition and social cognition are regarded as putative endophenotypes of schizophrenia or, in other words, a biological trait that constitute an intermediate phenotype of the disease (Couture et al., 2006; Galderisi et al., 2016; Jablensky, 2009; Pinkham et al., 2008). This area of inquiry has opened new venues to the study of the impact of those deficits in the functional outcome of the disorder and created potential targets of treatment and improvements in cognitive remediation treatments that go beyond symptom management.

For the past two decades, the Portuguese mainland and Portuguese Island Cohorts (PIC) have been a privileged target in schizophrenia research. Firstly, because the Portuguese territory has a relatively homogenous genetic base from the Mediterranean settlers that arrived the continent over 40 millennia ago, and still share several haplotypes (groups of alleles inherited from a single parent) with these founder populations (Arnaiz-Villena et al., 1997), secondly, because the PIC's genetic homogeneity and geographical conditions that grant increased environmental stability and access to patients and families (Pato et al., 1997; Venken and Del-Favero, 2007). Studies indicated a prevalence between 0.6-1%, with estimates pointing to a total of 48 thousand patients affected with schizophrenia in Portugal (Gouveia et al., 2017). The PIC studies presented a low lifetime prevalence (.228%) in the Azorean samples (Mundo et al., 2001), where most of the cases occurred within the same family, accounting for 68.9% of the affected subjects. Thus, in this subset, the prevalence of schizophrenia is much lower than those found in other populations (typically ~1%, American Psychiatric Association, 2013), but it occurs at a much greater rate within a family than what is reported in studies with different populations (typically ~10–15%) (Barreto Carvalho et al., 2019; Mundo et al., 2001). Due to their homogeneity and accessibility, Portuguese samples have been integrated into large genome-wide association studies (Bigdeli et al., 2013; Fanous et al., 2012; International Schizophrenia Consortium et al., 2009; Sklar et al., 2004; Venken and Del-Favero, 2007), revealing candidate genes and linkage to severe mental illnesses, including schizophrenia (Mundo et al., 2001; Pato et al., 2004, 1997; Ripke et al., 2014). However, to this date, no systematic studies have been carried out with this specific sample portraying the profile of schizophrenia from an endophenotypic standpoint. Thus, the goal of the current study is to characterize the impairments in neurocognitive and social cognition in affected patients and unaffected relatives and provide a characterization of the Portuguese affected population on an endophenotypic and functional level and comparing them to a control sample. Despite the exploratory nature of this study, we hypothesize that (a) most deficits are present in the domains related to memory, attention, and complex cognitive processes, such as verbal and abstract reasoning, and social cognition, (b) patient's relatives may exhibit intermediate deficits in those same processes in comparison to controls and affected participants and (c) the differences observed between samples will become more salient regarding the performance in tasks related with functional outcomes, due to the significant impact of cognitive deficits on functional outcomes (Green et al., 2019, 2015; Halverson et al., 2019).

1. Method

1.1. Participants

A sample of 163 adults (18 years old or older) enrolled in this study and were assigned to 3 groups. Inclusion criteria for each group were the following–a) Patients diagnosed with schizophrenia (SZ group) –Patients who were diagnosed with schizophrenia, for 6 or more months and who were currently stable or in remission (APA, 2013). The diagnosis was confirmed with the psychiatric staff or by consulting the patients' files, in addition to the administration of a clinical interview described in the measures section; b) First-degree relatives of patients with schizophrenia (PR group)–Participants who were a first-degree relative of a patient that diagnosed with schizophrenia (parent, sibling or descendant); c) Control Group (CG group)–Participants with no history of severe mental illness, and without a first-degree relative diagnosed with a psychotic disorder.

1.2. Procedures

The current study involved human participants and complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The research project was registered with the National Data Protection Committee (CNPD) and approved by the Ethical Boards of the University of Coimbra and Azores University. Permission to collect data was also granted by the boards or directorship of 4 mental health institutions from the Azores and Portuguese mainland. All participants were clarified about the study goals and data confidentiality, and participation was voluntary. Participants signed an Informed consent before research protocol administration.

The groups consisted of convenience samples mainly collected through snowball sampling method. Participants were invited to partake in the study and asked to provide further contacts of potential participants (e.g., family members or people from other social circles). Especially in the case of patients who might experience paranoid symptoms or participants come from vulnerable populations in a context where social stigma is a concern, the snowball sampling method is deemed adequate to increase participants' trust compared to recruitments carried out by individuals who do not belong to the target population (e.g. An unknown researcher) (Biernacki and Waldorf, 1981). In the specific case of individuals who previously enrolled in the Genomic Psychiatric Cohort (GPC) studies, only the information from those who authorized future contacts was retrieved. The patients from the mainland were recruited through institutions and private practitioners who cooperated with this study. Most participants from the control group were recruited through personal, social networks, advertisements placed in cooperating institutions, and other media.

1.3. Statistical analyses

Approximately 19% of participants (n =31) presented incomplete data in their questionnaires (e.g., Skipped one or more items in measures that were filled in paper format). Missing data pattern analysis was carried out and yielded 2.2% of raw data were missing at random and were replaced using linear trend at point (accounting for group assignment). Only one participant from the SZ group was unable to perform the computerized neurocognitive battery due to sensorimotor constraints, and the participant was excluded from analysis regarding the PennCNB variables.

Statistical analysis was performed in SPSS (IBM Corp. Released,

2013). A priori sample size calculations for 3-group ANOVA analyses yielded a required sample size of 159 participants to detect medium-sized effects ($f = .25$) with an $\alpha = .05$, and a statistical power of .80 (1-β). To ensure robustness and minimize type I errors when comparing samples with unequal variances and/or unequal sizes, all ANOVA statistics and p-values were reported using Welch's robust test of equality of means. To compensate for the large number of individual hypotheses tested in the current study, alpha levels for statistical significance are $\alpha = .001$. *Post-hoc* analyses were used to perform multiple comparisons across groups. In the cases in which the assumption of homogeneity of variance was met, we reported Bonferroni's *posthoc* results, and in the cases in which this assumption was not met, we reported Games-Howell *post-hoc*. Effect sizes were calculated with Cohen's *f*, in which values above .02 are considered small, values above .15 are considered medium, and values above .35 are considered large effect sizes.

Finally, we used a stepwise Discriminant analysis with Wilk's Λ method to identify which variable(s) allow us to significantly distinguish the 3 groups (CG, PR and SZ), and we used classificatory analysis with cross-validation to obtain the classification functions that allow the best prediction of group classification for future cases.

1.4. Measures

Sociodemographic and clinical information–All participants filled a brief sociodemographic and clinical information sheet. Participants from the first-degree relatives and patients filled a checklist to rule out the presence of symptoms of severe psychiatric illnesses (e.g., psychosis, schizophrenia, schizoaffective and bipolar disorder), and participants diagnosed with schizophrenia were interviewed with the Clinical Interview for Psychotic Disorders (CIPD; Martins, Barreto Carvalho, Castilho, Pereira, & Macedo, 2015), to ensure all inclusion criteria were met and that participant was able to participate. The interview allowed us to confirm the diagnosis based on DSM-5 criteria for psychotic and mood disorders and to evaluate the presence of addictive and substance-use-related disorders and other associated symptoms (social anxiety and trauma).

Response to stressful situation scale (RSSS; Barreto Carvalho et al., 2015). This scale comprises 19 items describing stress-inducing scenarios related to common life events. Each scenario is rated on a Likert-type scale ranging from 1 (no stress) to 10 (extreme stress) according to the degree of stress the individual would feel or has felt as a result of that occurrence. The RSSS includes a section in which individuals can report the presence/absence of several physiological, psychological, and behavioral responses they identify in scenarios of different intensity (lower, medium, or high-stress scenarios).

Community integration scale for adults with psychiatric problems–Brief version (CIS-APP, Barreto Carvalho and Cabral, 2014) The CIS-APP is a self-report measure aimed at adults with psychiatric problems, but that can also be rated by people without mental illnesses. This instrument comprises 12 items from the longer version of the CIS-APP (34 items) retained through CFA (Cabral et al., 2014). The instructions include a brief definition of "community" and items are rated on a 5-point Likert-type scale (0 = *completely disagree*; 4 = *completely agree*). The total score can range between 0 and 48 points. Higher scores indicate higher degrees of community integration. The Portuguese validation and the current study showed a good internal consistency ($\alpha = .87$).

Situational test of emotional understanding–Brief (STEU-B) (Allen et al., 2014b; da Motta et al., 2016a). The STEU-B is an ability test for Emotional Understanding, or the ability to understand emotions in the self and others, and how emotions can arise or evolve in complex situations. The STEU-B has 19 scenarios selected from the 42 item version of STEU using an IRT analysis (Allen et al., 2014b; MacCann and Roberts, 2008). Each item describes a different interpersonal scenario, to which participants are invited to choose the more likely emotional response of one of the persons in that situation (e.g., *Clara receives a gift. Clara is most likely to feel?* Response options–a) Happy; b) angry; c) frightened; d) bored; e) hungry). The STEU-B is presented in multiple-choice format, rated as correct/incorrect. Scores are converted into the measure, according to the procedures presented in the Portuguese validation studies using Rasch Model (da Motta et al., 2019b).

Table 1
PennCNB domains and tasks.

Episodic memory	Facial memory task*
	Word memory task*
	Visual object learning task*
Social cognition	Emotion recognition task (total)
	Emotion discrimination task
Executive function	Conditional exclusion task
	Letter-N-Back
	Continuous performance test
	Abstraction inhibition and working memory task (total)
Complex cognition	Raven's progressive matrices
	Line orientation task
	Verbal reasoning test
Sensorimotor	Finger-tapping task (dominant hand)
	Finger-tapping task (non-dominant)
	Motor praxis

* Immediate and delayed.

Situational test for emotional management–Brief (STEM-B) (Allen et al., 2014a; da Motta et al., 2016b). The STEM-B has 18 items and was based on the STEM-44 item version using an IRT analysis (Allen et al., 2014a; da Motta et al., 2020b). The STEM-B is presented in multiple-choice format, in each item, a scenario is described, and the participant must choose the most effective option for one of the persons in that situation. Responses are then rated as correct/incorrect and total scores are converted into a linear measure, according to the procedures described in the Portuguese validation studies. This instrument was constructed and validated by the IRT, obtaining a reliability index value of .94 and a Cronbach's alpha of .86 (Allen et al, 2015).

USCD Performance-based Skills Assessment 2–Portuguese version (UPSA-2-PT, da Motta et al., 2020a; Patterson et al., 2001)–The UPSA was developed for individuals with schizophrenia disorder and became one of the most used batteries to assess functional outcomes (Harvey et al., 2007; Kraus and Keefe, 2007). It consists of a series of role-play situations of similar complexity and is adequate for most individuals from western communities (e.g., Phone-calling, counting change, making a shopping list, using public transportation, planning an outing) and has been translated and adapted to several languages since the publication of its first version. The current study uses the UPSA-2 adapted to the Portuguese population (da Motta et al., 2020a). This battery evaluates performance in 5 domains (1) household chores; 2) comprehension/planning; 3) communication; 4) finances; and 5) mobility/transportation in everyday functioning and community living. The administration of the complete battery takes 20–30 min and a brief version (UPSA-brief, including only the financial and communication modules), can be used when individuals present severe impairment (Mausbach et al., 2007). Raw scores in each domain are converted to scores ranging from 0 to 20, and compute a global score ranging from 0 to 100 can be obtained by adding scores in each domain. The Portuguese version of the UPSA-2 has presented good psychometric properties, sensitivity, and discrimination ability between patients and healthy controls, with a cutoff score defined at 81.75 points (da Motta et al., 2020a).

University of Pennsylvania Computerized Neuropsychological Testing (da Motta et al., 2019a; Gur et al., 2010). This computerized neuropsychological test comprises 19 cognitive tasks assessing assess a specific brain system or process. Tasks can be grouped into domains (according to their neurobehavioral functions)–Episodic Memory, Social Cognition, Executive Control, and Complex Cognition. Comprehensive task descriptions can be found in the studies of Gur and colleagues (Gur et al., 2012, 2010, 2001b, 2001a) and the test properties are thoroughly

Table 2
Sample characteristics (N = 163).

	Control group (n = 97) N (%)	Patients' relatives (n = 28) N (%)	Patients diagnosed with schizophrenia (n =38) N (%)	X^2	*p*
Gender					
Male	45(46.4)	4(14.3)	31(81.6)	25.657	.000
Female	52(53.6)	24(85.7)	7(18.4)		
Marital status					
Single	50(51.5)	5(17.9)	31(81.6)	39.404	.000
Married	30(30.9)	20(71.4)	5(13.2)		
Divorced	9(9.4)	0(0)	1(2.6)		
Widowed	0(0)	1(3.6)	0(0)		
Civil union	8(8.2)	2(7.1)	1(2.6)		
Employment status					
Employed	60(61.9)	21(75.0)	17(44.7)	69.489	.000
Unemployed	9(9.3)	3(10.7)	5(13.1)		
Retirement	2(2.1)	3(10.7)	14(36.9)		
Student	21(21.6)	0(0)	2(5.3)		
Did not respond	5(5.2)	1(3.6)	0(0)		
Income					
Very low (<500€month)	7(7.2)	2(7.1)	14(36.8)	37.652	.002
Low (500 -1300€/month)	42(43.3)	14(50.0)	12(31.6)		
Medium (1300-2900€/month)	38(39.2)	8(28.7)	10(26.2)		
High (<2900€/month)	8(8.2)	4(14.2)	2(5.4)		
Did not respond	2(2.1)	0(0)	0(0)		
	M (SD)	**M (SD)**	**M (SD)**	***F***	***p***
Age (in years)	35.46(10.59)	46.61(11.48)	40.26(12.51)	11.343	.000
Years of education	15.46(3.19)	11.11(4.66)	11.29(3.70)	25.251	.000

described in the Portuguese validation studies (da Motta et al., 2019a). All tasks provide scores regarding reaction times (in milliseconds) and accuracy (number of correct responses). Composite scores of broader domains were calculated using unit-weighted scores of each task on that domain according to the latent model found in the Portuguese validation studies (Bobko et al., 2007; da Motta et al., 2019a) and as depicted in Table 1.

2. Results

2.1. Sample characteristics

Sample characteristics are presented in table 2. Participants from the CG group (n = 97) were more balanced regarding gender distribution, with 45 males (46.4%) and 52 (53.6%) females. While the control group presented a more balanced gender distribution, the gender ratio was significantly different between the patients' relatives (n = 28), in which participants were mostly females (n = 24, 85.7%), and diagnosed (n = 38) groups, who were mostly males (31 participants, 81.6%). This phenomenon is consistently found in studies of these natures due to the increased ratio of affected males over females, which often reaches a proportion of 4:1 (Aleman et al., 2003; APA, 2013; McGrath, 2006).

Regarding age, participants from the control group were between 18 and 61 years old (M = 35.46; SD = 10.59). Participants diagnosed with schizophrenia, with ages between 18 and 67 years old (M = 40.26; SD = 12.51) and did present statistically, significant differences from the

Table 3
Means, standard deviations and one-way analysis of variance of neurocognitive and social cognition by group.

	Group CG M(SD)	PR M(SD)	SZ M(SD)	F_{Welch}	*df*	*p*	*Post-hoc*	*Effect-size (Cohen's f)*
Executive Function								
Accuracy	.13(.58)	-.54(.76)	-.58(.87)	17.128	2, 53.026	.000	CG>PR**>SZ**	.46
Speed	-.09(.78)	.65(.85)	1.01(1.59)	16.432	2, 48.581	.000	CG<PR**<SZ**	.46
Complex cognition								
Accuracy	.24(.66)	-.86(.75)	-.47(.89)	29.455	2, 56.029	.000	CG>SZ**>PR**	.58
Speed	.06(.78)	.21(.90)	.30(1.16)	.854	2, 54.990	.431	-	
Episodic memory								
Accuracy	.16(.56)	-.70(.73)	-.37(.77)	20.758	2, 53.790	.000	CG>SZ**>PR**	.50
Speed	-.08(.68)	.60(.77)	.79(1.75)	11.957	2, 52.363	.000	CG<PR**<SZ*	.33
Social cognition								
Accuracy	.12(.67)	-.74(.98)	-.88(.91)	24.447	2, 52.692	.000	CG>PR**>SZ**	.54
Speed	.01(.79)	.34(.79)	.79(1.76)	4.593	2, 55.115	.014	CG<PR<SZ*	.27
STEM-B total	580.70(71.10)	545.32(58.01)	500.16(96.73)	12.136	2, 63.175	.000	CG>PR>SZ**	.47
STEU-B total	558.74(61.51)	495.08(73.75)	474.48(69.94)	25.207	2, 57.708	.000	CG>PR**>SZ**	.54
Sensorimotor								
Finger tapping (both hands)	.21(.85)	-.96 (1.08)	-.48 (1.65)	17.248	2, 55.134	.000	CG>SZ**>PR**	.38
Mouse praxis correct	.08(.20)	-.49 (2.53)	-.06 (.69)	1.426	2, 42.354	.250	-	
Mouse praxis (speed)	-.05(.97)	.86 (1.47)	1.12 (2.18)	8.624	2, 47.939	.001	CG<PR*<SZ*	.33

Note: Each domain included accuracy and speed scores from the following tasks: Executive function = Conditional Exclusion test, Continuous performance test, Letter'n'back, Attention, inhibition and memory task; Episodic Memory = immediate and delayed Faces, Word and Object learning tasks; Social Cognition = Emotion recognition and Emotion discrimination tasks; Complex Cognition = Raven's Progressive Matrices, Object Orientation task and Verbal Reasoning test. *Post-hoc* significance tests are in reference to control group (CG).

** $p \leq .001$

* $p \leq .005$

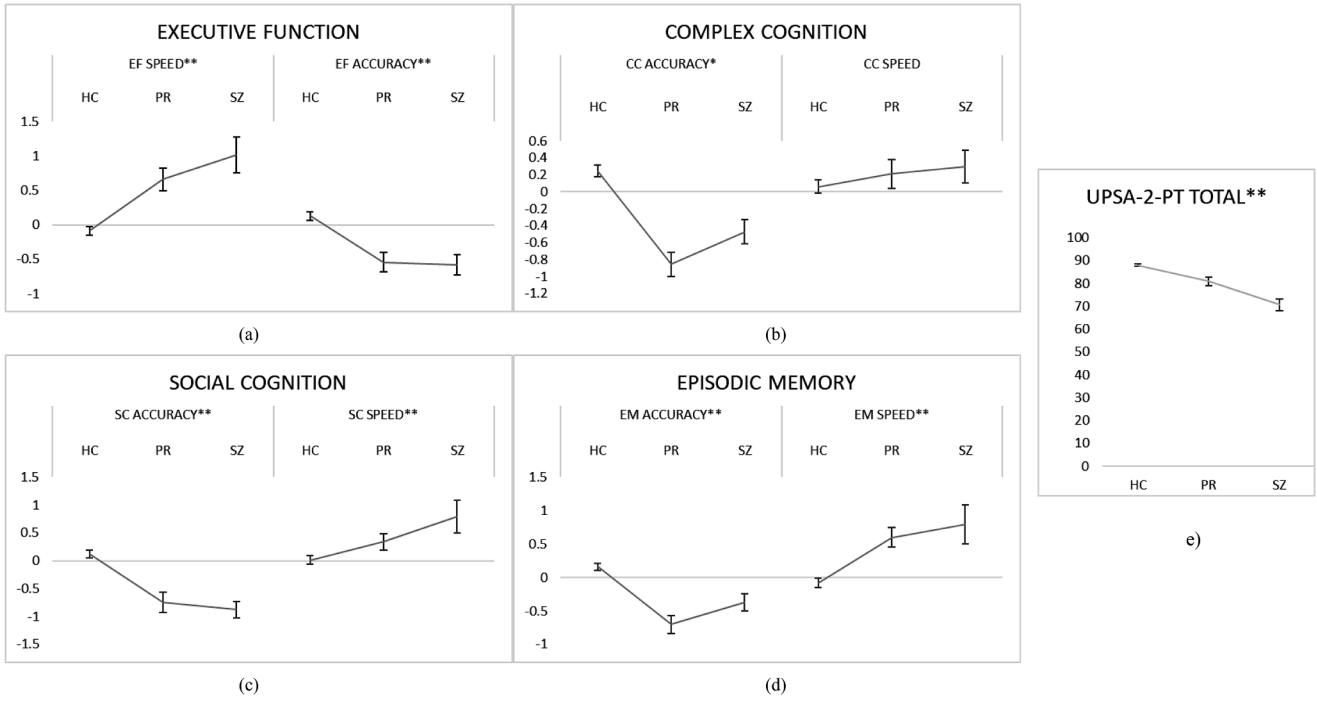

Fig. 1. Comparisons of standardized accuracy and speed scores in neurocognitive and social cognition domains, and of UPSA-2-PT total scores between controls (n = 97), first-degree relatives (n = 28), and patients diagnosed with schizophrenia (n =37).

control group. However, participants from the PR group were older, on average, with ages between 24 and 62 years old (M = 46.61; SD = 11.48).

Participants from the CG group had completed more average years of education (M = 15.46 years, SD = 3.19, corresponding to college attendance), compared to the PR and SZ groups, who completed, on average, mandatory education (M = 11.11 years, SD = 4.66; M= 11.29 years, SD = 3.70, respectively). Nevertheless, all groups had an average educational level above the national average of 9.2 years of formal education found in the population in 2017 (University of Oxford, 2020).

Participants from the CG and SZ groups were mostly single, whereas the PR group was mostly married. Considering the average age of the first marriage in Portugal was nearly 33 years old and has been increasing since 2016 for both males and females (INE and PORDATA, 2019), and the patients' group being on average 5 years older than the control group, this distribution may already reflect the existence of significant social skills deficits. Differences were also found regarding employment status and income, with the SZ group presenting a higher number of retired people/inactive participants and the lowest family income. All participants from the SZ group were being followed by a psychiatrist regularly and treated with antipsychotic medication, their condition was deemed stable, and participants were able to complete all the tasks included in the research protocol. Participants from the SZ group had an average onset of the disorder at 22.32 years old (SD = 5.43), a duration of diagnosed illness of 19.28 years (SD=13.11), and on average 14.24 months of untreated psychosis (SD = 35.80). Ten participants (27%) were living full-time in an institution but developed some occupational or socially useful activity.

2.2. Neurocognition and social cognition

Group comparisons in neurocognitive and social cognition domains are shown in table 3 and Fig. 1. Statistically significant differences were found across all domains regarding several accuracy scores and scores of the STEU-B ($F_{(2,57.708)} = 425.207$, $p \leq .001$) and STEM-B ($F_{(2,63.175)} = 12.136$, $p \leq .001$) tests, and post-hoc analyses showed the same pattern of differences in which participants from the CG score significantly higher than PR and SZ and no statistically significant differences between PR and SZ performance. The effect sizes of all differences concerning these variables were large, .47 and .54 for STEM-B and STEU-B, respectively (Table 3).

Concerning processing speed, statistically significant differences were found mainly in response times in the domains of executive functioning and episodic memory. Post-hoc analyses replicate the differences between groups, in which participants from the CG respond significantly faster than PR and SZ, and no statistically significant differences between PR and SZ response times are found (Table 3 and Fig. 1). Regarding social cognition processing speed, results show a statistically significant difference between groups ($F_{(2,55.115)} = 4.593$, $p = .014$), and post hoc analyses only show a significant difference between CG and SZ response times. However, because of stricter alpha levels of statistical significance used in this study (.001), this finding must be regarded with caution. Overall effect sizes of the differences between groups concerning speed scores were medium (ranging from $f = .27$ to .33) and large for executive functioning speed ($f = .46$). Finally, no statistically significant differences were found between groups regarding the processing speed of the Complex Cognition domain (table 3 and Fig. 1). More detailed results from each task can be found in the supplemental tables.

2.3. Functional outcome and self-report measures

Regarding functional outcomes, results from the total UPSA-2-PT showed a statistically significant difference across the total score ($F_{(1,46.959)} = 28.335$, $p \leq .001$, Fig. 1). *Post-hoc* analysis indicates that participants from the control group scored significantly higher than both patients' relatives and affected participants and the effect size of this difference was large ($f = .66$). Regarding each module, one-way ANOVA also showed statistically significant differences between groups. *Post-hoc* analysis showed the same pattern of results observed for the total score was found in the planning and transportation modules. In the financial domain, the only statistically significant difference was found between the CG and SZ group, and in the communication and household chores domains, the SZ scored significantly lower than both CG and PR. Effect

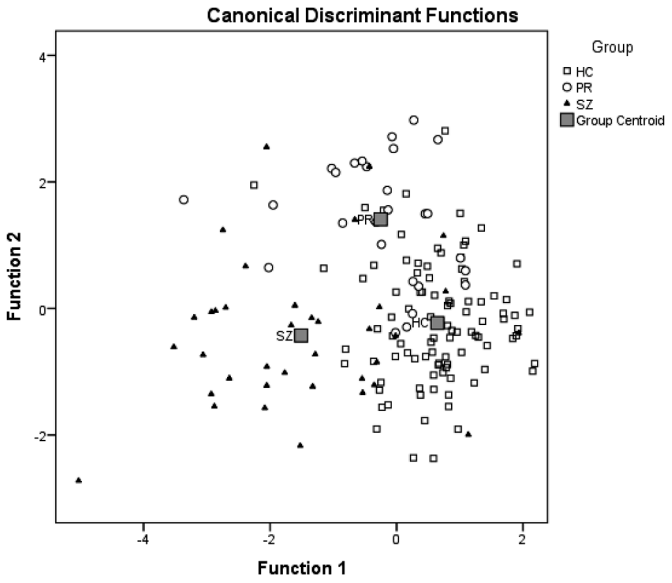

Fig. 2. Territorial map of scores of both discriminant functions.

sizes for all differences found in each UPSA-2-PT module were large (ranging from $f = .39$ to .45), except for the finance module in which the effect size was medium ($f = .35$).

There were no statistically significant differences between the three groups regarding stress responses and symptoms identified with the RSSS ($p > .05$). There was a statistically significant difference between groups in community integration ($F_{(1,66.404)} = 39.979$, $p \leq .001$), whereas the SZ group scored significantly lower than relatives and controls according to post-hoc analysis. The effect size of this difference was large ($f = .79$, Table 5).

2.4. Discriminant analysis

As a final step, we calculated a stepwise discriminant analysis including unit weighted composite scores of accuracy obtained in the domains of Complex Cognition, Social Cognition (including the STEU-B and STEM-B scores), Episodic Memory, Executive Function, Processing speed (all domains), and UPSA total scores, in addition, gender, age, and education. Two discriminant functions were extracted–The first function retained UPSA scores and Social cognition ($\Lambda = .393$, $X^2_{(12)} = 145.379$, $p \leq .001$), and explained 65.9% of variability between groups, and the second function retained complex cognition, gender, memory, and age ($\Lambda = .707$, $X^2_{(5)} = 53.955$, $p \leq .001$), which explained 34.1% of the variability between groups. Figure 2 depicts the territorial map of scores of every participant in both discriminant functions and supplemental table 6 provides the standardized canonical discriminant function coefficients. The percentage of participants correctly classified by the original classification was 79.5% and the cross-validation (i.e., each case is classified with classification functions without that case) has correctly classified 77.6% of participants.

3. Discussion

The current study sought to explore and characterize the endophenotypic aspects of neurocognitive, social cognition, and functional outcomes in schizophrenia by comparing affected and high-risk individuals (first-degree relatives of an affected patient) with controls. In this first effort to develop a set of in-depth studies of the neurocognitive and social cognition in the Portuguese population available through the GPC study, we resorted to a methodologically sound approach to explore a wide range of putative neurocognitive endophenotypes of schizophrenia. Findings can complement the large body of genetic research carried out with the mainland Portuguese and the PIC sample studies (Bigdeli et al., 2013; Fanous et al., 2012; International Schizophrenia Consortium et al., 2009; Sklar et al., 2004; Venken and Del-Favero, 2007). In addition, findings consistent with previous studies can point out the study of specific processes that can lead to innovations to intervention and rehabilitation and have great potential for future research venues with multidisciplinary and all-encompassing genotype-phenotype approaches to this complex disease.

The different assessment methods used in this study yielded congruent results, revealing major differences between the performance in groups of participants diagnosed with schizophrenia and an age-equivalent control group, and patients' relatives also presented a significant difference in performance across several neurocognitive and social cognition tasks, although their functional capacity was more preserved. Taken together, results indicate that both first-degree relatives and patients' groups have extensive and salient deficits in performance across episodic memory, executive function, social and complex cognition domains, in addition to a significant decline in processing speed performing tasks within the executive function and episodic memory domains. It became noticeable that affected and first-degree relatives tend to take longer and be less precise in responding to tasks that require the use of elementary cognitive processes separately, and that there is an increasingly prominent effect of impairment when different functions must coalesce to successfully perform more complex tasks. Previous studies have white-matter and other structural and functional abnormalities provided substantial support to theories of brain dysconnectivity in specific regions that may relate to impaired performance in affected and unaffected individuals (Alloza et al., 2016; Fornito et al., 2012; Roalf et al., 2013; Schmidt et al., 2015; Weinberger, 1987). This conclusion is further reinforced by the present findings in which deficits were present in complex cognition or higher-order social cognition processes, subjective reports of community integration, and in performance-based functional capacity assessment, in which the effect sizes of differences between groups had increased magnitudes when compared to those of more basic tasks.

The implications for real-world functioning are considerable. Concerning the functional outcomes, patients showed a significant impairment in performing tasks based on real-life scenarios. These results may be partially explained by institutionalizations and certain responsibilities being progressively attributed to the patient's caretakers upon the onset of illness. When family and social support is available, chronic patients can become less familiar and less proficient with certain day-to-day obligations and tasks over the years (e.g., more complex financial operations, household management). Although the effect of the medication has not been controlled in the current study, most atypical antipsychotics have not shown a significant impact on cognitive performance in previous studies (Tyson et al., 2006). Moreover, the patient's relatives also showed significant impairments in cognition and social cognition, while scoring slightly below the UPSA-2-PT cutoff score and significantly lower than controls (da Motta et al., 2020a). This finding suggests that much of the friction in carrying out day to day tasks that may account for the significant impairments that lead to loss of autonomy and is also common to unaffected family members, who were not exposed to antipsychotic medication, and do not have a history of psychotic episodes and institutionalizations.

It is important to emphasize that these unaffected relatives are, in turn, more likely to become caretakers of the affected family member. Hence, it is no less imperative to stress the importance of acknowledging the impact of those deficits in high-risk individuals. First-degree relatives tend to experience a significant degree of impairment, albeit less apparent, at the same time they may often become burdened with the additional role of aiding the affected family member. Taking into consideration the southern European cultural background, women are still more often responsible for caring for the children and household work (Altintas and Sullivan, 2016). It is not surprising that this role has expanded to other caretaking activities (e.g., caring for relatives with

Table 4
Means, Standard deviations and one-way analysis of variance of the USCD Performance-based Skills Assessment by group.

	Group							
	CG M(SD)	PR M(SD)	SZ M(SD)	F_{Welch}	*df*	*p*	*Post-hoc*	*Effect size (Cohen's f)*
UPSA-2-PT total	87.98(5.62)	80.92(9.32)	70.69(15.20)	28.335	2, 46.959	.000	CG>PR*>SZ**	.66
Modules								
Planning	18.91(1.28)	17.62(1.68)	16.03(3.43)	14.285	2, 49.750	.000	CG>PR*>SZ**	.43
Finances	18.65(1.64)	17.64(3.66)	16.03(3.43)	10.625	2, 46.051	.000	CG>PR>SZ**	.35
Comunication	13.08(2.88)	13.33(2.73)	10.00(4.231	8.847	2, 57.641	.001	CG> PR>SZ**	.39
Transportation	18.99(2.38)	14.73(5.55)	14.85(5.06)	17.874	2, 45.732	.000	CG>PR*>SZ**	.45
Household	18.35(2.86)	17.59(3.21)	13.16(7.39)	8.982	2, 51.844	.001	CG>PR>SZ**	.43

Note: *Post-hoc* significance tests are in reference to control group (CG).
** $p \leq .001$
* $p \leq .005$

psychiatric disorders) and persists until today, as also reflected by the gender distribution in the current study's sample because women tend to be less affected by schizophrenia and were also more prone to cooperate. Despite our findings showing no differences between the stress responses from participants across the three groups, several studies show different results, demonstrating that stress vulnerability and stress is higher among family members of affected individuals, particularly when the relative diagnosed with schizophrenia is a male (Awad and Voruganti, 2008; Caqueo-Urízar et al., 2014; Juntapim and Nuntaboot, 2018).

Understanding the underlying dysfunction of neuropsychological processes affecting performance in daily tasks to develop remediation efforts that can preserve, restore, or improve functional capacity allows clinicians to go beyond symptom improvements and are more fine-tuned to the participants' characteristics. The use of specific tests and tasks in the domains of neurocognition and social cognition provides the opportunity to devise more targeted evaluation and intervention strategies in clinical, occupational, or educational settings. This type of nomothetical research that focuses on specific traits presented by those affected or related to a patient affected by schizophrenia can play a fundamental role in the determination of treatment strategies, in the development of psychosocial interventions, and the development of more effective treatments for schizophrenia, as well as to the tailoring of specific targets to preventive programs (Fett et al., 2011; Grant, Lawrence, Preti, Wykes, & Cella, 2017). Such exploration can also help identify the mechanisms related to adjusted interpersonal functioning and psychological well-being, and improve interventions that promote different emotional skills and more adjusted behavior in affected patients. These types of interventions could also be implemented with relatives with the more subtle difficulties in those domains (e.g. Cognitive behavioral therapy, Mindfulness-based cognitive therapies, Social-emotional learning programs, interventions for empathy deficits, etc.; Dattilio et al., 2009; Liotti and Gilbert, 2011; Wölwer et al., 2005).

Functional skills have been referred to as an important output of interventions that promote recovery through cognitive changes and rehabilitation (Keefe et al., 2013; Nuechterlein et al., 2008), constituting an important feature to the evaluation of treatment efficacy. Most treatment approaches have focused exclusively on social cognition or neurocognition, neglecting the specific and complementary relationship between these domains and impact in daily functioning. This approach leads to little or no gains are palpable on what comes to functional outcome after intervention (Green et al., 2019; Halverson et al., 2019; Paquin et al., 2014). Interventions focused on social cognition skills complemented with modules for improving executive functioning and more complex cognitive processes could be more effective as they can, at least partially, act as an infrastructure of social cognition on what comes to higher-order skills. Therefore, it becomes crucial to further clarify the pathways through which cognitive gains may translate into actual functional skills and outcome improvement in future studies.

While one of the current study's main strengths is the inclusion of a geographically diverse sample of the Portuguese population and resource to varied assessment methodologies, it is not free from methodological limitations. Because sample size and sampling method may impose some restrictions in the generalization of results, we carried out more robust and conservative approaches to hypothesis testing to prevent inflation of type I errors, while maintaining error II rates at the conventional level. Furthermore, the sheer amount of lower- and higher-order processes that constitutes putative neurocognitive endophenotypes impedes that all processes are given the same attention, or its interrelationship be addressed in a single study (e.g., impact of lower-level sensory processing deficits on higher-order neurocognitive processes). Nevertheless, even with those constrictions, our findings reproduced similar studies carried out in more heterogeneous populations that offered substantive evidence of the decline in processing speed, attention/vigilance, memory, reasoning and problem-solving and social cognition (Fett et al., 2011; Green et al., 2004; Lysaker et al., 2014; Martínez-Domínguez et al., 2015; Nuechterlein et al., 2008; Schmidt et al., 2011). Current findings were also partially congruous with recent research suggesting the cognitive deficit pattern observed in patients diagnosed with schizophrenia is similar to regular processes of aging, as their performance can be systematically poorer in comparison to an age equivalent group with similar education levels (Harvey and Rosenthal, 2018b). Future studies should aim to further study the differential impact of these different cognitive impairments and the regular aging process in functional outcomes in this population, with larger samples and accounting for possible subtler interactions between sociodemographic characteristics and performance across different neuropsychological domains.

In sum, the implications of these findings are twofold–On the one hand, they contribute to future studies attempting to narrow down the specific processes and devise specific hypotheses about the underlying psychophysiological mechanisms affected by schizophrenia. This approach allows researchers to move beyond symptom reduction/control and which is less permeable to the noise resulting from heterogeneous phenotypes, changeable symptom classification criteria for categories of disorders, and traditional clinical assessment methods (Allsopp et al., 2019). On the other hand, findings allow future intervention efforts to target and remediate impairments in specific processes, to develop more effective psychosocial intervention and treatments for schizophrenia, and to include more specific approaches into preventive programs aiming to prevent neurocognitive decline (Fett et al., 2011). It is, thus, important to emphasize the specific challenge of finding new ways of improving executive functions taking into consideration the magnitude of those deficits in each individual, as it is a major predictor of social, vocational, and functional outcomes in patients diagnosed with schizophrenia (Coulacoglou and Saklofske, 2017). These aspects are also relevant for guiding specific adaptation and adjustments to daily tasks the help improving the everyday functioning and autonomy of people affected with schizophrenia (and decrease caretakers' burden) by profiting from unaffected processes that can

Table 5
Means, standard deviations and one-way analysis of variance of the response to stressful situation and community integration scales by group.

	Group CG M(SD)	PR M(SD)	SZ M(SD)	F_{Welch}	*df*	*p*	*Post-hoc*	*Effect-size (Cohen's f)*
RSSS total	95.01(21.03)	93.58(26.88)	102.85(26.14)	1.501	2, 55.921	.232	-	-
# of symptoms (low stress)	2.19(2.10)	1.81(2.47)	3.10(2.53)	2.549	2, 57.447	.087	-	-
# of symptoms (medium stress)	2.99(1.85)	2.89(2.71)	3.30(2.50)	.277	2, 53.449	.759	-	-
# of symptoms (high stress)	5.22(2.36)	4.75(3.46)	4.38(2.61)	1.527	2, 55.578	.226	-	-
Community integration scale	51.80(5.19)	53.74(3.76)	42.28(6.86)	39.979	2, 66.404	.000	CG<PR>SZ**	.79

Note: *Post-hoc* significance tests are in reference to control group (CG).
** $p \leq .001$
*$p \leq .005$

compensate for the identified deficits, fostering more personalized and fine-tuned psychosocial interventions.

Fig. 2 and Table 4

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author statement

All team members (were involved in the general tasks concerning the elaboration of all studies in this paper, and processing the presented manuscript. Célia Barreto Carvalho, Paula Castilho and Michele T. Pato (academic advisors) have contributed to the design, construction of evaluation protocol, manuscript reviews and all methodological aspects concerning this paper. Carolina da Motta (PhD grant holder) contributed with data collection and statistical analysis, and in manuscript preparation, revision and proof-editing.

Conflict of interests

None of the authors has a conflict of interest to disclose.

Acknowledgments

This research was supported by the first author's Ph.D. Grant (SFRH/BD/110308/2015), sponsored by FCT (Foundation for Science and Technology), Portugal, and co-sponsored by ESF (European Social Fund), Brussels, through Portuguese POPH (Human Potential Operational Program). The authors would like to thank the institutional review boards, directors and staff from the Associação para a Recuperação de Cidadãos Inadaptados da Lousã (ARCIL), Associação Quinta das Pontes and Unidade de Cuidados Avançados de Esquizofrenia Resistente ao Tratamento (UCAERe-T) for their collaboration in this study, and also Carolina Pereira for helping us to prepare the manuscript for submission.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.114140.

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