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Original

Theory of Mind as an endophenotype for schizophrenia spectrum disorder: Study in first episode of psychosis patients and first-degree relatives

Georgelina Abreu-Fernández [a,b,1], Nancy Murillo-García [a,b,1], Víctor Ortiz-García de la Foz [a,c], Rebeca Magdaleno Herrero [a,b], Ángel Yorca-Ruiz [a,b], Rosa Ayesa-Arriola [a,c,d,*]

[a] Research Group on Mental Illnessess, Valdecilla Biomedical Research Institute (IDIVAL), Santander, Spain
[b] Doctoral School University of Cantabria (EDUC), Santander, Spain
[c] Centro Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
[d] Department of Psychiatry, University Hospital Marqués de Valdecilla, Santander, Spain

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ABSTRACT

Background: Deficits in Theory of Mind (ToM) had been suggested as a possible endophenotype for unaffected relatives of first episode of psychosis (FEP) patients. There are a limited number of studies which have evaluated ToM deficits among the siblings and parents of FEP patients.
Aim: This study aimed to explore ToM deficits and its correlates among FEP patients, their siblings, parents, and controls.
Methodology: FEP patients ($N = 102$), their parents ($N = 135$), siblings ($N = 97$), and controls ($N = 167$) were evaluated on ToM performance with the Reading the Mind in the Eyes Test (Eyes Test). Interview for sociodemographic variables of age, sex, years of education, and IQ estimation and neurocognitive tests were administered to all groups.
Results: FEP patients had a significantly lower performance on the Eyes Test compared to their siblings and controls. However, no significant differences were found between siblings and parents or siblings and controls.
Conclusion: Attending our results, we found no evidence for ToM deficits as an endophenotype of SSDs. Furthermore, ToM accuracy may be mediated by interaction with other cognitive domains and play a protective role against psychosis in unaffected siblings.

Introduction

Recently, researchers have shown increased interest in studying the abilities that comprise Social Cognition (SC), including Theory of Mind (ToM). ToM is a highly studied domain of SC among individuals experiencing a first episode of psychosis (FEP).[1–5] ToM refers to the complex ability to regulate social interaction skills and to understand one's own and others' emotional perceptions.[6] ToM has been described as an important part of the functional outcomes of social living,[7] such that deficits in ToM have been associated with poor social functioning.[8] ToM deficits have been identified among patients who experienced an FEP and among those diagnosed with chronic schizophrenia,[9] however it has not been fully explored among their first-degree relatives (FDRs).

Studies conducted with FDRs of FEP patients are of great interest because they can help explain whether or not a given deficit is endophenotypic to the schizophrenia spectrum disorder (SSD). To meet the criteria to be considered an endophenotype, a given measure must not only be heritable, state-independent, associated with illness in the population, and co-segregate within families, but, must also be found in non-affected family members at a higher rate than in the general population.[10] Previous studies have investigated ToM ability among unaffected FDRs, however, they have varied in FDR populations and schizophrenia diagnoses.[11–15] For example, in terms of FDR populations, some studies examined ToM

* Corresponding author.
E-mail address: rayesa@humv.es (R. Ayesa-Arriola).
[1] Contributed equally.

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among mothers,[16] or siblings[17] while others failed to specify.[15,18,19] Studies published to date, in terms of their featured SSD populations, have varied between ultra-high risk,[8,14] FEP,[8,14] and those with chronic schizophrenia.[13,15] Taken together, despite their variation in methods, the results suggest that FDRs are intermediary between patients and controls. Due to this, a number of authors have proposed[8,13,14,16–18] that ToM is a candidate endophenotype of schizophrenia.

The objective of this study was to investigate ToM in FEP patients and unaffected FDRs (i.e., siblings and parents). Based on the evidence that relatives of FEP patients have ToM deficits,[3,14,18,20,21] and to explore the reliability of ToM as a potential endophenotype in FEP patients, we hypothesized that FDRs would perform worse on tests of ToM when compared to controls, and that siblings would perform at an intermediate level between controls and parents of FEP patients. We aimed equally to explore the connections between ToM and other neurocognitive domains.

Methods

Subjects

This study was conducted among 134 outpatients who had at one time experienced an FEP, 244 non-psychotic FDRs (146 parents; 98 siblings), and 202 controls. Written informed consent was obtained from all participants according to international research ethics standards (approval numbers: NCT0235832, and 2017.247).

The patient group was recruited between 2001 and 2018 as part of the Program for Initial Phases of Psychosis (PAFIP).[22,23] All patients met the following criteria: between 15 and 65 years of age; living in the catchment area; experiencing a first episode of psychosis; no prior treatment with antipsychotic medication for more than six weeks; and met the DSM-IV criteria for SSD. The diagnoses were confirmed using the Structured Clinical Interview (SCID-I) for DSM-IV[24] conducted by an experienced psychiatrist six months after the baseline visit.

The FDRs group, recruited in relation to the project "PAFIP-FAMILIAS",[25] consisted of relatives of individuals from the PAFIP group who met the following inclusion criteria: over 15 years of age; good knowledge of the Spanish language; were a consanguineous sibling or parent of the subject with FEP; and had the ability and availability to give written informed consent. Family members with psychiatric diagnoses, intellectual disability, cerebral organic pathology, and/or history of substance use-related disorders according to DSM-V criteria were excluded.

The inclusion criteria for controls, recruited as part of the PAFIP program[22] entailed the same age range and linguistic requirements as those applicable to patients and relatives. For both FDRs and controls, exclusion criteria was having current or past psychiatric history, neurological, or general medical illnesses as determined by the abbreviated version of the Comprehensive Assessment of Symptoms and History.[26]

Measures and procedures

Sociodemographic variables

Sociodemographic variables including age, sex, and years of education were collected for all participants. For FEP patients, global functioning was evaluated by the Global Assessment of Functioning scale (GAF).[27]

Theory of Mind assessment

The "Reading the Mind in the Eyes" test (Eyes Test)[28] was used as a measure of ToM. The revised version consists of 36 pictures of individuals' eyes with four possible descriptions, e.g., "serious", "ashamed", "bewildered", and "alarmed". In the task, participants are asked to select one of the answers which best describes the mental state of the person based on the photograph of their eyes. Half of the photos portray females and half portray males. The Eyes Test assesses complex social cognitive ability by measuring participants' ability to decode intentions through the eyes. Studies using the Eyes Test have offered evidence of differences in mentalizing between FEP patients and FDRs.[2,18]

Neurocognitive assessment

Neurocognitive assessments were carried out by trained neuropsychologists. The cognitive domains evaluated were: verbal memory (Rey Auditory Verbal Learning Test; *list recall score*)[29]; visual memory (Rey Complex Figure, *delayed recall*)[30]; working memory (Wechsler Adult Intelligence Scale, Third Edition (WAIS-III), *standard total score of the digits forward and backward subtests*)[31]; executive function (Trail Making Test, *trail B-A score*)[32,33]; processing speed (WAIS-III, *standard total score of the digit symbol subtest*)[31]; motor dexterity (Grooved Pegboard Test, *time to complete with dominant hand*)[34]; attention (Continuous Performance Test, *correct responses*)[35]; estimated IQ (WAIS-III, *vocabulary subtest*).[31] We converted negative scores to positive prior standardization. Subsequently, we transformed all raw scores were into *Z* scores by using the mean and standard deviation of a group of healthy volunteers described in previous studies.[30,31] We estimated the Global Cognitive Functioning (GCF) by converting *T* scores of all the neuropsychological tests mentioned above to deficit scores, wherein higher scores indicate greater impairment.[36]

Statistical analysis

Statistical analyses for sociodemographic measures, ToM assessment, and neurocognition were conducted using SPSS, version 20 software (IBM, New York, NY, USA). Analysis of variance (ANOVAs) ran to test for group differences. For neurocognitive variables, ANCOVAs were including the covariates sex, age, years of education and estimated IQ. Chi-squared and *t*-tests, as required, were used for post hoc comparisons between FEP patients, siblings, parents, and controls. Partial correlations were used to explore the association between ToM and other cognitive domains while controlling for age and education. All statistical tests were two-tailed, and significance was determined at the 0.05 level. Post hoc comparisons were Bonferroni corrected.

Results

Sociodemographic information

Table 1 shows comparisons between groups on sociodemographic variables. There was a significantly higher proportion of men in the group of patients (61.2%) and in the control group (60.9%) than in the relatives ($X^2 = 35.5$; $p < 0.001$). Parents and siblings were significantly older (age of parents: $M = 61.66$, $SD = \pm 7.73$; age of siblings: $M = 40.29$, $SD = \pm 13.16$) than patients and controls. Siblings had completed more years of education ($M = 12.56$, $SD = \pm 3.62$) than parents ($M = 10.26$, $SD = \pm 3.54$), patients ($M = 10.65$, $SD = \pm 3.41$), and controls ($M = 10.84$, $SD = \pm 2.74$). Functioning assessment in FEP patients showed that 72 (58%) had good functioning (GAF $\geq$ 70), 40 (32.25%) moderate difficulty (GAF $\geq$ 50 and <70), and 12 (9.68%) severe impairment (GAF < 50).

Table 1
Descriptive statistics and ANOVA for sociodemographic variables.

	Patients *N* = 134 Mean (SD)	Parents *N* = 146 Mean (SD)	Siblings *N* = 98 Mean (SD)	Controls *N* = 202 Mean (SD)	ANOVA Value	*p*
Age (years)	26.83 (8.38)	61.66 (7.73)	40.29 (13.16)	29.7 (8.16)	$F = 5.09$	$p = 0.024$
Education (years)	10.65 (3.41)	10.26 (3.54)	12.56 (3.62)	10.84 (2.74)	$F = 27.89$	$p < 0.001$
Intelligence quotient	97.94 (12.15)	102.94 (11.10)	100.79 (11.77)	100.63 (10.78)	1.49	$p = 0.217$
Sex	*N* (%)	*N* (%)	*N* (%)	*N* (%)		
Male	82 (61.2)	55 (37.7)	33 (33.7)	123 (60.9)	$X^2 = 35.5$	$p < 0.001$
Female	52 (38.8)	91 (62.3)	65 (66.3)	79 (39.1)		

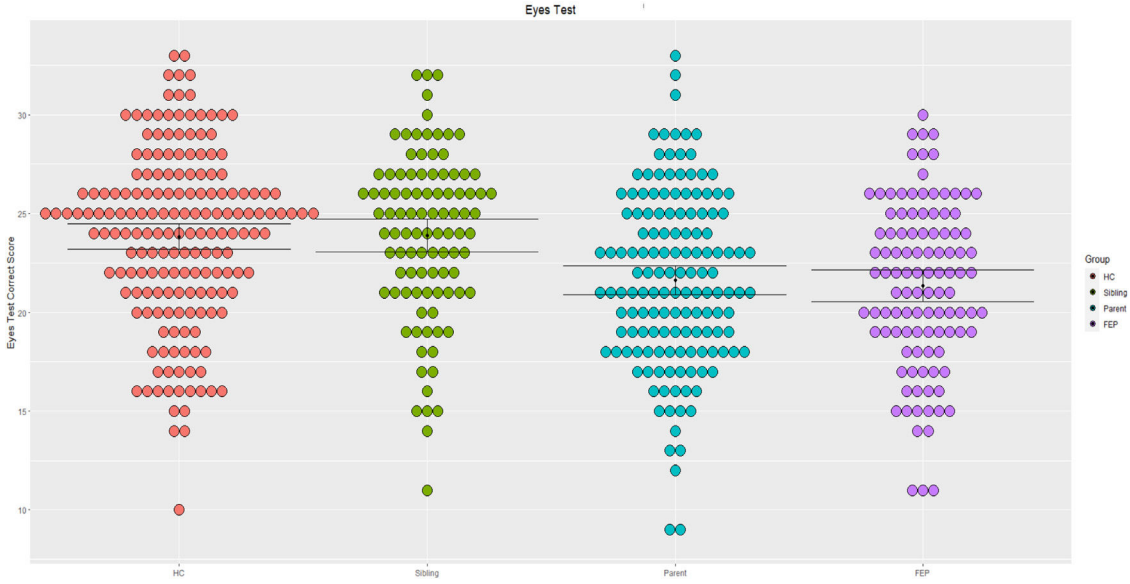

Fig. 1. Eyes Test mean scores comparisons between FEP patients, parents, siblings, and controls.

Table 2
ANCOVAs for *Z*-score of neuropsychological test.

	A = Patients *N* = 102		B = Parents *N* = 135		C = Siblings *N* = 97		D = Controls *N* = 167		ANCOVA			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Statistic	Value	*p*	Comparisons
Eyes Test	−0.53	0.93	−0.46	0.99	0.04	0.94	0.00	0.98	*F*	8.282	<0.001	A < D*** ; A < C*
Verbal memory	−0.47	0.91	−0.71	0.99	−0.08	1.00	0.01	1.00	*F*	7.926	<0.001	A < D***
Visual memory	−0.41	0.97	−1.02	0.73	−0.06	0.86	−0.01	1.03	*F*	9.728	<0.001	A < C A < D***
Processing speed	−1.43	1.11	0.30	0.89	0.31	0.99	−0.01	1.00	*F*	51.532	<0.001	A < B A < C A < D*** ; B < D*
Working memory	−0.36	0.82	−0.50	0.92	0.00	0.90	−0.06	0.99	*F*	3.561	0.014	A < C A < D*
Executive function	−0.96	1.79	−1.90	2.47	−0.52	1.37	0.01	0.98	*F*	12.753	<0.001	A < D B < D*** ; C < D**
Motor dexterity	−0.90	1.53	−1.79	2.56	−0.07	1.32	−0.01	1.00	*F*	11.337	<0.001	A < D*** ; A < C B < C B < D**
Attention	−2.21	3.94	−2.11	3.75	−0.85	2.79	0.00	1.03	*F*	13.508	<0.001	A < D*** ; A < C*
GCF	1.00	0.85	1.08	0.87	0.41	0.55	0.30	0.45	*F*	32.733	<0.001	A > C A > D B > D*** ; B > C*

GCF = global cognitive functioning; sex, age, estimated IQ and education (years) were used as covariates; group comparisons are reported using Bonferroni post hoc comparisons.
* $p < (0.05)$.
** $p < (0.01)$.
*** $p < (0.001)$.

Eyes Test and neurocognition

Results from the Eyes Test (raw scores) are presented in Fig. 1. In addition *Z* scores for Eyes Test and the neurocognitive tests with age, sex, years of education and estimated IQ as covariates are summarized in Table 2. The FEP patients performed poorer on the Eyes Test compared to their siblings ($p \leq 0.050$) and controls ($p < 0.001$).

Patients performed significantly worse than at least one of the three comparison groups (i.e., parents, siblings, and controls) on all neurocognitive domains. Post hoc comparisons indicated that patients performed significantly worse than controls in all domains (verbal memory: $F = 7.926$, $p < 0.001$; visual memory: $F = 9.728$, $p < 0.001$; processing speed: $F = 51.532$, $p < 0.001$; working memory: $F = 3.561$, $p = 0.014$; executive function: $F = 12.753$, $p < 0.001$; motor dexterity: $F = 11.337$, $p < 0.001$; and attention: $F = 13.508$, $p < 0.001$). Patients performed worse than their parents in processing speed ($p < 0.001$). Patients also showed significantly lower scores than their siblings on visual memory ($p < 0.001$), working memory ($p < 0.001$), motor dexterity ($p < 0.001$) and attention ($p < 0.001$).

Parents performed below controls in processing speed ($p \leq 0.050$) and motor dexterity ($p \leq 0.010$); while both parents

Table 3
Partial correlations for *Z*-score on FEP patients, parents, siblings, and controls.

	Patients	Parents	Siblings	Controls
Eyes Test/verbal memory	0.284**	0.260**	0.279**	0.155*
Eyes Test/visual memory	−0.014	0.028	0.236*	0.105
Eyes Test/processing speed	−0.003	0.144	0.152	0.065
Eyes Test/working memory	0.048	0.030	0.099	0.215**
Eyes Test/executive function	0.105	0.247**	0.331**	0.129
Eyes Test/motor dexterity	0.113	0.078	0.214*	−0.003
Eyes Test/attention	0.217*	0.095	0.163	0.238**
Eyes Test/GCF	−0.137	−0.341***	−0.418***	−0.197**
Eyes Test/GAF	0.075			

GCF = global cognitive functioning.
* $p < (0.05)$.
** $p < (0.01)$.
*** $p < (0.001)$.
Sex, age, estimated IQ and education (years) were used as covariates.

($p < 0.001$) and siblings ($p < 0.001$) performed lower than controls in executive function. Finally, worse GCF was found for patients and parents compared to siblings and controls.

ToM correlations in groups

Partial correlations with age, sex, years of education and estimate IQ were performed between ToM measures and each neurocognitive domain and reported in Table 3. ToM and verbal memory correlated positively in all groups. In the domain of executive function, both parents and siblings positively correlated with the Eyes Test, while in visual memory and motor dexterity, only siblings showed positive correlations. Finally, a negative correlation was found for both FDRs and controls in terms of GCF. GAF did not show any significant correlation.

Discussion

This study investigated ToM in parents and siblings of FEP patients. Our aim was to better understand the role of ToM in these participants to test whether it could be a potential endophenotype of SSD. We confirmed that FEP patients underperformed in ToM controls and siblings. Even though relatives appeared to have intermediate values between patients and controls, this was not confirmed by statistical differences. This contradicts our hypotheses and previous findings.[17] We also explored correlations between ToM and other neurocognitive domains that suggest a need for further research.

Correlations are often used to examine relationships between cognitive domains but can also be illustrative of similarities and differences between groups. Our results showed a number of low correlations for all participants. In terms of verbal memory, positive correlations with ToM were consistent across groups. This is similar to previous findings,[1,37] suggesting a stable relationship between elements of language processing during the task. Notably, the need to access semantic content in the ToM task requires similar demands in the Rey Auditory Verbal Learning Test. In terms of visual memory, only siblings showed a correlation. Previous findings suggest that visual working memory underlie mental imagery,[38] which could be influencing the performance in the Eyes Test. As regards of executive function, parents and siblings showed a positive correlation with ToM. Therefore, the greater planning and response resolution abilities of FDRs compared to patients may explain why that they also perform better on complex tasks such as the Eyes Test.[6] In addition, the negative correlations between ToM and GCF for FDRs and controls corroborates that greater global cognitive impairment is related to lower performance in the Eyes Test. Similar results have been previously described by Mondragón-Maya et al.[39] in relatives of individuals at high risk of psychosis. In sum, verbal memory is the domain that correlates with ToM in the four groups, probably due to the verbal component of the Eyes Test. However, while in FEP patients ToM only correlates with verbal memory and attention, correlations in parents and siblings add executive function, and exclusively in siblings visual memory and motor dexterity. GCF correlates with ToM in all but FEP patients group, showing a particularly strong correlation in parents and siblings. Only in controls, correlations between ToM and working memory were observed. This information suggest differences in brain activation during the performance of Eyes task demand that could be very useful in the development of neuropsychological and rehabilitation programs.

Our results suggest that ToM performance is impaired in FEP patients but not in their parents and siblings. The deficits in ToM in patients are consistent with previous findings.[2,18,40] However, our findings on a similar ToM performance between controls and FDRs of FEP patients contradict other studies.[12–14,41] The metanalysis by Bora and Pantelis[8] found mixed results, leading them to be cautious as to the status of ToM as a trait marker of schizophrenia, due to small sample sizes, variation in FDR populations, and differences in a number of ToM tests. According to Gottesman and Gould,[42] an endophenotype must be heritable, state-independent, associated with illness in the population, and found in relatives of patients at a higher rate than in the general population. As we found no ToM affectation in relatives, our results do not contribute to the completion of such criteria. On the contrary, we suggest that ToM may be a protective factor against psychosis, as unaffected siblings performed similarly to healthy controls. Because social cognition plays an important role in psychosis,[43] the siblings may have also a better overall functioning. The ToM accurate performance of siblings may be related to other protective factors such as IQ and education, which are similar and higher respectively in this group compared to controls.

Differences in the ToM performance of FDRs observed across studies could be due to the selection of different measurement instruments. These include the Happé's Strange Stories,[44] the Hinting Task[45] and the Eyes Test,[28,46] the latter of which was used in our study. The Hinting Task is supposed to assess cognitive ToM, the Eyes Test affective ToM, and the Happé's Strange Stories is used to test both domains.[47] Therefore, these conceptual differences must be considered while interpreting the evidence. Although we found no evidence of familial impairment in affective ToM, we cannot rule out the possibility that cognitive ToM may be a better candidate for an endophenotype of psychosis. As there are not enough studies comparing the two domains of ToM in family designs within the FEP population, further exploration is needed.

Moreover, differences between men and women must be considered regarding ToM performance, as indicated previously.[6,15,48] Ibáñez et al.[49] showed that individual differences in ToM are partially attributed to sex, wherein females use to show higher

empathy scores. These differences are also supported by a neuroanatomical correlate, as the medial prefrontal cortex enhances cognitive ToM performance in women, but not in men.[50] Sex comparisons are in the best interest for us, and can be consulted in Supplementary, but their interpretation and discussion beyond the scope of this study.

Strengths and limitations

The strengths of this study lie are its sampling and design. This study addresses some of the limitations presented in previous works. For instance, we incorporated three groups: a sample FEP patients, their relatives, and a control group. Also, the covariates years of sex, age, education, and estimated IQ were accounted for in the analyses. However, the study has limitations; for example, there were many variables of interest that were beyond the scope of this study, such as measures of daily life functioning, which would have added to the depth of this study. Finally, with regards to assessment of ToM, the present study was limited to the assessment of only the Eyes Test. Different types of ToM tests have been used in some previous studies with relatives,[3,18,41] and future research should attempt to replicate similar findings with large samples of FEP patients, FDRs, and controls using these measures as well.

Synthesis/conclusions

Based on our results, it is not possible to conclude that ToM is as an endophenotype of SSDs. Furthermore, ToM accuracy and brain areas implicated in this correct function may play a protective role against psychosis in unaffected siblings. This knowledge's points toward possible advances in prevention, early detection, and the development of specialized programs for patients suffering from this disease, as well as for their family members.

Conflict of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version available at https://doi.org/10.1016/j.sjpmh.2023.09.004.

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