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Social cognition in individuals with schizophrenia, autism spectrum disorder and controls

Cognição social em indivíduos saudáveis, com esquizofrenia e com transtorno do espectro do autismo

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ABSTRACT

Objective: The aim of this study was to compare the social cognition profiles of male adults with ASD (n = 15), SCHZ (n = 16) and controls (n = 20). Change the second sentence of the abstract. **Methods:** A cross-sectional assessment of social cognition domains with emotional face perception with eye tracking was performed, and two IQ measures (Verbal IQ and Performance IQ) (Wechsler Adult Intelligence Scale), and the DSM-IV Structured Clinical Interview were applied. **Results:** There were no significant differences in terms of average performance in social cognition tests or eye tracking tasks between the ASD and SCHZ groups. However, both had lower performances in most cases when compared to the control group. In the social cognition tasks, individuals in the control group performed better than both clinical groups. **Conclusion:** Although differences were identified between individuals with ASD and SCHZ, it was not possible to determine patterns or to differentiate the clinical groups.

KEYWORDS

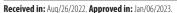
Autism spectrum disorders, schizophrenia, social cognition, eye tracking.

RESUMO

Objetivo: O objetivo deste estudo foi comparar os perfis de cognição social de adultos do sexo masculino com TEA (n = 15), SCHZ (n = 16) e controles (n = 20). **Métodos:** Foram aplicadas uma avaliação transversal dos domínios de cognição social com percepção emocional com rastreamento ocular, duas medidas de QI (QI verbal e QI de desempenho) (Escala de Inteligência Adulta de Wechsler) e a Entrevista Clínica Estruturada DSM-IV. **Resultados:** Não houve diferenças significativas em termos de desempenho médio em testes de cognição social ou tarefas de rastreamento ocular entre os grupos ASD e SCHZ. No entanto, ambos tiveram desempenhos mais baixos na maioria dos casos, quando comparados ao grupo controle. Nas tarefas de cognição social, os indivíduos do grupo controle tiveram melhor desempenho do que ambos os grupos clínicos. **Conclusão:** Embora tenham sido identificadas diferenças entre indivíduos com TEA e SCHZ, não foi possível determinar padrões ou diferenciar os grupos clínicos.

PALAVRAS-CHAVE

Transtorno do espectro autista, esquizofrenia, cognição social, tecnologia de rastreamento ocular.



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INTRODUCTION

Humans are social beings whose survival depends on the relationships they establish with others in the community. Adequate social interactions are fundamental for the adaptive functional outcome of an individual, being directly linked with functionality and inclusion in society, as well as the ability to relate to social groups¹. These interactions are possible through a skill set known as social cognition.

Social cognition is an umbrella term comprising a wide range of cognitive processes and behavioral competencies which allows us to perceive, interpret, understand and generate responses to socially relevant stimuli^{2,3}. Ostrom⁴ describes social cognition as a domain that involves the perception, interpretation, and processing of social information, while Fiske and Taylor⁵ characterize it as the way people make sense of others. Brothers¹ defines it as the set of mental operations that include the human capacity to perceive the intentions and dispositions of interlocutors. These definitions about the nature of social cognition are quite relevant, but also give a broad view of the construct. Thus, for the purpose of this work, we will focus on emotional processing and theory of mind⁶.

Emotional processing (or emotional recognition) is the ability to infer another individual's emotion through facial expression, body language, tone of voice or a combination of these elements, while theory of mind is characterized as the understanding of the subjective nature of mental states⁶.

Research has shown that developmental disorders and psychiatric disorders, such as Autism Spectrum Disorder (ASD) and Schizophrenia (SCHZ), are characterized by marked deficit in communication, social interactions, affects and emoticons, suggesting comparable levels of social cognitive impairment⁷⁻¹⁰. According to the diagnostic criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), both conditions involve impairments in social interaction¹¹.

Studies that compared social cognitive performance in ASD and schizophrenia show that individuals with ASD perform significantly worse than individuals with schizophrenia in emotion recognition tasks, and that this difference becomes less pronounced with increasing age. With respect to other dimensions of social cognition, available evidence is contradictory, and aggregated data do not show meaningful differences between the two diagnostic groups¹².

However, both disorders exhibit differences and similarities with regard to Social Cognitive Performance^{8,13}. Assessments that can differentiate better the impairments in social cognition in the two disorders are necessary, to provide more accurate diagnosis and develop better focused intervention strategies¹². Thus, it is important to understand the differences in social cognition profile between clinical

groups and typical development individuals. Moving beyond diagnostic categories and characterizing social cognitive deficits can enhance understanding of shared pathways across these disorders.

It is also possible, however, that at least some of the difficulty encountered by individuals with ASD, for example, when interacting with neurotypical individuals is due to a failure of individuals to read the mental and emotional states of ASD interaction partners¹⁴. It should be considered a broader perspective of social difficulties in ASD, that considers the individual's impairments but also potential and willingness of social partners¹⁵. The Double Empathy Problem (DEP) refers to the hypothesis that interactions involving autistic and non-autistic people are susceptible to frequent misunderstandings, due to the concept of empathy in relation to autistic people and their interactions with nonautistic people¹⁶. According to the theory of the DEP, these issues are due to a breakdown in reciprocity and mutual understanding that can happen between people of very different dispositions. It is a "double problem" as both groups – autistic and non-autistic – experience a lack of understanding for the other group¹⁶. The DEP theory can also be expanded to the population with schizophrenia, as they also suffer from the stigma resulting from their clinical condition.

Therefore, the aim of this study was to compare the performance of individuals with ASD, SCHZ and neurotypical adults from a Brazilian sample, in social cognition tasks, such as emotion perception patterns of eye gaze towards social stimuli. Following recent findings in the literature ^{9,12,13}, our hypothesis would be that the results would indicate deficits in both clinical groups in emotion perception, with a lowered performance in relation to the group of a population with typical development.

METHODS

Participant selection

This study was conducted at the ASD-MACK Laboratory of the *Universidade Presbiteriana Mackenzie*, in São Paulo, SP, Brazil. This study was approved by the university ethics committee (CAAE: information omitted for blinding purposes). Informed consent was obtained from all individual participants included in the study.

Volunteers were selected and divided into three agematched groups: individuals with ASD, individuals with SCHZ, and neurotypical adults for the control group. Inclusion criteria for the three groups were: males over 18 years of age with a minimum fourth grade education and an IQ > 70. The DSM-IV Structured Interview for Axis I Disorders (SCID) was used to screen individuals from the SCHZ group and individuals presenting psychotic symptoms were excluded.

The ASD and neurotypical group showed no psychotic symptoms for this scale. The participants were recruited among the patients treated at the Autism Spectrum Disorders Laboratory of the *Universidade Presbiteriana Mackenzie* and the Schizophrenia Program of the *Universidade Federal de São Paulo* (Proesq-Unifesp). All volunteers participated in an individual, face-to-face meeting of approximately 80 minutes, the time required to explain the study's purpose and perform data collection.

For the control group, clinically healthy individuals with typical developmental were recruited from the general community. Only individuals without a family history of DSM-V Axis I disorders and who were not taking drugs that acted on the central nervous system were included were recruited from the community.

To assess intelligence, IQ was estimated according to two subtests of the Wechsler Adult Intelligence Scale (WAIS-III): a verbal subtest (vocabulary) and a performance subtest (digit symbol). The American Psychiatric Association's Global Assessment of Functioning (GAF) (2002) was used in this work with the aim of evaluating the social, occupational and psychological functioning of the participants. The scale has a score of 0-100 for the level of functionality and constitutes the V axis of the DSM-IV and was applied as an objective measure of the functional aspect of individuals. The highest range on the GAF scale is from 91 to 100 and indicates superior functioning. Moderate symptoms or difficulty in functioning are rated from 51 to 60 and severe symptoms are rated from 41 to 50. Individuals presenting a serious danger to themselves, or others are rated in the lowest range, from 1 to 10.

Tests and tasks

Three different computerized tests were used to evaluate of social cognition. The first was the Facial Emotion Identification Test (FEIT), developed by Horan *et al.*¹⁷ using a set of photos by Paul Ekman¹⁸. Participants were presented with 56 colored photographs, eight for each of the six universal emotions (happy, sad, angry, afraid, surprised, disgusted), plus neutral expressions. Participants were asked to examine each face in the photographs and define what emotion was being expressed, based on seven possible choices that were presented alongside the image.

To measure the theory of mind dominion, emotional perspective taking (EPT)¹⁹ was assessed by showing the participants 10 photographs of five basic emotions: happy, sad, angry, afraid, surprised, disgusted, as well as a neutral expression. At first, participants were shown a photograph of a social interaction between two individuals for four seconds, one of whose faces was covered. In the second

step, which had no time limit, another image featuring two expressions was shown, and the participants had to choose which expression best fit the previous image. The purpose of this task was to assess the participant's understanding of an emotional situation and the perspective of other individuals in different emotional states.

The third instrument, the Emotion in Biological Motion test (EmoBio), was developed at the University of California Los Angeles based on the work of Heberlein *et al.*²⁰. It consists of 25 videos, within few seconds, that depict the human body in motion, with the joints and head represented by points of light. Body movement and posture were used to express four basic emotions: happy, sad, angry, afraid, surprised, as well as a neutral expression. Participants were instructed to choose the word that best describes the movement based on a list of six words (happy, sad, angry, afraid, surprised, and neutral).

A Tobii 1750 eye tracker (Tobii Technology, Danderyd, Sweden) and ClearView software were used to record and assess the volunteers' eye movements during completion of each of the previous tasks. By detecting ocular movement parameters based on fixations and saccades, the technology can determine where the subject gazes and how he visually analyzes different situations. During the FEIT and EPT tests, the apparatus and program were used to measure the time that the volunteer did not look for any social stimulus. In the FEIT test, social areas of the faces in the photographs were selected, especially the eyes, nose, and mouth. The time spent looking at non-social areas of the face was also considered.

Statistical analyses

SPSS® 17 for Windows (SPSS Inc.) was used for a quantitative analysis of the results. The significance level was set at 5% for all tests. To understand any significant difference between groups (control, ASD, and SCHZ), a sociodemographic data analysis was performed. Continuous variables were tested for normality with the Kolmogorov-Smirnov test. Analysis of variance (ANOVA) was used for estimated IQ, and the Kruskal-Wallis test was used for age to assess intergroup difference, since age distribution was not normal. Categorical variables were analyzed with the chi-square test. In order to compare the groups in relation to the social cognition tests, a logistic regression analysis was performed. In this model, the dependent variable referring to the two groups to be compared: Control group x SCHZ group, Control group x ASD group and ASD group x SCHZ group, and as independent variables, the confounding variables were placed: estimated IQ and socioeconomic level (2 categories: AB/CD), and the variables of interest (Social Cognition tests).

RESULTS

A total of 54 volunteers were selected, four of whom were excluded: two did not score at least 70 on the IQ test and one did not meet the established criteria for an ASD diagnosis. Thus, 51 patients were divided into three groups: ASD n =15, SCHZ n = 16 and controls n = 20. The participants were aged between 18 and 35 years, and the mean age was similar among the groups (ASD: 22 years, SCHZ: 23 years and Controls: 23 years; Kruskal-Wallis H test p = .515; η 2 = 0.014). The ASD and SCHZ groups had similar educational levels (53% and 56% completed high school, respectively) (Table 1), whereas 95% of the control group had attended college (x² p = .001) (Table 1). Regarding employment, 53.3% of the ASD group, 50% of the controls, and 31.3% of the SCHZ group were employed (x^2 p = .008) (Table 1). The socioeconomic level of the SCHZ group was lower than the other groups $(x^2 p = 0.007)$ (Table 1). Among the patients diagnosed with SCHZ, 62% (n = 10) had had their first psychotic episode in the previous 1 to 6 years, while 37% (n = 6) had had their first episode in the previous 7 to 10 years.

Functionality scale

The performance of ASD and SCHZ was lower than controls in the Global Assessment of Functioning Scale (GAF) (x^2 , p < .001) (Table 2). While all controls scored between 71 and 90 (consisting of two ranges: 71-80 and 81-90), only 20% and 12.5% of the ASD and SCHZ individuals, respectively, scored in these ranges. There was no significant difference between the performance of Groups ASD and SCHZ (x^2 p = .785).

Table 1. Participant education level and employment

Intellectual ability

An ANOVA (Table 3) revealed significant differences in total IQ among the three groups (p < .001), with an effect size of $\eta 2 = 0.435$. Post-hoc comparison showed that the control group's average IQ was 120, which was higher than either the ASD, 103 (p = .009) or SCHZ, 97 (p < .001) groups. The IQ difference between the two patient groups was not significant (p = .570). In the performance IQ sub-analysis, the control group scored significantly higher that the ASD (p = .004) and SCHZ (p < .001) groups. In the verbal IQ sub-analysis, the SCHZ group's performance was lower than the control group (p < .001), but there was no difference between the ASD and control groups (p = .115). There was no difference between the clinical groups in performance IQ (p = .983) or verbal IQ (p = .154).

Social cognition tests

According to the ANOVA, the three groups differed in FEIT, EmoBio and EPT scores (FEIT, p=.003, EmoBio, p=.017, EPT p=.005). According to the analysis of the groups combined two by two, with the Bonferroni correction for multiple comparisons, a comparison was made between groups in relation to the three tests: Ekman, Emobio and Derntl. There were significant differences in the performance of the Ekman test between the control group and the ASD group (p=.003; partial $\eta 2=.204$), as well as significant differences between the control group and individuals with SCHZ (p=.049; partial $\eta 2=.112$). In both cases, individuals in the control group performed better on the task.

		Group		
		Control (n = 20)	ASD (n = 15)	Schizophrenia (n = 16)
Age		23.20 ± 4.8	22.80 ± 5.2	23.56 ± 3.6
Education	High school	5%	53%	56%
	University or more	95%	47%	44%
Socio-Economic Status	A/B	65.0%	66.7%	18.8%
	C/D	35.0%	33.3%	81.3%
Occupation	Unemployed	5.0%	20.0%	56.3%
	Working	45.0%	53.3%	31.3%
	Student	50.0%	26.7%	12.5%

Table 2. Global Assessment of Functioning (GAF) scores according to group

	Grade		Group		
	uraue	Controls	ASD	Schizophrenia	
AFS	31-50	0	20%	31.3%	
	51-70	0	60%	56.3%	
	71-90	100%	20%	12.5%	

Table 3. Mean IQ, performance test and verbal test results for ASD, schizophrenia and control groups

	Group	Mean	Confidence Interval	Standard Deviation	Amplitude (min-max)	p-value
QI	Control	120.58	[116.91-124.25]	7.836	106-134	0.000
	ASD	103.05	[92.82-113.29]	18.485	69-125	
	Schizophrenia	96.69	[91.73-101.66]	9.324	80-111	
Wais – performance subtest	Control	14.20	[12.10-14.30	2.505	11-19	0.000
	ASD	10.07	[9.28-12.85]	3.826	4-16	
	Schizophrenia	9.69	[8.12-10.13]	2.272	6-14	
Wais – vocabulary subtest	Control	13.20	[13.03-15.37]	2.353	8-17	0.004
	ASD	11.07	[7.95-12.19]	3.218	5-15	
	Schizophrenia	9.13	[8.48-10.90]	1.893	6-13	

According to the Bonferroni tests, the performance of ASD and SCHZ was lower than controls on the FEIT test (p = .003 and p = .049). On the EmoBio test, ASD's performance was lower than SCHZ group (p = .025), and there was a nonsignificant trend in ASD group (p = .094). Likewise, on the EPT test, SCHZ's performance was lower than controls (p = .005), and the difference between groups ASD and control was marginally significant (p = .099). Both clinical groups did not differ regarding p-value, and all effect sizes were small (FEIT: p = 0.863 and partial η 2 = .024; EmoBio: p = .094 and partial η 2 = .004; EPT: p = 0.897 and partial η 2 = .023.

The ability to identify neutral expression on the FEIT test was lower in group ASD (70.83% accuracy) than group SCHZ (85.94%) (p = .048).

In the FEIT test, the ability to distinguish "Disgusted" was significantly lower in group ASD (56.67%) than control group (91.88%) (p = .009). There was a significant difference in the ability to distinguish "Sad" between group SCHZ (68.65%) and controls (95.63%) (p = .004), as well as a non-significant trend between group ASD (73.33%) and controls (p = .063). "Disgusted" was often confused with "Angry" in the FEIT test, occurring in 38.33% and 11.62% of groups ASD and SCHZ, respectively. "Sad" was confused with a neutral expression by 9.17% of group ASD and 14.06% of group SCHZ. "Happy" was confused with a neutral expression by 10% of group ASD, but by no one in group SCHZ. There was no clear pattern of errors in control group (Table 4). In the EPT test, which assessed emotions, the lowest percentage of responses for fear occurred in group SCHZ (77.86%), followed by group ASD (80.60%) and control group (90.06%). There was no significant difference between groups ASD and SCHZ (p = .09) (Tables 5 and Table 6).

When controlled for confounding variables, there were no significant differences between the groups in the EmoBio test.

Eye tracking analysis

In the eye tracking analysis, the percentage of duration in which the individual did not look for any social stimulus in

the Ekman and Derntl tests (EPT) was analyzed. For the Ekman test, the eyes, nose and mouth were selected in the social areas of static faces, as well as the other areas looked at by the subjects (non-social areas). If we compare the percentage of duration in which the individual did not look at any social stimulus between groups, it is observed that, in all emotions, the ASD group is the one with the lowest percentage of time to fix social areas, while the other groups present an oscillation of percentages, showing themselves relatively close.

For all emotions, the ASD group had the lowest percentage of visual fixation time on social areas. In the other groups, the percentages oscillated but were relatively close. There were significant differences between the three groups ($F_{[2.47]}=6.56$, p=.003). There was a significant difference between the control group and the ASD group regarding visual fixation, in which the ASD group had a longer visual fixation time on non-social figures fixation (p=.003), while the SCHZ and control groups had similar and non-significant fixation time (p=.57). However, the clinical groups did not significantly differ (p=.863) (Figure 1).

On the EPT test, the percentage of visual fixation time on non-social areas was also measured. Control group had the lowest percentage for all emotions. The clinical groups oscillated according to emotion: while the percentage was identical for "Happy", "Sad" and "Surprised", Group ASD was lower than SCHZ group for fear and neutral expression. Group SCHZ had the lowest visual fixation time for "Disgusted". The ANOVA between the groups in the EPT test was not statistically significant (p = .270).

Table 4. Logistic regressions for the three groups of participants

Control x ASD			
FEIT total	.020		
FEIT disgust	.009		
FEIT Sadness	.063		
Control x Schizophrenia	.000		
FEIT Sadness	.004		
FEIT fear	.090		
ASD x Schizophrenia			
FEIT neutrality	.048		
FEIT disgust	.082		

Table 5. Percentage of error in FEIT test emotions

Groups	Emotions	% emotion identification	Confidence interval	Mistaken emotion (higher %)
ASD	Disgust	56.67%	[40.15%-73.19%]	38.33% Anger
	Neutral	70.83%	[69.10%-85.57%]	10% Happiness
	Sadness	73.33%	[59.28%-87.39%]	9.17% Neutral
Schizophrenia	Sadness	68.75%	[53.76%-83.74%]	14.06% Neutral
	Disgust	82.03%	[67.04%-97.02%]	11.62% Anger
	Neutral	85.94%	[71.57%-100%]	No standard error identified
Control	Disgust	91.88%	[86.76%-96.99%]	No standard error identified
	Sadness	95.63%	[90.87%-100%]	
	Neutral	96.88%	[91.55%-100%]	

Table 6. Results of the EPT test in the accuracy of emotion recognition – Comparison between three groups

Groups	Emotion	% emotion identification	Confidence interval
ASD	Fear	80.60%	[61.49%-82.51%]
Schizophrenia	Fear	77.86%	[56.50%-71.00%]
Control	Fear	90.06%	[70.54%-83.46%]

DISCUSSION

It was observed that the clinical groups could not be distinguished by the social cognition tests, although performed significantly worse when compared to the control group. Similar levels of social cognitive impairment were present in individuals with SCHZ and ASD, as identified in previous studies^{10,12,13}.

There was a similar pattern of confusion between the clinical groups and the control group since both presented the same difficulty in relation to the recognition of facial expressions. There was a considerable percentage of errors for disgust among ASD and SCHZ individuals, who primarily confounded it with anger, which is consistent with the findings of Widen and Russel²¹ in American preschoolers.

Sasson *et al.*²² reported that although individuals with ASD or may share an abnormality in utilizing facial information for assessing emotional content in social scenes, they differ in their ability to search for socially relevant cues from complex stimuli. Nevertheless, according to these authors' results, individuals with either disorder fixate less on the faces of their interlocutors than controls. Studies also provide data on facial emotion perception that evidenced a better performance by participants with SCHZ compared to those with ASD, suggesting that different cognitive processes may underlie emotion recognition difficulties in these two disorders¹².

Although the EmoBio and EPT are relatively complex tests, there were no significant differences between the groups, unlike other findings in the scientific literature. Nackaerts *et al.*²³ reported differences between individuals with ASD and controls reading body language, i.e., that they

recognize emotions in different ways. These authors also tracked eye movement during a set of tasks and found that the movement of individuals with ASD tends to be more saccadic, with shorter fixation and duration than the control group.

Okruszek *et al.*²⁴ found that the results of schizophrenia patients were similar to those of healthy subjects, although the clinical group had lower performance in distinguishing communicative from non-communicative actions and in selecting among five alternatives to describe certain actions.

Although previous studies have pointed to greater differences between the EmoBio and EPT tests, they may not have affected the participants in this study. One hypothesis suggests that the socioeconomic level of individuals with ASD allows them access to high quality medical, psychological and educational services, reducing the impact of some deficits caused by the disorder or even preventing them from worsening during childhood and adolescence. The SCHZ individuals in the present sample had the disorder for fewer years than those in the other cited studies, which could have contributed to better social cognition.

On the FEIT test, the emotion identification task, eye gaze patterns from group ASD were not significantly different from group SCHZ. However, according to the analyses, the clinical groups presented a lower rate (or even absence) of visual fixation in the mouth region compared to control group. Other eye tracking studies that have focused on facial scanning strategies have found less visual fixation in individuals with ASD. Other studies, such as Klin *et al.*²⁵, Pelphrey *et al.*²⁶, Phillips & David²⁷, Williams *et al.*²⁸ have found that both ASD and SCHZ individuals have abnormal face tracking patterns.

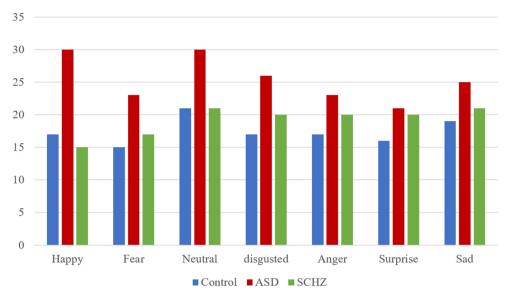


Figure 1. Percentage of gaze duration for non-social stimuli.

One of the main limitations of the study is the small, male-predominant sample. Further research is needed with better correction and matching between clinical and control groups according to IQ and socioeconomic status. Another limitation of the study is the laboratory-based tasks to measure social cognition. It should also be pointed out that the present study relied on visual stimuli, which involve more basic levels of complexity. Since, according to Sasson *et al.*²², more complex stimuli could differentiate the groups, in future studies it will be necessary to explore more diverse stimuli, including audio-verbal context and textual information, in an attempt to find differences between the clinical groups.

Some studies have shown that ASD individuals are significantly more impaired than patients with schizophrenia in emotion perception, but age significantly influences the effect size of this difference in performance, meaning that with increasing age the difference in emotion perception ability between ASD and SCHZ individuals disappears¹². This may reflect a deterioration of social cognitive skills in SCHZ patients with increasing illness duration and an age-dependent improvement of emotion perception skills in ASD, probably as a result of social learning and accumulating social experience. Such hypotheses corroborate the DEP²⁹, since it states that the difficulties in social cognitions presented by individuals in these clinical groups may be the result of social misunderstandings interactions.

CONCLUSIONS

The present study aimed to define distinct patterns of social cognition among ASD and SCHZ individuals (clinical groups) and neurotypical adults (control group) in a Brazilian sample.

Although the overall performance of both clinical groups was significantly worse that the control group, no different performance patterns could be found between ASD and SCHZ and thus, no distinction could be made based on the assessments used. The present work contributes to the literature by adding a Brazilian sample to the discussion of social cognition in individuals with ASD and SCHZ. However, more studies are needed to explore potential differences in social cognition between individuals with ASD and SCHZ.

The data that support the findings of this study are available on request from the corresponding author JGN. The data are not publicly available due to the fact that contain information that could compromise research participant privacy/consent.

FUNDING

The authors did not receive support from any organization for the submitted work.

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Mackenzie Presbyterian University (Date: 30/03/2017/CAAE No.: 68331017.8.0000.5639).

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

INDIVIDUAL CONTRIBUTIONS

All authors are responsible for the reported research and have participated in the conception and design, analysis and interpretation of data and writing or revision of the manuscript, and who have approved the manuscript as submitted.

CONFLICTS OF INTEREST

The authors declare they have no conflict of interest. The authors have no relevant financial or non-financial interests to disclose.

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