Neuropsychological Trends

30
November 2021

Processing speed and clinical features of schizophrenia: comparison between men and women

Yvonne Flores-Medina [1] **- Adriana Sosa-Millán**[2] **- Alejandra Mondragón-Maya** [3]

[1] *Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Mexico City, Mexico*

[2] *Residencia en Neuropsicología Clínica, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Mexico City, México*

[3] *Carrera de Psicología, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Mexico City, Mexico*

DOI: https://dx.doi.org/10.7358/neur-2021-030-flor

ale.mondragon@comunidad.unam.mx

ABSTRACT

Evidence about differences in processing speed (PS) performance between men and women with schizophrenia is inconclusive. Moreover, PS deconstruction into its subcomponents has not been compared among sexes. The aim of this study was to compare PS and its subcomponents (i.e., response processing – RP; accuracy – AC; and psychomotor speed - PmS) performance between men and women with schizophrenia and to explore its associations with clinical variables. Fifty-six patients (36 men, 20 women) were recruited. The PS domain tasks from the MATRICS Consensus Cognitive Battery were used. Women outperformed men in RP and AC but were slower in PmS. For men, correlations were found between functionality, RP and AC; age of onset was associated with AC; in women, illness duration and symptomatology correlated with AC. Sex-related differences regarding PS performance in schizophrenia resemble those observed in healthy individuals. Remediation strategies should consider sex differences in PS for more accurate interventions.

Keywords: schizophrenia; processing speed; sex differences; clinical features; cognition

1. Introduction

Schizophrenia is a chronic psychotic disorder characterized by behavioural, perceptual, affective, and cognitive disturbances. Such disturbances are associated with poor functional outcome and quality of life in these patients (Ojeda et al., 2012b). Epidemiological studies have reported that schizophrenia prevalence worldwide is about 1%, being more frequent in men than in women, with a mean ratio of 1.4:1 (Abel et al., 2010). Furthermore, some schizophrenia clinical features seem to differ between males and females. Commonly, age of onset is earlier in men than women, whereas the former tend to display full symptomatology in their early twenties, whilst the latter develop the full-blown syndrome at their thirties. Symptomatology predominance is different, since men show higher negative symptoms while women display more positive and affective disturbances. In general, women have better clinical and functional prognosis than men (Falkenburg & Tracy, 2014). Research has shown that most patients with schizophrenia have neuropsychological impairments, so they usually fall short of their predicted cognitive function, based on pre-morbid intelligence and parental education levels (Tripathi et al., 2018; Zanelli et al., 2019). Retrospective studies suggest that cognitive deficits are among the initial manifestations of the disorder in individuals who were later diagnosed with schizophrenia (Tripathi et al., 2018).

Cognitive impairment is currently considered as a core feature of schizophrenia. It has been proposed as an independent and specific trait of the disorder, regardless nuclear psychiatric symptoms (Green et al., 2004; Kern et al., 2004). Those deficits are robust and extensive, with a 1.5 to 2.5 standard deviation gap between patients and healthy controls on composite scores as measured by standard neurocognitive tasks (Chen et al., 2019; Keefe, 2014). Evidence suggests that cognitive symptoms contribute to greater disability amongst individuals with schizophrenia than positive symptoms, which are more recognizable and manageable (Carruthers et al., 2019). The most consistently reported cognitive symptoms include slower processing speed (PS), impairment in sustained and focused attention, poor performance in conceptualization, planning, cognitive flexibility, verbal fluency, problem solving and working memory tasks. Additionally, deficits to encode and retrieve information in tasks with high cognitive demand, which depend on cognitive control and relational memory functions, have been observed (Guo et al., 2019; Mortimer, 2008; Nuechterlein et al., 2015; Orellana & Slachevsky, 2013; Reichenberg, 2010). On the other hand, the functions relatively preserved in schizophrenia are verbal knowledge, and linguistic comprehension and naming (García-Laredo, 2018).

The white matter aberrant microstructure explains at least in part, the

neurocognitive dysfunction in schizophrenia; the failure in connectivity implies abnormal integration of incoming information and the consequent low cognitive performance observed in patients when compared to healthy controls. Thus, memory, attention and executive function deficits are described as a disruption of cortico-cerebellar-thalamic-cortical circuits (Alloza et al., 2016; Tripathi et al., 2018).

Interestingly, the PS domain depends on the integrity of white matter (Alloza et al., 2016), in this sense it is not surprising the widely documented impairment of PS in patients with schizophrenia (Cella & Wykes, 2013; Knowles et al., 2015; Ojeda et al., 2012a).

Furthermore, evidence suggests that PS in schizophrenia mediates the performance of other cognitive tasks, so that the deficit observed in tests of attention, working memory or executive functioning may be due, in part, to the underlying PS impairment associated with the condition (Ojeda et al., 2012a; Rodríguez-Sánchez et al., 2007).

However, PS is not a unitary process, it can be divided into three subcomponents: response processing (RP), accuracy (AC) and behavioural execution or psychomotor speed (PmS; Cella & Wykes, 2013). Such PS deconstruction has shown that these subcomponents are differentially correlated with clinical variables in this population. Cella and Wylkes (2013) reported significant associations between clinical features, such as social withdrawal with RP; illness duration with AC; and age and symptom severity with PmS.

Although impairment of PS in schizophrenia has been widely and consistently reported (Knowles et al., 2010) comparisons between males and females have yielded contradictory results. Some studies have observed significant differences in PS, where women outperformed men (Longenecker et al., 2010; Torniainen et al., 2011) whilst others have reported similar scores between both males and females (Bozikas et al., 2010; Ittig et al., 2015). Inconsistencies may be due to methodological aspects like the assessment tools used. For instance, different tasks such as simple motor tasks, number sequencing, letter sequencing, number-letter switching, visual pattern tasks, or letter/category fluency tests have been used in such studies, so that the lack of a consensus on the specific measurement of the construct is evident (Knowles et al., 2015, Kochunov et al., 2016, Krukow et al., 2017). Another important factor includes the clinical characteristics of the samples, which may show variations in time of untreated psychosis, medication regime, chronicity, and comorbidities, among others. Furthermore, on such studies, PS was assessed with the classical approach, in which the participant must execute a time-limited task and the total score corresponded to the number of hits achieved.

To our knowledge, the novel subcomponent approach proposed by Cella

and Wykes (2013) has not been explored when comparing PS performance among male and female patients. Moreover, the PS domain could be assessed using standardized and consensual cognitive tools, like the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008), which has become the "gold standard" to evaluate cognition in schizophrenia and related disorders. The use of such instruments facilitates the replicability and comparison between studies. In a previous work from our group, we adapted the subcomponent model using the PS tasks included in the MCCB Central and South America version (Nuechterlein et al., 2008), which was useful to differentiate the cognitive profile between schizophrenia and schizoaffective disorder patients (Mondragón-Maya et al., 2019).

The aim of the present study was to compare the performance of PS, in terms of response processing (RP), accuracy (AC) and behavioural execution or psychomotor speed (PmS) between men and women with schizophrenia using the PS domain tasks included in the MCCB, and to explore the associations between clinical features and PS variables. We expected to find differences in PS performance between men and women considering the divergence among sexes regarding cognition and clinical features. We hypothesized that women would outperform men in all PS variables and that clinical features would associate differentially with PS among sexes.

2. Methods

2.1 Participants

Fifty-six patients (36 men and 20 women) diagnosed with schizophrenia according to DSM-5 criteria (APA, 2013) were recruited at the National Institute of Psychiatry "Ramón de la Fuente Muñiz" (INPRFM) in Mexico City. All participants were over 18 years old, had achieved at least six years of formal education, and were under pharmacological treatment at the time of the assessment. Additionally, participants were considered clinically stable if they achieved a score between 60 and 90 points at the Positive and Negative Syndrome Scale (PANSS), Spanish Version (Fresán et al., 2005). Exclusion criteria included: additional diagnosis of any neurological or psychiatric condition, comorbid substance abuse (excluding nicotine), clinical diagnosis of intellectual disability or perceptual impairment that could restrict the assessment.

2.2 Instruments

Clinical data (i.e., age of onset, illness duration, number of hospitalizations) were obtained from the patient's medical record and through a clinical interview. Symptom severity was assessed with the PANSS (Fresán et al., 2005); the Functioning Assessment Short Test (FAST; González-Ortega et al., 2010) was used to explore functionality.

The following tests, which are included in the MCCB (Nuechterlein et al., 2008), were used for PS assessment:

- Trail Making Test - Version A (TMT-A) – Participants must draw a sequential line to connect numbers, which are widespread along a sheet of paper.
- Verbal Fluency Test Animals (VF) – Participants must name all the animals they can think of during a one-minute period.
- Brief Assessment for Cognition in Schizophrenia - Symbol Coding (BACS-SC) – Participants must write down the number which corresponds to a specific symbol along a set of symbols during a 90-second period.
- Continuous Performance Test – Identical Pairs (CPT-IP) – A computerized task in which participants must push a button every time two identical numbers appear in the screen consecutively. The task is divided into three progressively demanding conditions: two-digit (CPT-2), three-digit (CPT-3) and four-digit (CPT-4) numbers.

PS subcomponents were operationalized as follows:

- RP (time necessary to mentally compute and plan the response): time (i.e., seconds) used for TMT-A completion, BACS-SC hits in 90 seconds.
- AC (number of errors committed along the task): number of errors in TMT-A, VF, BACS-SC and false alarms in CPT-IP (all conditions).
- PmS (time necessary to execute the behavioural response): reaction times of CPT-IP (all conditions).

2.3 Procedure

Patients were invited to enroll the study and were given an informed consent letter which was approved by the Ethics and Research Committee of the INPRFM. The PANSS was scored by psychiatrists. Research assistants with master's degree in Neuropsychology performed the neurocognitive and functionality assessment in a single session, into a quiet, sound-controlled,

illuminated room. Tests were administered according to the MCCB manual, the complete assessment lasted approximately 90 minutes.

2.4 Statistical analysis

Demographic and clinical data were analysed with descriptive statistics. Clinical and PS comparisons between men and women were performed with Mann-Whitney U test, since data did not show a normal distribution as indicated by the K-S normality test. Effect sizes were calculated with the Cohen's d test. A Spearman correlation analysis was used to explore the association between PS and its subcomponents and clinical features for men and women (i.e., age of onset, illness duration, number of hospitalizations, symptom severity, and functionality). Statistical significance was set at $p < .05$.

3. Results

The sample was comprised predominantly by males (64.28%), with an age range of 21-61 years, and 6-19 years of formal education. Demographic and clinical data are shown in Table 1. All patients were under pharmacological treatment, 29.3% were taking risperidone, which was the most frequent medication, followed by olanzapine and aripiprazole with 16.6% each one, clozapine (12.9%), haloperidol and sulpiride (9.3%), and triflouperazine, zuclopenthixol and quetiapine with 2% respectively.

Table 1. Demographic and clinical data

	Men n = 36		Women n = 20		Mann-Whitney U test	p
	M	SD	M	SD		
Age	33	11	39	13	261	.09
Years of education	13	3	13	3	311	.39
Age of onset	22	7	27	9	208	.04*
Illness duration	10	7	11	10	299	.78
Number of hospitalizations	.78	1.3	1.5	.8	123	.05
PANSS	81	16	75	15	132	.34
FAST	29	12	29	12	245	.83

M = Mean; SD = Standard Deviation; PANSS = Positive and Negative Syndrome Scale; FAST = Functioning Assessment Short Test.
*p = .05, **p = .01

Table 2 shows the comparisons between men and women on the performance of PS and its subcomponents. Raw scores and T values for each PS test are included, as well as raw scores of the PS subcomponents. Differences between groups were observed in BACS-SC hits (U = 239; p = .03); CPT-2 errors (U = 232; p = .04) and CPT-3 reaction times (U = 173; p = .004).

Correlation analyses were performed with age onset, illness duration, number of hospitalizations, symptom severity, functionality and PS subcomponents and total score, the data are presented in Table 3. For the men group, significant correlations were observed for age of onset and AC; and functionality with total PS, RP and AC subcomponents. For women, illness duration and symptom severity correlated with AC, and RP with functionality. For the total sample, significant correlations were found for illness duration, and PmS and AC subcomponent scores; and total PS and RP were associated with functionality.

Table 2. Comparison of PS and its subcomponents performance between men and women

	Men n=36			Women n=20			Mann-Whitney U test	p	1- β	d
	M	SD	Median	M	SD	Median				
PS (T scores)										
TMT-A	23	16	22	27	13	27	308	.37	.41	.10
BACS-SC	28	14	26	34	10	37	248	.09	.15	.09
VF	38	10	47	41	9	47	283	.19	.69	.52
PS Index	24	14	34	30	12	34	262	.09	.42	.42
PS (Raw Scores)										
TMT-A	61	32	48	56	22	55	342	.88	.89	.05
BACS-SC	37	12	39	45	11	50	239	.03*	.66	.72
VF	17	5	18	19	5	22	299	.30	.73	.47
Response processing										
TMT-A seconds	61	32	48	56.6	22	55	342	.88	.89	.05
BACS-SC Hits	38	13	24	45.4	11	50	239	.03*	.66	.72
Accuracy (Errors)										
TMT-A	2.9	3.9	2	2.4	4.5	1	293	.46	.92	.61
BACS-SC	.31	.96	0	1.2	4.4	0	329	.91	.91	.00
VF	.49	.81	0	1.05	1.4	0	267	.17	.33	.17
CPT-2	2.1	3.2	1	1.8	3.6	1	232	.04*	.08	.01
CPT-3	3.4	2.8	2	2.8	3.4	2	282	.44	.44	.05
CPT-4	7	4.1	2	6.9	3.5	2	301	.56	.56	.04
Psychomotor Speed (RT)										
CPT-2	556	76	557	555	148	569	227	.273	.305	.10
CPT-3	569	98	591	618	192	647	173	.004**	.758	1.06
CPT-4	621	90	647	620	184	607	271	.414	.051	.02

M = Mean; SD = Standard Deviation; PS = Processing Speed; TMT-A = Trail Making Test – A; BACS – SC = Brief Assessment of Cognition for Schizophrenia – Symbol Coding; CPT-IP = Continuous Performance Test – Identical Pairs.
*p = .05, **p = .01

Table 3. Spearman correlational analyses of clinical and PS variables for men, women and the entire group

	PS Index	Response Processing		Accuracy				Psychomotor Speed		
		TMT-A	BACS-SC	TMT-A	VF	CPT-2	CPT-3	CPT-4	CPT-2nt	CPT-3nt
Men										
Age of onset	.21	-.08	.018	-.36*	.10	-.15	-.17	-.11	-.03	.10
FAST	-.42*	.11	-.47**	.06	-.09	.11	.39*	.39*	.21	.08
Women										
Illness duration	.14	-.05	-.37	-.29	.58**	-.17	-.02	-.30	.29	.45
PANSS	.04	-.28	-.09	-.62*	.37	-.47	-.43	-.69**	-.25	-.34
FAST	-.31	-.01	-.53*	.03	.41	-.26	-.14	-.32	-.30	-.06
Entire group										
Illness duration	.20	-.08	-.09	-.17	.31*	-.12	-.12	-.16	.26	.33**
FAST	-.38**	.07	-.48**	.05	.15	-.07	.12	.16	-.06	-.001

PS = Processing Speed; PANSS = Positive and Negative Syndrome Scale; FAST = Functioning Assessment Short Test; TMT-A = Trail Making Test – A; BACS – SC = Brief Assessment of Cognition for Schizophrenia – Symbol Coding; VF = Verbal Fluency; CPT-IP = Continuous Performance Test – Identical Pairs.
*p = .05, **p = .01

4. Discussion

The aim of this report was to compare the performance of PS and its subcomponents between men and women with schizophrenia using the PS domain tasks included in the MCCB, and to explore the associations between clinical variables and PS, including its subcomponents.

All patients achieved low scores, corresponding to 1.5 standard deviations below the norm in all tasks (i.e., TMT-A, BACS-SC, VF, PS total score). Such pattern is consistent with other studies which have widely reported PS disturbance in schizophrenia (Alloza et al., 2016; Knowles et al., 2010;

Karbasforoushan et al., 2015). Between-sex comparisons revealed women outperformed men in BACS-SC hits, had fewer mistakes in CPT-2, and showed longer reaction times in CPT-3. These results were partially consistent with our first hypothesis, since we expected women would achieve higher scores in all PS tasks when compared to men.

The outperformance of women over men in BACS-SC is consistent with previous studies (Leger & Neill, 2016; Zhang et al., 2017). It must be noted that in the present study, BACS-SC is considered an index of RP, since it demands multiple cognitive processes for its completion (i.e., memory, cognitive control, and executive functioning) as discussed by Knowles et al. (2015). Leger and Neill (2016) observed that among schizophrenia patients, women tend to achieve higher scores than men in high-cognitive demanding tasks, including BACS-SC. One possible explanation for the better cognitive functioning in women is sex-associated differences in white matter integrity, Yang et al. (2020) recently observed that female patients displayed better cognitive performance than male patients on the TMT-A, the Hopkins Verbal Learning Test and the Spatial Span Test in the Wechsler Memory Scale, such performances were negatively correlated with fractional anisotropy values.

Furthermore, a review by Roivainen (2011) regarding sex differences in the performance of PS tasks among healthy individuals, revealed that women consistently show an advantage over men when completing tasks which involve written digits and alphabets, such as BACS-SC. Thus, it seems that the differential sex-related performance observed in healthy individuals, remains stable among patients with schizophrenia.

We also observed that females outperformed males in the AC subcomponent, since they got significantly fewer mistakes in CPT-2. Although to our knowledge, no sex-comparison studies focused on the CPT task AC subcomponent have been performed in schizophrenia patients, research on healthy subjects has reported that females are more accurate in their responses than males (Burton et al., 2010; Miranda et al., 2013). However, it is important to note that the outperformance in PS for women with schizophrenia does not necessarily involve other cognitive domains. Mu et al. (2020) observed that female patients scored significantly lower in MCCB's category fluency, attention, and reasoning/problem solving tasks when compared to male patients.

In our study, women outperformed men in all CPT-IP conditions, however only CPT-2 reached statistical significance. Probably, since CPT-2 was the less demanding condition, less variability was found in the performance of both groups. However, as the conditions turned more demanding, the performance became more variable and the differences among groups failed to reach significance. Nonetheless, the performance pattern among sexes is similar

between healthy controls and schizophrenia patients.

The comparison analysis also showed that men displayed faster reaction times than women in CPT-3. This variable corresponds to the PmS subdomain. Our results are partially consistent with those reported by Ittig et al. (2015), who observed that the difference in reaction times among sexes became significant as the task demand increased in a N-back task. In the present study, the difference was evident in the CPT-3 condition but not at CPT-2 or CPT-4. We hypothesize that the inconsistency between the three conditions relays on the task demand, which increased progressively every condition. Thus, CPT-2 was a low-demanding condition, whereas both groups displayed similar reaction times during its execution. CPT-3 was more demanding, so it took longer to respond, especially for women. Finally, CPT-4 was the most demanding condition, it is possible that patients were not capable of adequately process the task due to its difficulty, thus the reaction times were similar again among groups. These results are also consistent with studies in healthy individuals which have widely reported that men display faster reaction times than women (Roivainen, 2011).

Broadly, the sex-related factors hypothesis could explain the differences between males and females on PS performance. This hypothesis suggests that some variables like cognitive symptoms, prevalence, symptom severity and treatment response significantly differ between men and women, because of hormonal and neurodevelopmental discrepancies among sexes (Li et al., 2016). For instance, the estrogenic hypothesis posits that this hormone may delay the onset of schizophrenia in women (Falkenburg & Tracy, 2014; Seeman, 2012). Since early onset is associated with more severe cognitive symptoms (Rajji et al., 2009), estrogen could represent a protective factor for women, which could explain in part, the outperformance we observed in RP and AC. Both subcomponents index the cognitive process behind a time-limited task (RP) and the task performance quality (AC), in which women outperformed men. In the other hand, men outperformed women in PmS, which correspond to a more rapid motor response, regardless of its quality (i.e., correct, incorrect).

Regarding correlational analyses, we observed differential associations between PS, its subcomponents and clinical variables for males and females, which was consistent with our second hypothesis. Correlations in the male group showed an inverse association between age of onset and AC, whereas an earlier illness onset was related to more mistakes in TMT-A. This finding suggests that early onset may be implicated in the decrease of error monitoring process in men. Interestingly, several authors have reported an association with both early and late onset and lower performance in several tasks implicated in the PS domain (Bergh et al., 2016). It must be noted that in such studies, sex was not considered in the statistical analyses, so mixed results could be partially

explained. Functionality was correlated with global PS index, RP and AC. These findings are consistent with recent studies by Lahera et al. (2017), Lewandowski et al. (2020), and Dixit et al. (2018), in which deficits in PS were strongly associated to functional impairment in schizophrenia patients.

A hypothesis about how the deficit in PS may negatively influence functionality, involves the mechanisms underlying the decrease in RP. Patients may spend a large proportion of the time on the early operations of a task, leaving a limited time for motor execution, which may be maladaptive for a time-limited task. These conditions can be similar to daily-life activities, such as work or school, in which time-limited tasks must be performed. Another possibility is that the information that is firstly processed may be forgotten while a secondary task is performed or a late process needs to be completed; if so, the relevant information will not be available when needed and the sense of the task at hand will be lost. These hypotheses correspond to the limited-time and simultaneity mechanisms described by Salthouse (1996) for PS; the impairment of either of the two mechanisms translates into a loss of processing efficiency which limits the patient's functional capacity to perform several activities. Thus, the relationship between PS and functionality, as well as the sex-related differences, should be studied in future research.

Correlations in the female group showed that illness duration was negatively associated with AC. These findings are consistent with Cella and Wykes (2013), who found that AC was predicted by illness duration. Silver and Goodman (2007) observed similar associations in a behavioural task involving error monitoring. However, these studies did not analyse the results among sexes separately. The evidence regarding sex differences, can be observed through the event-related potentials technique, whereas the error-related negativity (ERN), error positivity (Pe) and correct-response negativity (CRN) are considered valid electrophysiological markers for error monitoring. Such electrophysiological markers have shown differences associated with sex regarding the error monitoring process, since men show greater amplitude of ERN compared to women (Fischer et al., 2016). Additionally, such process appears to deteriorate progressively over the illness course, which has been demonstrated through the CRN component (Perez et al., 2012). We also found significant negative correlations between PANSS total score and AC measures, indicating that reduced symptomatology was associated with a higher number of mistakes in TMT-A and CPT-4. Such unexpected finding could reflect the differential interaction among two neural systems affected in schizophrenia. The first one is the salience network (SN), which involves psychotic symptomatology like hallucinations and referential ideation among patients (Knolle et al., 2018; Palaniyappan et al., 2012). The second one is the central executive network (CEN), which is related to cognitive symptoms,

predominantly executive functioning disturbance (Speechley et al., 2013). Chen et al. (2016) reported that schizophrenia patients have a reduced connectivity among such networks. It is possible that variables like medication could differentially affect them, so that it could reduce the severity of positive symptomatology, thus improving the SN. However, CEN could not necessarily be affected by medication. If so, patients would keep displaying error monitoring disturbances, despite of the evident clinical symptomatology improvement.

Finally, as expected, correlational analyses for the entire group showed some redundancy, since most of the significant results were observed among the sex groups separately. The only significant result which was not evident in the separate analyses was a positive association between illness duration and PmS. This finding is consistent with other studies which reported decreased PmS related to illness chronicity (Gold et al., 1999; Sponheim et al., 2010).

The differences found regarding the relationship between clinical and neurocognitive measures support the assumption about the influence of sex over particular symptoms in schizophrenia (Linke et al., 2015). Several studies highlight the significant sex-age interaction in the development of white matter connectivity (Gong et al., 2011). Our findings imply that men and women differ in connectivity brain networks, resulting in discrepancies of information processing performance (Gong et al., 2011; Ma et al., 2016). These differences could also generate specific dysfunctional patterns of PS and its subcomponents.

What is the importance of such differences on cognitive processing? The impairment of a particular PS subcomponent requires specific compensation strategies to cope with the deficit. If we consider PS as a general cognitive domain and a PS low score as a general deficit, we may lose relevant information to design accurate interventions (Knowles et al., 2012). The results found in the present study imply that the assessment of cognitive impairment in schizophrenia requires the consideration of variables such as sex to provide an accurate description of neurocognitive functioning and the consequent intervention design.

4.1 Limitations

The current study has some limitations that must be addressed. Our study included a small sample size; further research with a representative clinical sample must be conducted to confirm our results. Another important limitation is the lack of a control group, which could have brought relevant information regarding the different performance of PS among sexes in healthy individuals. Moreover, the sex distribution of the sample was not entirely

balanced, since more men were recruited. Finally, it must be noted that patients were under pharmacological treatment, which could also influence their cognitive performance.

5. Conclusion

Sex-related differences regarding PS performance in schizophrenia resemble those observed in healthy individuals. The analysis of PS subcomponents could bring more information about the cognitive profile of patients with schizophrenia and the relation with clinical characteristics. Remediation strategies should consider sex differences in PS for more accurate interventions.

References

Abel, K.M., Drake, R., & Goldstein, J.M. (2010). Sex differences in schizophrenia. *International Review of Psychiatry, 22*(5), 417-428. https://doi.org/10.3109/09540261.2010.515205

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC.

Alloza, C., Cox, S.R., Duff, B., Semple, S.I., Bastin, M.E., Whalley, H.C., & Lawrie S.M. (2016). Information processing speed mediates the relationship between white matter and general intelligence in schizophrenia. *Psychiatry Research and Neuroimaging, 254,* 26-33. https://doi.org/10.1016/j.pscychresns.2016.05.008

Bergh, S., Hjorthøj, C., Sørensen, H. J., Fagerlund, B., Austin, S., Secher, R. G., Jepsen, J. R., & Nordentoft, M. (2016). Predictors and longitudinal course of cognitive functioning in schizophrenia spectrum disorders, 10 years after baseline: The OPUS study. *Schizophrenia Research, 175*(1-3), 57–63. https://doi.org/10.1016/j.schres.2016.03.025

Bozikas, V. P., Kosmidis, M. H., Peltekis, A., Giannakou, M., Nimatoudis, I., Karavatos, A., Fokas, K., & Garyfallos, G. (2010). Sex differences in neuropsychological functioning among schizophrenia patients. *The Australian and New Zealand Journal of Psychiatry, 44*(4), 333–341. https://doi.org/10.3109/00048670903489833

Burton, L., Pfaff, D., Bolt, N., Hadjikyriacou, D., Silton, N., Kilgallen, C., Cofer, J., & Allimant, J. (2010). Effects of gender and personality on the Conners Continuous Performance Test. *Journal of Clinical and Experimental Neuropsychology, 32*(1), 66–70. https://doi.org/10.1080/13803390902806568

Carruthers, S. P., Van Rheenen, T. E., Gurvich, C., Sumner, P. J., & Rossell, S. L. (2019). Characterizing the structure of cognitive heterogeneity in schizophrenia spectrum disorders. A systematic review and narrative synthesis. *Neuroscience & Biobehavioral Reviews*, *107*, 252-278. https://doi.org/10.1016/j.neubiorev.2019.09.006

Cella, M., & Wykes, T. (2013). Understanding processing speed—its subcomponents and their relationship to characteristics of people with schizophrenia. *Cognitive Neuropsychiatry, 18*(5), 437-451. https://doi.org/10.1080/13546805.2012.730038

Chen, Q., Chen, X., He, X., Wang, L., Wang, K., & Qiu, B. (2016). Aberrant structural and functional connectivity in the salience network and central executive network circuit in schizophrenia. *Neuroscience Letters*, *627*, 178–184. https://doi.org/10.1016/j.neulet.2016.05.035

Chen, P., Ye, E., Jin, X., Zhu, Y., & Wang, L. (2019). Association between thalamocortical functional connectivity abnormalities and cognitive deficits in schizophrenia. *Scientific Reports, 9*(1), 2952. https://doi.org/10.1038/s41598-019-39367-z

Dixit, A., Khan, K. A., & Hasan, B. (2018). Processing speed and verbal fluency as predictors of functional disability among patients with schizophrenia. *Indian Journal of Health & Wellbeing, 9*(3), 473–475. http://www.iahrw.com/index.php/home/journal_detail/19#list

Falkenburg, J., & Tracy, D.K. (2014). Sex differences in schizophrenia: A review of gender differences, *Psychosis, 6*(1), 61-69. https://doi.org/10.1080/17522439.2012.733405

Fischer, A. G., Danielmeier, C., Villringer, A., Klein, T. A., & Ullsperger, M. (2016). Gender influences on brain responses to errors and post-error adjustments. *Scientific Reports*, *6*(1), 24435. https://doi.org/10.1038/srep24435

Fresán, A., de la Fuente-Sandoval, C., Lóyzaga, C., García-Anaya, M., Meyenberg, N., Nicolini, H., & Apiquian, R. (2005). A forced five-dimensional factor analysis and concurrent validity of the Positive and Negative Syndrome Scale in Mexican schizophrenic patients. *Schizophrenia Research, 72*(2-3), 123-129. https://doi.org/10.1016/j.schres.2004.03.021

García-Laredo, E. (2018). Cognitive impairment in schizophrenia: Description and cognitive familiar endophenotypes. A review of the literature. In F. Irtelli (Ed.), *Psychosis—Biopsychosocial and Relational Perspectives*. InTech. https://doi.org/10.5772/intechopen.78948

González-Ortega, I., Rosa, A., Alberich, S., Barbeito, S., Vega, P., Echeburúa, E., Vieta, E., & González-Pinto, A. (2010). Validation and use of the functioning assessment short test in first psychotic episodes. *The Journal of Nervous and Mental Disease, 198*(11), 836–840. https://doi.org/10.1097/NMD.0b013e3181f97bf9

Gold, S., Arndt, S., Nopoulos, P., O`Leary, D.S., & Andreasen, N.C. (1999). Longitudinal study of cognitive function in first-episode and recent-onset schizophrenia. *American Journal of Psychiatry, 156,* 1342-1348. https://doi.org/10.1176/ajp.156.9.1342

Gong, G, He, Y., & Evans, A. (2011). Brain connectivity: Gender makes a difference. *The Neuroscientist, 17(5)*, 575-591. https://doi.org/10.1177/1073858410386492

Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S., & Marder, S. R. (2004). Approaching a consesus cogntive battery for clinical trials in Schizophrenia: The NIMH-MATRICS conference to select cogntive domains and test criteria. *Biological Psychiatry, 56*, 301-307. https://doi.org/10.1016/j.biopsych.2004.06.023

Guo, J. Y., Ragland, J. D., & Carter, C. S. (2019). Memory and cognition in schizophrenia. *Molecular Psychiatry*, *24*(5), 633-642. https://doi.org/10.1038/s41380-018-0231-1

Ittig, S., Studerus, E., Papmeyer, M., Uttinger, M., Koranyi, S., Ramyead, A., & Riecher-Rössler, A. (2015). Sex differences in in cognitive functioning in at-risk mental state for psychosis, first episode psychosis and healthy control subjects. *European Psychiatry, 30*(2), 242-250. https://doi.org/10.1016/j.eurpsy.2014.11.006

Karbasforoushan, H., Duffy, B., Blackford, J. U., & Woodward, N. D. (2015). Processing speed impairment in schizophrenia is mediated by white matter integrity. *Psychological Medicine, 45*(1), 109–120. https://doi.org/10.1017/S0033291714001111

Keefe, R. S. (2014). The longitudinal course of cognitive impairment in schizophrenia: an examination of data from premorbid through posttreatment phases of illness. *The Journal of Clinical Psychiatry*, *75*(Suppl 2), 8–13. https://doi.org/10.4088/JCP.13065su1.02

Kern, R.S., Green, M. F., Nuechterlein, K. H., & Deng, B.-H. (2004). NIMH MATRICS survey on assesmment of neurocognition in schizophrenia. *Schizophrenia Research, 72*(1), 11-19. https://doi.org/10.1016/j.schres.2004.09.004

Knolle, F., Ermakova, A. O., Justicia, A., Fletcher, P. C., Bunzeck, N., Düzel, E., & Murray, G. K. (2018). Brain responses to different types of salience in antipsychotic naïve first episode psychosis: An fMRI study. *Translational Psychiatry*, *8*(1), 196. https://doi.org/10.1038/s41398-018-0250-3

Knowles, E.E., David, A.S., & Reichenberg, A. (2010). Processing speed deficits in schizophrenia: Reexamining the evidence. *American Journal of Psychiatry, 167*(7)*,* 828-835. https://doi.org/10.1176/appi.ajp.2010.09070937

Knowles, E. E., Weiser, M., David, A. S., Dickinson, D., Glahn, D., Gold, J., Davidson, M., & Reichenberg, A. (2012). Dedifferentiation and substitute strategy: deconstructing the processing-speed impairment in schizophrenia. *Schizophrenia Research, 142*(1-3), 129–136. https://doi.org/10.1016/j.schres.2012.08.020

Knowles, E.E., Weiser, M., David, A.S., Glahn, D.C., Davidson, M., & Reichenberg, A. (2015). The puzzle of processing speed, memory, and executive function impairments in schizophrenia: Fitting the pieces together. *Biological Psychiatry, 78*(11)*,* 786-793. https://doi.or/10.1016/j.biopsych.2015.01.018

Kochunov, P., Rowland, L. M., Fieremans, E., Veraart, J., Jahanshad, N., Eskandar, G., Du, X., Muellerklein, F., Savransky, A., Shukla, D., Sampath, H., Thompson, P. M., & Hong, L. E. (2016). Diffusion-weighted imaging uncovers likely sources of processing-speed deficits in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America, 113*(47), 13504–13509. https://doi.org/10.1073/pnas.1608246113

Krukow, P., Karakuła-Juchnowicz, H., Juchnowicz, D., Morylowska-Topolska, J., Flis, M., & Jonak, K. (2017). Processing speed is associated with differences in IQ and cognitive profiles between patients with schizophrenia and their healthy siblings. *Nordic Journal of Psychiatry*, *71*(1), 33-41. https://doi.org/10.1080/08039488.2016.1204469

Lahera, G., Ruiz, A., Brañas, A., Vicens, M., & Orozco, A. (2017). Reaction time, processing speed and sustained attention in schizophrenia: Impact on social functioning. *Revista de Psiquiatría y Salud Mental, 10*(4)*,* 197-205. https://doi.org/10.1016/j.rpsmen.2017.10.006

Leger, M., & Neill, J. C. (2016). A systematic review comparing sex differences in cognitive function in schizophrenia and in rodent models for

schizophrenia, implications for improved therapeutic strategies. *Neuroscience and Biobehavioral Reviews, 68,* 979–1000. https://doi.org/10.1016/j.neubiorev.2016.06.029

Lewandowski, K. E., Cohen, T. R., & Ongur, D. (2020). Cognitive and clinical predictors of community functioning across the psychoses. *PsyCh Journal, 9*(2), 163–173. https://doi.org/10.1002/pchj.356

Li, R., Ma, X., Wang, G., Yang, J., & Wang, C. (2016). Why sex differences in schizophrenia?. *Journal of Translational Neuroscience, 1(1),* 37–42. https://doi.org/10.3868/j.issn.2096-0689.01.006

Linke, M., Jankowski, K. S., Ciołkiewicz, A., Jędrasik-Styła, M., Parnowska, D., Gruszka, A., Denisiuk, M., Jarema, M., & Wichniak, A. (2015). Age or age at onset? Which of them really matters for neuro and social cognition in schizophrenia? *Psychiatry Research, 225*(1-2), 197–201. https://doi.org/10.1016/j.psychres.2014.11.024

Longenecker, J., Dickinson, D., Weinberger, D.R., & Elvevag, B. (2010). Cognitive differences between men and women: A comparison of patients with schizophrenia and healthy volunteers. *Schizophrenia Research, 120*(1-3), 234-235. https://doi.org/10.1016/j.schres.2009.12.009

Ma, X., Wang, G., Yang, J., & Wang, C. (2016). Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based analysis of MRI. *Schizophrenia Research, 55(*1-2), 41-54. https://doi.org/10.1016/S0920-9964(01)00224-9

Miranda, M.C., Rivero, T.S., & Bueno, O.F.A. (2013). Effects of age and gender on performance on Conners´ Continuous Performance Test in Brazilian adolescents. *Psychology & Neuroscience, 6*(1), 73-78. https://doi.org/10.3922/j.psns.2013.1.11

Mondragón-Maya, A., Flores-Medina, Y., Ramos-Mastache, D., Rosel, M., Olivares, J.L., Escamila-Orozco, R., & Saracco-Alvarez, R. (2019). Processing speed differences between schizophrenia and schizoaffective disorder: A pilot study. *Psychiatria Danubina, 31*(3), 355-357. https://doi.org/10.24869/psyd.2019.355

Mortimer, A. M. (2008). The neuropsychology of schizophrenia. *Psychiatry*, 7(10), 435–439. http://doi.org/10.1016/j.mppsy.2008.07.016

Mu, L., Liang, J., Wang, H., Chen, D., Xiu, M., & Zhang, X.Y. (2020). Sex differences in association between clinical correlates and cognitive impairment in patients with chronic schizophrenia. *Journal of Psychiatric Research, 202*, 131-194. https://doi.org/10.1016/j.jpsychires.2020.09.003

Nuechterlein, K. H., Green, M. F., Calkins, M. E., Greenwood, T. A., Gur, R. E., Gur, R. C., Lazzeroni, L. C., Light, G. A., Radant, A. D., Seidman, L. J., Siever, L. J., Silverman, J. M., Sprock, J., Stone, W. S., Sugar, C. A., Swerdlow, N. R., Tsuang, D. W., Tsuang, M. T., Turetsky, B. I., & Braff, D. L. (2015). Attention/vigilance in schizophrenia: performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS). *Schizophrenia Research, 163*(1-3), 38–46. https://doi.org/10.1016/j.schres.2015.01.017

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese 3rd , F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S.E., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., … Marder, S.R. (2008). The MATRICS Consensus Cognitive Battery, Part 1: Test selection, reliability and validity. *American Journal of Psychiatry, 165*, 203-213. https://doi.org/10.1176/appi.ajp.2007.07010042

Ojeda, N., Peña, J., Schretlen, D. J., Sánchez, P., Aretouli, E., Elizagárate, E., Ezcurra, J., & Gutiérrez, M. (2012a). Hierarchical structure of the cognitive processes in schizophrenia: the fundamental role of processing speed. *Schizophrenia Research, 135*(1-3), 72–78. https://doi.org/10.1016/j.schres.2011.12.004

Ojeda, N., Sánchez, P., Peña, J., Elizagárate, E., Yoller, A. B., Gutiérrez-Fraile, M., Ezcurra, J., & Napal, O. (2012b). An explanatory model of quality of life in schizophrenia: the role of processing speed and negative symptoms. *Actas Españolas de Psiquiatría, 40*(1), 10–18. https://www.actaspsiquiatria.es/repositorio/14/75/ENG/14-75-ENG-10-18-158379.pdf

Orellana, G., & Slachevsky, A. (2013). Executive functioning in schizophrenia. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00035

Palaniyappan, L., White, T. P., & Liddle, P. F. (2012). The concept of salience network dysfunction in schizophrenia: from neuroimaging observations to therapeutic opportunities. *Current Topics in Medicinal Chemistry, 12*(21), 2324–2338. https://doi.org/10.217

Perez, V. B., Ford, J. M., Roach, B. J., Woods, S. W., McGlashan, T. H., Srihari, V. H., Loewy, R. L., Vinogradov, S., & Mathalon, D. H. (2012). Error monitoring dysfunction across the illness course of schizophrenia. *Journal of Abnormal Psychology, 121*(2), 372–387. https://doi.org/10.1037/a0025487

Rajji, T.K., Ismail, Z., & Mulsant, B.H. (2009). Age at onset and cognition in schizophrenia: Meta-analysis. *British Journal of Psychiatry, 185,* 286-293. https://doi.org/10.1192/bjp.bp.108.060723

Reichenberg, A. (2010). The assessment of neuropsychological functioning in schizophrenia. *Dialogues in Clinical Neuroscience, 12*(3), 383–392. https://doi.org/10.31887/DCNS.2010.12.3/areichenberg

Rodríguez-Sánchez, J.M., Crespo-Facorro, B., González-Blanch, C., Pérez-Iglesias, R., Vázquez-Barquero, J.L., & PAFIP Group Study (2007). Cognitive dysfunction in first-episode psychosis: The processing speed hypothesis. *British Journal of Psychiatry, 191*(S51), s107-s110. https://doi.org/10.1192/bjp.191.51.s107

Roivainen, E. (2011). Gender differences in processing speed: A review of recent research. *Learning and Individual Differences, 21,* 145-149. https://doi.org/10.1016/j.lindif.2010.11.021

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403–428. https://doi.org/10.1037/0033-295x.103.3.403

Seeman, M.V. (2012). Menstrual exacerbation of schizophrenia symptoms. *Acta Psychiatrica Escandinavica, 59*, 347-398. https://doi.org/10.1111/j.1600-0447.2011.01822.x

Silver, H., & Goodman, C. (2007). Impairment in error monitoring predicts poor executive function in schizophrenia patients. *Schizophrenia Research, 94*(1-3), 156-163. https://doi.org/10.1016/j.schres.2007.04.019

Speechley, W. J., Woodward, T. S., & Ngan, E. T. (2013). Failure of conflict to modulate central executive network activity associated with delusions in schizophrenia. *Frontiers in Psychiatry*, *4*, 113. https://doi.org/10.3389/fpsyt.2013.00113

Sponheim, S. R., Jung, R. E., Seidman, L. J., Mesholam-Gately, R. I., Manoach, D. S., O'Leary, D. S., Ho, B. C., Andreasen, N. C., Lauriello, J., & Schulz, S. C. (2010). Cognitive deficits in recent-onset and chronic schizophrenia. *Journal of Psychiatric Research, 44*(7), 421–428. https://doi.org/10.1016/j.jpsychires.2009.09.010

Torniainen, M., Suvisaari, J., Partonen, T., Castaneda, A. E., Kuha, A., Perälä, J., Saarni, S., Lönnqvist, J., & Tuulio-Henriksson, A. (2011). Sex differences in cognition among persons with schizophrenia and healthy first-degree relatives. *Psychiatry Research, 188*(1), 7–12. https://doi.org/10.1016/j.psychres.2010.11.009

Tripathi, A., Kar, S. K., & Shukla, R. (2018). Cognitive deficits in schizophrenia: Understanding the biological correlates and remediation strategies. *Clinical Psychopharmacology and Neuroscience, 16*(1), 7–17. https://doi.org/10.9758/cpn.2018.16.1.7

Yang, M., Gao, S., Xiong, W., & Zhang, X.Y. (2020). Sex-differential associations between cognitive impairments and white matter abnormalities in first episode and drug-naïve schizophrenia *Early Intervention in Psychiatry*, 10, 1111. https://doi.org/10.1111/eip.13059

Zanelli, J., Mollon, J., Sandin, S., Morgan, C., Dazzan, P., Pilecka, I., Reis Marques, T., David, A. S., Morgan, K., Fearon, P., Doody, G. A., Jones, P. B., Murray, R. M., & Reichenberg, A. (2019). Cognitive Change in Schizophrenia and Other Psychoses in the Decade Following the First Episode. *The American Journal of Psychiatry, 176*(10), 811–819. https://doi.org/10.1176/appi.ajp.2019.18091088

Zhang, B., Han, M., Tan, S., De Yang, F., Tan, Y., Jiang, S., Zhang, X., & Huang, X. F. (2017). Gender differences measured by the MATRICS consensus cognitive battery in chronic schizophrenia patients. *Scientific Reports, 7*(1), 11821. https://doi.org/10.1038/s41598-017-12027-w