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**Processos Cognitivos em Indivíduos com Esquizofrenia da América
Latina: Investigação de Fatores Demográficos, Sociais e Clínicos**

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Processos Cognitivos em Indivíduos com Esquizofrenia da América Latina: Investigação de Fatores Demográficos, Sociais e Clínicos

Dissertação apresentada como requisito parcial para a obtenção do título de Mestre em Psiquiatria e Ciências do Comportamento, à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento

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RESUMO

Contexto: A população da América Latina é uma das mais diversas do mundo pela mistura de diferentes grupos étnicos. No entanto, enfrenta desafios únicos provenientes da violência e da desigualdade. Não existem estudos em larga escala descrevendo as características dessa população e os possíveis impactos do meio nos desfechos da esquizofrenia. Portanto, nosso objetivo é descrever o desempenho cognitivo de uma amostra representativa de indivíduos latino-americanos com esquizofrenia e sua relação com fatores funcionais e clínicos. Além disso, nosso objetivo é analisar como os fatores socioeconômicos se relacionam com o desempenho cognitivo em pacientes e controles. **Métodos:** Foram incluídos 1125 participantes de 5 países da América Latina (Argentina, Brasil, Chile, Colômbia e México): 814 indivíduos com esquizofrenia e 311 controles saudáveis. Todos os participantes fizeram parte de projetos de pesquisa que incluíam avaliação cognitiva pela MCCB e avaliações clínicas. **Resultados:** Os pacientes apresentaram pior desempenho cognitivo comparados aos controles, que foram generalizados entre os domínios. A idade e o diagnóstico foram preditores independentes, indicando trajetórias semelhantes de envelhecimento cognitivo para pacientes e controles. A educação teve um papel significativo na melhor cognição dos pacientes, que também foi influenciada pela sintomatologia dos indivíduos. Os fatores sociais de renda e escolaridade dos pais foram mais relacionados a maiores comprometimentos cognitivos em pacientes do que em controles. **Conclusões:** Os pacientes não mostraram evidências de envelhecimento cognitivo acelerado; no entanto, eles foram mais afetados por um ambiente desfavorecido do que os controles. Esse achado pode indicar uma vulnerabilidade de indivíduos com psicose que poderia levar os pacientes a serem mais impactados pela exposição crônica a fatores sociais.

Palavras-chave: esquizofrenia, cognição, fatores sociais, países de baixa e média renda

ABSTRACT

Background: Latin America's population is one of the most diverse in the world because of its mix of ancestries and ethnic groups. However, it faces unique challenges derived from violence and inequality. There are no large-scale studies describing the characteristics of this population and possible impacts of the environment to disease outcomes. Therefore, our aim is to describe the cognitive performance of a representative sample of Latin American individuals with schizophrenia and its relationship to functional and clinical factors. Additionally, we aim to analyze how socioeconomic factors relate to cognitive performance in patients and controls. **Methods:** We included 1125 participants from 5 Latin American countries (Argentina, Brazil, Chile, Colombia, and Mexico): 814 individuals with schizophrenia and 311 unaffected subjects. All participants were part of research projects that included cognitive evaluation with MCCB and clinical assessments. **Results:** Patients had worse cognitive performance than controls, which was generalized across domains. Age and diagnosis were independent predictors, indicating similar trajectories of cognitive aging for both patients and controls. Education played a significant role in better cognition in patients, which was also influenced by individuals' symptomatology. The social factors of income and parental education were more related to cognitive impairments in patients than in controls. **Conclusions:** Patients did not show evidence of accelerated cognitive aging; however, they were most impacted by a deprived environment than controls. This finding might indicate a vulnerability of individuals with psychosis that could prompt patients to be more impacted by chronic exposure to social factors.

Keywords: schizophrenia, cognition, social factors, low- and middle-income countries

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1 INTRODUÇÃO

A esquizofrenia é um transtorno mental crônico identificado como uma das principais causas de incapacidade do mundo (1) e com grande redução na qualidade de vida de indivíduos diagnosticados (2). É caracterizada pela presença de sintomas relacionados a três grupos principais: *sintomas positivos* (psicóticos, ou seja, delírios e alucinações), *sintomas negativos* (embotamento afetivo, prejuízo motivacional, isolamento social, entre outros) e *sintomas cognitivos* (pior performance em diversos domínios cognitivos quando comparados a controles). Contudo, a grande variabilidade na apresentação desses sintomas também se mostra uma característica central da esquizofrenia. Os sintomas positivos tendem a ter um curso marcado por relapsos e remissão, ainda que alguns indivíduos tenham sintomas psicóticos residuais ao longo do curso da doença. Um aspecto importante para a resposta ao tratamento parece ser a duração dos sintomas psicóticos não-tratados, onde as primeiras semanas após o início dos sintomas parecem ser cruciais para o curso da doença (3). Apesar disso, os sintomas negativos e cognitivos tendem a ser crônicos e associados aos importantes déficits de funcionamento social e ocupacional observados na esquizofrenia (4).

Os tratamentos disponíveis geralmente envolvem o uso de diversos antipsicóticos em longo-prazo (5), que se mostram efetivos para os sintomas positivos para a maior parte dos pacientes (6). Ainda assim, independente da resposta terapêutica, os tratamentos farmacológicos atuais não conseguem abranger integralmente a complexidade e gravidade da esquizofrenia, tendo pouco ou nenhum impacto nos sintomas negativos e cognitivos (7). Existem algumas evidências de um melhor efeito, porém pequeno, nos sintomas cognitivos de alguns antipsicóticos de segunda geração quando comparados aos de primeira geração (8), mas que não é suficiente para uma reabilitação cognitiva e funcional desses pacientes. Mais recentemente, buscando preencher esta lacuna, novos alvos terapêuticos vêm sendo explorados. Uma meta-análise avaliando medicamentos de estimulação cognitiva mostrou um tamanho de efeito pequeno positivo para sintomas cognitivos gerais quando combinados em diferentes sistemas de neurotransmissores. Contudo, os estudos existentes ainda não têm poder suficiente para gerar conclusões robustas, e são necessárias mais pesquisas envolvendo outros sistemas (9). Outras intervenções psicossociais combinadas aos tratamentos

farmacológicos, como protocolos de remediação cognitiva, também têm demonstrado poucos efeitos na recuperação global do indivíduo (10). Uma recente meta-análise demonstrou efeitos significativos de intervenções cognitivas compensatórias, com uma relativa durabilidade, que também apresentavam pequenos efeitos em sintomas positivos e negativos da esquizofrenia (11). Todos esses estudos indicam uma grande variabilidade nas amostras descritas na literatura, o que pode trazer importantes confundidores aos achados. Desta forma, a melhor compreensão dos fatores envolvidos na heterogeneidade da esquizofrenia poderá permitir melhores manejos de indivíduos com esta doença, uma vez que a recuperação do indivíduo em todos os domínios sintomatológicos atualmente é pouco comum, o que leva a prejuízos psicossociais e laborais importantes e característicos (12).

Pessoas com esquizofrenia apresentam defechos funcionais que afetam amplamente os domínios de empregabilidade, vida autônoma e relacionamentos interpessoais (13). Elas usualmente não conseguem se manter em empregos competitivos e atingir níveis educacionais esperados para o seu contexto. Elas também demonstram dificuldades em usar transporte público, cozinhar, gerenciar dinheiro e aderir de forma correta aos medicamentos prescritos. Assim, comumente não conseguem se adequar aos papéis sociais básicos, e desta forma podem ficar isoladas socialmente por não conseguirem manter conversações, expressar necessidades e sentimentos, ou desenvolver relacionamentos próximos e significativos (14). Ao longo do tempo, as trajetórias de funcionamento social e ocupacional parecem se manter estáveis, apesar de haver bastante heterogeneidade entre os indivíduos (15).

Existem vários estudos na literatura investigando os possíveis preditores dos defechos funcionais na esquizofrenia. A sintomatologia parece ser um fator central, especialmente considerando os sintomas negativos da doença, mesmo que presentes em pequena intensidade (16). Além disso, existe a influência de outros domínios psicológicos e motivacionais, além do impacto de condições de saúde (17–20). Contudo, um dos importantes preditores parece ser o funcionamento cognitivo desses indivíduos. Estudos iniciais demonstraram a influência de domínios cognitivos específicos (21), com tamanhos de efeito médios a grandes para funções como memória verbal e funções executivas (22). Entretanto, uma pior performance cognitiva geral está consistentemente associada a piores prejuízos funcionais na

literatura (23), independentemente de idade, sexo ou estágio da doença (24). Desta forma, a compreensão dos mecanismos envolvidos nos processos cognitivos se torna fundamental para o entendimento da esquizofrenia.

É amplamente descrito na literatura que pessoas com esquizofrenia apresentam prejuízos globais e heterogêneos em diversos domínios cognitivos, incluindo processos de atenção, memória episódica, memória de trabalho e funções executivas (25). Esses achados se mantêm mesmo em indivíduos com alto risco para desenvolver transtornos psicóticos (26) e em pacientes em estágio inicial da doença antes do início do tratamento farmacológico (27). Desta forma, a cognição parece já estar moderadamente prejudicada muito antes do diagnóstico (28), e inclusive existem evidências de um pior desempenho acadêmico antes do desenvolvimento de sintomas positivos da doença (29). Contudo, o curso das alterações cognitivas ainda é controverso, principalmente pela diversidade de suas apresentações (30). Esses prejuízos são semelhantes aos de outras psicopatologias, como o transtorno bipolar e o transtorno esquizoafetivo, apenas diferindo em severidade (31,32). Além disso, existe uma relação entre os genes associados ao risco para desenvolver esquizofrenia e os genes associados à performance cognitiva (33), demonstrando uma influência biológica desse processo. Os prejuízos cognitivos também parecem se correlacionar com variáveis sócio-demográficas (como baixa escolaridade), clínicas (como maior número de hospitalizações e maior tempo de doença), e de tratamento (como uso de antipsicóticos) (34).

Contudo, os estudos tradicionais de cognição usualmente analisam diferenças entre médias de pacientes e controles saudáveis. Este método não considera completamente as diferenças entre indivíduos destes grupos, ignorando a existente heterogeneidade cognitiva e potencialmente diminuindo sua validade externa. Apesar disso, existem alguns estudos na literatura que têm mostrado que indivíduos com esquizofrenia poderiam ser divididos em subgrupos entre aqueles que apresentam prejuízos globais severos, prejuízos leves a moderados, e quase sem prejuízos cognitivos (35–39), tanto em pacientes em primeiro episódio (40) quanto em pacientes crônicos (41). Ainda não existe um consenso claro sobre o número de subgrupos de performance cognitiva nesses pacientes, uma vez que os diferentes achados apontam de duas a quatro soluções. Contudo, um subgrupo representativo de déficits acentuados parece estar presente em todos os estudos

descritos na literatura (42). Esses clusters cognitivos estariam associados a variáveis clínicas e psicossociais (39), além de diferenças no funcionamento intelectual (39) e em achados de neuroimagem (43,44). Um aspecto interessante deste tipo de análise é a possibilidade de encontrar subgrupos mais homogêneos que estariam potencialmente relacionados a mecanismos neurobiológicos específicos.

Entretanto, ainda não foram investigados os possíveis impactos de fatores sociais e ambientais nas trajetórias cognitivas. Por exemplo, estudos anteriores demonstraram que viver em ambientes urbanos aumentaria o risco para esquizofrenia (45,46), e que esse efeito poderia ser parcialmente mediado pela criminalidade aumentada nesses contextos (47). Além disso, a esquizofrenia parece ser mais frequente em piores condições socioeconômicas (48,49). Fatores sociais, como o nível socioeconômico, aumentam o risco para desenvolver esquizofrenia (50) e influenciam o desenvolvimento cognitivo e emocional de indivíduos através do impacto no desenvolvimento de regiões neurais específicas. Contudo, isto parece receber pouca atenção na psiquiatria e neurociências (51). Recentemente, Gooding et al. (52) descreveu que somente com uma perspectiva mais ampla dos pesquisadores em reconhecer e indicar que a maior parte da população não reside em países ricos, industrializados, ou mesmo democráticos, poderá dar conta das necessidades de um mundo diverso.

Neste contexto, a América Latina surge como uma oportunidade para estudar o impacto de fatores sociais no contexto da esquizofrenia, uma vez que é responsável por 8,45% da população mundial (53) e apresenta uma complexidade e diversidade populacional onde ao redor de 80% das pessoas vive em centros urbanos (54). Além disso, as grandes cidades latino-americanas são em geral superpopulosas, violentas, e têm um alto grau de desigualdade social e pobreza (55). Contudo, nem todos são expostos a esses fatores, uma vez que uma pequena parcela da população tem acesso a padrões de primeiro mundo (56). Essa grande diversidade social permite que se tenha uma amostra na qual é possível investigar os impactos de fatores ambientais e sociais sobre o desempenho cognitivo de indivíduos, de forma a melhorar a compreensão dos mecanismos associados ao funcionamento de transtornos mentais graves.

A relevância deste estudo se justifica, portanto, uma vez que o mesmo visa investigar perfis de alterações cognitivas em indivíduos com esquizofrenia,

explorando os possíveis impactos ambientais e sociais. O prejuízo cognitivo pode ser considerado parte importante da doença e que interfere no curso e prognóstico do transtorno, mas que tem uma heterogeneidade de apresentação nos indivíduos. A compreensão deste aspecto do estado psicopatológico pode auxiliar na elaboração de intervenções mais efetivas.

2 OBJETIVOS

2.1 OBJETIVO GERAL

Investigar a performance cognitiva de indivíduos com esquizofrenia e controles saudáveis de cinco países da América Latina.

2.2 OBJETIVOS ESPECÍFICOS

- Avaliar as diferenças de performance cognitiva de indivíduos com esquizofrenia e controles saudáveis;
- Replicar achados descritos na literatura com relação ao efeito global e heterogêneo dos déficits cognitivos em indivíduos com esquizofrenia;
- Investigar os efeitos da idade e do gênero na performance cognitiva de indivíduos com esquizofrenia e controles saudáveis;
- Avaliar os efeitos dos fatores sociais de renda familiar e escolaridade dos pais em indivíduos com esquizofrenia e controles saudáveis;
- Explorar subgrupos de performance cognitiva em indivíduos com esquizofrenia e sua relação com fatores sociodemográficos e clínicos.

3 MÉTODOS

3.1 DELINEAMENTO

Este foi um estudo transversal incluindo dados já existentes da *ANDES Network - Rede Latino-Americana de Pesquisadores em Esquizofrenia e Psicose Precoce*. Os dados utilizados nesta pesquisa são oriundos de 9 locais em 5 países: Argentina, Brasil, Chile, Colômbia e México. Os projetos foram conduzidos de forma independente em cada local e, desta forma, não eram idênticos entre si. Com isso, alguns dados não estão presentes para algumas amostras.

3.2 PARTICIPANTES

Foram incluídos indivíduos com diagnóstico de esquizofrenia ou em primeiro episódio psicótico não-afetivo. Além disso, em cinco locais da Rede também foram incluídos controles sem diagnóstico de transtornos mentais graves.

3.3 CONDUÇÃO DO ESTUDO

O banco de dados disponível inclui dados clínicos, sociodemográficos e de desempenho cognitivo de indivíduos com esquizofrenia e controles saudáveis. Foram consideradas as seguintes variáveis:

Variáveis clínicas (para pacientes): tempo de doença, idade de diagnóstico, sintomatologia avaliada pela Positive and Negative Syndrome Scale (PANSS), número de hospitalizações.

Variáveis cognitivas: avaliado através da MATRICS Consensus Cognitive Battery (MCCB) (57). A MCCB avalia 7 domínios cognitivos (derivados de 10 subtestes), além de um composite geral: 1) *velocidade de processamento* (Trail Making Test – A; Brief Assessment of Cognition in Schizophrenia: Symbol coding; Category fluency test, animal naming); 2) *atenção/vigilância* (Continuous Performance Test: Identical Pairs); 3) *memória de trabalho visual e verbal* (Wechsler Memory Scale, spatial span subset; Letter Number Span test); 4) *memória e*

aprendizagem verbal (Hopkins Verbal Learning Test-Revised); 5) *memória e aprendizagem visual* (Brief Visuospatial Memory Test-Revised); 6) *raciocínio e resolução de problemas* (Neuropsychological Assessment Battery, mazes subtest); 7) *cognição social* (Mayer-Salovey-Caruso Emotional Intelligence Test: managing emotions branch). Não foram incluídos os resultados de cognição social por existirem poucos dados no banco disponível. Foram considerados os resultados dos subtestes individuais e de um escore composto com a média dos escores-z calculados a partir do desempenho dos controles.

Fatores sociais: nível educacional, nível educacional dos pais, e renda familiar.

3.4 ANÁLISE ESTATÍSTICA

As análises estatísticas foram realizadas no software R (<https://www.Rproject.org/>) e estão descritas no artigo, no item Resultados desta Dissertação.

3.5 CONSIDERAÇÕES ÉTICAS

O estudo não envolveu coleta de dados por usar banco de dados anonimizado já existente. De qualquer forma, os projetos de pesquisa de coleta de dados dos locais específicos foram aprovados por seus respectivos comitês de ética e seguiram a Declaração de Helsinki, abrangendo os princípios bioéticos de autonomia, beneficência, não-maleficência, veracidade e confidencialidade.

4 RESULTADOS

Complete title: Effects of Environmental Inequality in Cognition of People With Schizophrenia: Results From a Latin American Collaboration Network with 1125 Subjects

Running title: Cognition in Schizophrenia Across Latin America

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Abstract

Background: Cognition heavily rely on social determinants and genetic background. Latin America comprises approximately 8% of global population and faces unique challenges, many derived from specific demographic and socioeconomic variables, such as violence and inequality. While such factors have been described to influence mental health outcomes, no large-scale studies with Latin-American population have been carried out. Therefore, we aim to describe the cognitive performance of a representative sample of Latin American individuals with schizophrenia and its relationship to clinical factors. Additionally, we aim to investigate how socioeconomic factors relate to cognitive performance in patients and controls.

Methods: We included 1125 participants from 5 Latin American countries (Argentina, Brazil, Chile, Colombia, and Mexico): 814 individuals with schizophrenia and 311 unaffected subjects. All participants were part of research projects that included cognitive evaluation with MATRICS Consensus Cognitive Battery and clinical assessments.

Results: Patients showed worse cognitive performance than controls across all domains. Age and diagnosis were independent predictors, indicating similar trajectories of cognitive aging for both patients and controls. More education played a significant role in better cognition in patients. Cognition was also influenced by symptomatology. The social factors of income and parental education were more related to cognitive measures in patients than in controls.

Conclusions: Patients did not show evidence of accelerated cognitive aging; however, they were most impacted by a deprived environment than controls. These findings highlight the vulnerability of cognitive capacity in individuals with psychosis in face of demographic and socioeconomic factors in low and middle-income countries.

Keywords: schizophrenia, cognition, social factors, low- and middle-income countries

Introduction

Individuals with schizophrenia show reduced cognitive performance compared to unaffected subjects in a wide range of domains¹, which is consistently associated with worse functional outcomes², regardless of age, gender, or illness chronicity³. These deficits are present since early stages of the disease, even in drug-naïve patients⁴, and there is evidence of cognitive compromise since before diagnosis⁵. However, the trajectory of cognitive change is still controversial in the literature. Most studies report no further decline in cognition after the first episode⁶, but recent studies with longer duration of follow-up have raised the possibility of a deteriorating trajectory with ageing^{7,8}. Also, there is great heterogeneity in the cognitive deficits in schizophrenia⁹. Recent literature has been trying to identify subgroups that might elucidate common mechanisms and risk factors, considering the variability within this population¹⁰. Data-driven techniques revealed subgroups of cognitively spared, intermediate cognitive impairments and deficit subtypes¹¹. It is unclear, though, whether these findings result from diverse subgroups or only divisions in a linear continuum.

Schizophrenia and other psychotic disorders carry a genetic load related to cognitive performance and education attainment¹² that is shared across different populations¹³. Nonetheless, a biocultural approach indicates that cultural patterns could influence neurobiology and inflammation in mental disorders¹⁴. Curiously, only a few studies investigate the effects of diversity and cultural differences in schizophrenia's cognitive heterogeneity. In this context, Latin America arises as an opportunity for studying the impact of social factors on people with schizophrenia's cognitive performance, while at the same time looking into an understudied region of the world.

Latin America is a multiethnic and multicultural continent formed from a mixture of different pre-colonial indigenous cultures, European colonizers (mostly Spanish and Portuguese), and African ethnic groups who were brought as slaves during the colonization. It is home to almost 650 million people – around 8.45% of the world's population¹⁵, and has highly urbanized regions, with an estimated 80% of the population living in cities¹⁶. Moreover, because of its historical economic and political instability, there are over 36 million Latin American immigrants living abroad¹⁷, making the study of this population relevant beyond the continent's geographical limits. Latin America has significant and evident economic inequalities¹⁸. The

inequities experienced by its population go beyond income and lead to social discrimination and exclusion from exercise of rights, autonomy, and access to opportunities and education^{19,20}. These result in major health inequalities, both in access and outcomes¹⁹, implicating in factors such as reduction in life expectancy at birth²¹. Furthermore, it faces challenges linked to extreme violence, such as reduced life expectancy due to excess mortality related to homicide in young people²². Such a different setting compared to highly industrialized western societies pose a valuable opportunity for the study of cognition, providing the opportunity to re-test previously known associations, but also to examine pending controversies under new light, such the effects of socioeconomic factors in cognition.

We therefore here examined the cognitive performance of 1125 Latin American individuals with schizophrenia and healthy controls from 5 Latin American countries. We first focused on testing whether previously reported findings in schizophrenia and cognition, such as the global effect, were replicated in such a different environment. We then sought to contribute to the discussions on the cognitive trajectory in schizophrenia by examining a possible differential association of age and cognition in our cross-sectional study, and the role of the environment. Additionally, we aimed to analyze how socioeconomic factors relate to cognitive performance in people with schizophrenia and healthy controls. Finally, we also explored whether patients clustered in different subgroups according to cognition.

Methods

Participants

This study is part of the ANDES network, which unites several groups from different countries across Latin America to promote science²³. We included 1125 participants from 5 Latin American countries: Argentina, Brazil, Chile, Colombia, and Mexico, of which 814 were individuals diagnosed with schizophrenia or first-episode non-affective psychosis, and 311 were unaffected subjects. All participants were part of individual research projects that included cognitive and clinical assessments.

Supplementary Table 1. describes each country's demographic characteristics, including population, Gross National Income (GNI) per capita, Gini coefficient, and Human Development Index (HDI) rating and rank. The per capita GNI (purchasing power parity) for the countries studied ranged from 12,896 to 21,972 2011 USD and Gini coefficients ranged from 40.6 to 53.3 (income distribution

inequality). In terms of HDI (overall development), Chile and Argentina are ranked as "Very High", while Mexico, Brazil, and Colombia are ranked "High".

All centers recruited patients with schizophrenia or an associated diagnosis from clinical centers. Some included healthy controls from different sources. All patients and controls participated willingly and voluntarily and were given the proper consent forms. Their local ethical committee approved each site's project. Table 1. describes inclusion and exclusion criteria used for patients and controls in each center.

Assessment

Participants underwent a cognitive assessment through the MATRICS Consensus Cognitive Battery (MCCB). Because of differences in study design, some individuals completed only some of the subtests included in the battery. Additional data related to sociodemographic and clinical factors were collected. Symptomatology in patients was assessed through the Positive and Negative Syndrome Scale (PANSS).

Data Analysis

Statistical analyses were completed in R (version 4.0.0) and RStudio (version 1.3.959). We transformed MCCB subtest raw scores into z-scores using the mean and standard deviation of the unaffected individuals. We used a reversed score of the Trail Making Test to maintain the direction of the other subtests. Then, we created a cognitive composite with the sum of z-scores divided by the number of subtests completed. Our first level of analysis was to compare groups regarding sociodemographic and cognitive data using independent samples t-test and chi-square test. We then investigated the relationship between cognitive performance and sociodemographic and clinical data through linear regression models. Linear mixed-effects models with site as a random effect were performed to confirm that findings from linear models were not due to site differences. Finally, we explored subgroups of cognitive performance through hierarchical cluster analysis with the squared Euclidian distance and Ward linkage as the agglomeration procedure. The dendrogram's inspection was used as a criterion to establish the appropriate number of clusters to retain. We then compared the data-driven subgroups of cognitive performance regarding sociodemographic and clinical variables using independent

samples t-test and chi-square test. Descriptive data were expressed as mean and standard deviation, and significance was set at $p < .05$, 2-tailed.

Results

Cognitive performance, clinical and demographic factors

Table 2. presents the sociodemographic, clinical, and cognitive data. Patients had similar age than unaffected participants. However, the patient's group had more males and had less working or studying individuals. Patients also had fewer years of education, parent's years of education, and family income than controls. Regarding cognition, as expected, we found a worse performance of patients compared to controls in the cognitive composite (Figure 1A.; $t(1078)=18.669$, $p<.001$, Cohen's $d=1.296$), and in each subtest individually (Figure 1B.).

In patients, in linear models controlling for age, sex, and years of education, age of onset ($F(4,502)=47.95$, $p<.001$, $t=0.797$, $p=.426$) and illness duration ($F(4,535)=51.92$, $p<.001$, $t=-1.544$, $p=.123$) were not related to the overall cognitive performance (Supplementary Figure 1A.-1B.). Better cognitive performance was related to fewer symptoms in the PANSS total score ($F(4,447)=42.58$, $p<.001$, $t=-5.746$, $p<.001$) and its subscales (positive: $F(4,448)=40.36$, $p<.001$, $t=-5.093$, $p<.001$; negative: $F(4,448)=46.35$, $p<.001$, $t=-6.675$, $p<.001$; general: $F(4,448)=37.54$, $p<.001$, $t=-4.142$, $p<.001$) (Supplementary Figures 1C.–1F.).

The effects of aging and gender in patients and controls

We performed a linear regression model including the cognitive composite as the dependent variable, age, gender and group as the independent predictors, and the interaction between age x group and gender x group ($F(5,1002)=118.0$, $p<.001$, $Adj.R^2=.367$). We found that age ($t=-7.373$, $p<.001$), gender ($t=-2.183$, $p=.03$), and group ($t=-8.347$, $p<.001$) were all independent predictors of cognitive performance, with no group by age ($t=0.911$, $p=.362$) or group by gender ($t=0.809$, $p=.418$) interactions. This indicated that ageing was associated with a similar global cognitive decline in both patients and controls (Figure 2A.), and that male participants performed slightly better than females.

Exploring cognition in a relatively deprived setting: association with education and socioeconomic factor indicators

We found a group by education interaction ($t=5.251$, $p<.001$) in a model with cognitive composite as dependent variable, and years of education by group as predictors, controlling for age and gender ($F(5,771)=172.7$, $p<.001$, $Adj.R^2=.525$), indicating that education was more important for the cognitive performance of patients than for controls (Figure 2B.). The same was found for parents' years of education ($F(5,426)=108.8$, $p<.001$, $Adj.R^2=.556$), where the interaction suggested a more significant effect for the patient's parents education ($t=2.686$, $p=.008$), although in a less pronounced way than the patient's education (Figure 2C.).

Finally, a model with cognitive composite as dependent variable, and income by group as predictors, controlling for age and gender ($F(5,239)=66.85$, $p<.001$, $Adj.R^2=.574$) found a group by income interaction ($t=4.471$, $p<.001$). Patients with more income scored higher in cognitive performances, while income was not associated with cognitive performance in controls (Figure 2D.).

Investigating subgroups of cognitive performance

We conducted a hierarchical cluster analysis with only the patients with complete data considering the subtests z-scores of the MCCB (Supplementary Figure 2.). We identified two subgroups of cognitive performance: the first group had the majority of patients ($n=374$, 73.76%) and had lower middle performances than mean scores of healthy controls (z-scores between -1.03 and -.052). The second subgroup ($n=133$, 26.23%) presented performances considered as clinical deficits in all domains (z-scores below -1.5) (Figure 3.).

Patients from the first subgroup were younger, had more personal and parental education, and had fewer years of illness, psychiatric hospitalizations, and symptoms (lower PANSS scores) than the second subgroup. Additionally, the first group had an increased estimated IQ in relation to the other group. There were no differences regarding age at onset and family income (Supplementary Table 2.).

Effects of site

Linear mixed-effects model with site as a random factor were performed to ascertain that all results previously mentioned were not due to site differences. No differences were found between models' results.

Discussion

This is the first large and representative study to characterize the cognitive deficits of schizophrenia from a Latin American population. Using this sample from an under-reported region of the world, we were able to confirm certain associations frequently found in the literature, as well as shed light on new controversies. We found that patients had worse cognitive performance than healthy controls, which was generalized across all cognitive domains. Age was an independent predictor of cognitive performance, and we did not find any evidence suggesting that this association was different in patients and controls. Education was significantly related to cognitive performance in both groups, but gains in education were associated with larger increases in cognitive function in schizophrenia. When we looked at the social factors of income and parental education, we found that a deprived environment was related to worse cognitive impairments in patients, which was different from controls. This finding might indicate a vulnerability of individuals with psychosis that could prompt patients to be more impacted by chronic exposure to social factors, as we can observe in poor and developing countries such as in Latin America. Finally, not all patients presented with severe deficits, and the gravity of impairments were related to sociodemographic and clinical variables. These findings will be discussed below.

As expected, patients performed worse than healthy controls in all subtests of the MCCB and the cognitive composite. Cognition was also related to symptomatology, particularly negative symptoms. These results were expected since these findings have been widely reported in different regions of the world and remained robust over the decades²⁴. Nonetheless, there were no studies with representative data from Latin America reporting this outcome, which is why these results are important for a broader understanding of a diverse world. Further, as prior reports, we found high heterogeneity in the cognitive performance of individuals. Our data-driven clustering indicated that almost 75% of patients presented performances considered as lower-middle compared to unaffected individuals. A 2-cluster solution has been found in previous studies. Our results suggest a smaller group for severe deficits (26.23% as opposed to 50% in other studies). A severe subtype appears to be common to all investigations of clusters, and several studies report differences in clinical and socioeconomic findings among groups¹¹, which supports our results. Moreover, the subgroups of cognitive performance seem to be present in related

diagnoses such as bipolar disorder, which might indicate that they are not distinct profiles but possibly different cognitive trajectories²⁵.

A sample of individuals with schizophrenia from Australia divided into preserved, deteriorated, and compromised groups based on estimated premorbid IQ and current cognitive performance showed difference in socioeconomic status. Additionally, the compromised patients, e.g., individuals with a significant decline from estimated premorbid IQ, showed greater childhood adversities and lower socioeconomic status than the deteriorated patients, e.g., both current and estimated premorbid impairments²⁶, suggesting that social factors might impact both cognitive development and exposure to childhood adversity. Interestingly, there seems to be a difference between the observed and the expected global cognitive ability of patients, and even "normal" performers, as indicated by normative data, might be impaired compared to their expected abilities²⁷. This might suggest that, in addition to biological neurodevelopmental abnormalities²⁸, individuals at risk for triggering severe mental disorders may be more vulnerable to social factors during development. A study of the Philadelphia Neurodevelopmental Cohort (US) found that lower socioeconomic status was related to both reduced performances in different cognitive domains and lower volume across brain regions, including white and gray matter, that was related to an accelerated neurodevelopment²⁹. We recently showed that, in patients from Latin America, income was related to total gray matter volume in unaffected individuals but not in patients with psychosis. This potentially indicates that less brain vulnerability in patients (e.g., less gray matter loss) would be sufficient to become unwell in adverse environments, and that considering the upbringing of patients is critical to understanding schizophrenia's anatomy (Crossley et al., accepted for publication). The difference between patients and controls in the impact received by deprived environments was also seen in our sample related to cognitive performances, where income and parental education were more related to worse impairments in cognition for patients.

Conversely, we found that patients did not show a steeper cognitive decline in the cognitive composite than controls. Although our data is cross-sectional, we have a wide range of ages in our large sample (13-66 years), which might bring an idea of a longitudinal profile. The cognitive aging in schizophrenia and related disorders is still unestablished³⁰. Some evidence suggests early deficits with stable trajectories after the first episode³¹. A longitudinal study by the Genetic Risk and Outcome of

Psychosis (GROUP, Netherlands and Belgium) found five cognitive trajectories that remained stable after 3 and 6 years in individuals with schizophrenia³². However, others point to accelerated cognitive aging. The Suffolk County Mental Health Project (US) showed that patients with a first psychotic hospitalization, after 18 years, presented declines in some cognitive domains that were clinically significant and larger than expected due to normal aging⁷. This was similar to the Aetiology and Ethnicity in Schizophrenia and Other Psychoses study (AESOP, UK) that followed first-episode psychosis after 10 years and found a cognitive decline in specific domains after illness onset in patients with schizophrenia⁸.

There is evidence that suggests that cognitive reserve might protect from accelerated cognitive aging declines³³. In our sample, we found that education was more important to cognitive performance in patients than in controls, supporting this hypothesis. Years involved in formal learning is one of the main components of cognitive reserve. Individuals with increased cognitive reserve might show better functional and cognitive performances, in addition to better clinical outcomes³⁴. Our results revealed that increased positive, negative and general psychopathology symptoms were all associated with worse cognitive performance, even after controlling for the effects of age and education. This might indicate that patients with increased psychopathology have worse disease trajectories associated with poorer cognitive performances³², since the overall symptomatology tend to persist over time³⁵. Interestingly, these cognitive trajectories do not seem to be related to the age of onset³², as seen in our sample. Therefore, the relationship between clinical variables and cognition was supported by previous literature.

Our study had some limitations. However, we used a mixed-model approach to manage the inter-site differences. We also did not control for possible confounders, such as duration of untreated psychosis, medication use, and other lifestyle factors, and we did not show data related to functional outcomes. Moreover, we did not present T-scores from the MCCB domains. It should be noted that there are different findings regarding the interpretation of cognitive data when comparing different cultures with the same normative scores, even in well-developed and high-income countries³⁶. Therefore, it is preferred to compare patients with unaffected individuals from the same cultural and socioeconomic background – as conducted in our study.

There are different findings in the literature between low- and middle-income countries (LMIC) and high-income countries (HIC). Individuals from LMIC report higher stress sensitivity and prevalence of psychotic experiences³⁷. Moreover, urbanicity does not seem to be related to increased risk for psychosis in developing countries, different from what has been described regarding HIC³⁸. Nonetheless, similarities have also been reported between findings from LMIC and HIC, such as the generalized cognitive impairments in drug-naïve individuals with psychosis³⁹, and the relationship between more prolonged duration of untreated psychosis and poorer clinical improvement and increased functional disability⁴⁰. However, even though several Latin American countries focused on the expansion of universal health coverage to reduce health access inequalities during the last decades⁴¹, there is still a significant concern regarding the treatment gap for mental disorders in LMIC⁴², which might prevent better outcomes for these patients.

LMIC publish fewer scientific reports related to mental disorders compared to HIC, although it has been increasing during the last decades⁴³. The few that exists are usually underpowered, mainly because of the lack of government research funding and research capacity. Therefore, the scientific community could greatly benefit from the “consolidation of more regional, interdisciplinary and international research networks”⁴⁴, since that “people working and living in LMICs are better placed to define issues of importance to their populations than are people living thousands of miles away in HICs — who often fund research based on their own interests”⁴⁵. Within this perspective, our study aimed to bring – from a collective effort – a contribution to the development of cognitive research in schizophrenia and related disorders in Latin American and other LMIC. Further research is needed in combination with more practical measures from the scientific community, such as funding focused on LMIC and the promotion of the Schizophrenia International Research Society (SIRS) membership to represent the world’s diversity⁴⁶.

In conclusion, this was the first large-scale study describing the characteristics of individuals with schizophrenia and related disorders from Latin America and the possible impacts of the environment on disease outcomes. As expected, patients showed general and heterogeneous cognitive deficits compared to unaffected individuals. Patients did not show evidence of accelerated cognitive aging; however, we found that they were most impacted by a deprived environment than controls. These findings indicate the need for public policy to protect children and youth from

the effect of social adversities, especially for those at risk or experiencing schizophrenia or other severe mental disorders. The ANDES Network brings a unique chance to study psychosis in disadvantaged settings, which are frequently less represented in research publications. Future studies from the ANDES Network will further explore the effects of the environment on cognition to better understand the mechanisms involved in this crucial dysfunction.

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Figure Legends

Figure 1.

A. Comparison of the MCCB cognitive composite (z-score) between healthy controls (HC) and individuals with schizophrenia (SZ). B. Comparison of each subtest of the MCCB (z-score) between healthy controls (HC) and individuals with schizophrenia (SZ).

Figure 2.

Relationship between demographic and social factors and MCCB cognitive composite (z-score) in healthy controls (HC) and individuals with schizophrenia (SZ), controlling for age and gender.

Figure 3.

Mean cognitive performance in each subtest z-scores between subgroups of individuals with schizophrenia.

Table 1. Sample characteristics

Site	Sample Size	Inclusion and Exclusion Criteria
Argentina Buenos Aires FLENI Institute	46 patients 46 controls	Patients were recruited from an outpatient unit. Inclusion criteria: (a) DSM-IV-TR criteria for schizophrenia as determined by a semi-structured interview administered by a psychiatrist; (b) ages between 18-65 years; (c) stable for >2 weeks without change in medication or inpatient care. Exclusion criteria: (a) substance abuse in the last 6 months; (b) intellectual disability. Healthy controls were also recruited. Exclusion criteria: (a) current or previous history of psychiatric disorder; (b) ongoing psychotropic treatment.
Brazil Porto Alegre HCPA/UFRGS	24 patients 45 controls	Patients were recruited from an outpatient unit. Inclusion criteria: (a) DSM-IV-TR criteria for schizophrenia as determined by the Structured Clinical Interview for DSM-IV administered by a psychiatrist; (b) ages between 18-65 years; (c) stable for >6 months. Healthy controls were also recruited. Exclusion criteria: (a) current or previous history of psychiatric disorder; (b) first-degree family history of major psychiatric disorder.
Brazil São Paulo UNIFESP	267 patients 85 controls	Patients were recruited from an outpatient unit. Inclusion criteria: (a) DSM-IV-TR criteria for schizophrenia as determined by the Structured Clinical Interview for DSM-IV administered by a psychiatrist; (b) >18 years old; (c) stable for >4 weeks without change in medication; (d) >4 years of education; (e) estimated IQ >80. Exclusion criteria: (a) substance abuse in the last year; (b) history of traumatic brain injury or neurological disorder. Healthy controls were also recruited.
Brazil São Paulo HCFMUSP	40 patients	Patients were recruited from an outpatient unit. Inclusion criteria: (a) DSM-IV-TR criteria for schizophrenia; (b) ages between 18-55 years; (c) stable for >8 weeks without change in medication, and no inpatient care for the last 3 months; (d) >5 years of education. Exclusion criteria: (a) substance use disorders; (b) comorbid axis I disorders; (c) intellectual disability; (d) history of traumatic brain injury and/or neurological disorder; (e) suicide risk.
Chile Santiago Horwitz Psychiatric Institute Youth Inpatient Unit	107 patients 51 controls	Patients were recruited from an adolescent and youth inpatient unit. Inclusion criteria: (a) F20-F29 diagnosis according to ICD-10 as determined by a psychiatrist; (b) going through non-affective first-episode psychosis; (c) estimated IQ >70. Healthy controls were also recruited. Exclusion criteria: (a) current or previous history of psychiatric or neurological disorder; (b) first-degree family history of major psychiatric disorder.
Chile Santiago Horwitz Psychiatric Institute Outpatient Unit	32 patients	Patients were recruited from an outpatient unit. Inclusion criteria: (a) Schizophrenia diagnosis within the previous 5 years; (b) ages between 16-25 years; (c) ≤ 4 in the PANSS positive and negative subscales; (d) estimated IQ >70; (e) Hamilton Depression's scale suicide item = 0. Exclusion criteria: (a) morbid obesity; (b) EEG abnormalities; (c) history of seizures.
Chile Valdivia	57 patients	Patients were recruited from an outpatient units. Inclusion criteria: (a) DSM-IV-TR criteria for schizophrenia, schizoaffective or schizotypal disorder as determined by the Structured Clinical Interview for DSM-IV administered by a psychiatrist; (b) ages between 15-35 years; (c) clinically stable; (d) early onset of the disorder. Exclusion criteria: (a) substance abuse in the last 6 months; (b) suicide risk; (c) intellectual disability.
Colombia Medellín San Vicente Foundation University Hospital	101 patients	Inclusion criteria: (a) DSM-IV-TR criteria for schizophrenia; (b) ages between 18-60 years; (c) >6 and <16 years of education. Exclusion criteria: (a) intellectual disability; (d) history of traumatic brain injury or neurological disorder.
Mexico Mexico City Instituto Nacional de Neurología y Neurocirugía	122 patients 84 controls	Antipsychotic-naïve patients were included in two groups: 1. individuals experiencing first-episode-non-affective psychosis (untreated psychotic symptoms for <74 weeks) 2. Individuals with chronic schizophrenia (untreated psychosis >74 weeks). Exclusion criteria: (a) substance use disorders; (b) comorbid axis I disorders. Healthy controls were also recruited.

Table 2. Sociodemographic, clinical and cognitive data

Variables	Individuals with schizophrenia or FEP (n = 814)	Healthy controls (n = 311)	Group comparisons
Sociodemographic			
Age	30.82 (\pm 10.95)	31.12 (\pm 11.67)	t(1105) = .40, p = .69
Sex [n, male/female]	532/208	137/174	$\chi^2(1) = 73.36$, p < .001
Occupational Status [n]			$\chi^2(3) = 113.3$, p < .001
No work, no study	225	5	
Work	74	34	
Study	59	55	
Retirement or government aid	12	0	
Years of Education	11.19 (\pm 3.13)	14.39 (\pm 4.26)	t(872) = 11.93, p < .001
Parent's Years of Education	10.59 (\pm 4.71)	14.29 (\pm 4.33)	t(459) = 8.414, p < .001
Income	457.78 (\pm 333.55)	1361.45 (\pm 1755.32)	t(243) = 6.312, p < .001
Clinical			
Age at Onset	22.03 (\pm 6.67)	-	
Illness Duration	9.36 (\pm 9.77)	-	
Number of hospitalizations	1.81 (\pm 2.95)	-	
PANSS Positive	18.06 (\pm 8.38)	-	
PANSS Negative	21.39 (\pm 8.03)	-	
PANSS General	37.72 (\pm 13.65)	-	
PANSS Total	77.04 (\pm 27.03)	-	
MCCB (raw scores)			
TMT	58.52 (\pm 39.11)	35.45 (\pm 14.63)	t(1076) = -9.619, p < .001
BACS SC	35.72 (\pm 13.35)	55.53 (\pm 14.80)	t(905) = 19.943, p < .001
HVLT-R Tot	19.53 (\pm 5.51)	26.25 (\pm 4.35)	t(1035) = 18.355, p < .001
WMS-III SS	13.33 (\pm 4.29)	16.39 (\pm 3.80)	t(908) = 10.268, p < .001
LNS	9.73 (\pm 3.99)	13.89 (\pm 3.43)	t(905) = 15.095, p < .001
NAB Mazes	12.01 (\pm 6.95)	17.92 (\pm 6.80)	t(905) = 11.89, p < .001
BVMT-R Tot	17.45 (\pm 8.75)	25.27 (\pm 8.27)	t(802) = 12.286, p < .001
Fluency	16.73 (\pm 5.72)	23.26 (\pm 5.75)	t(1033) = 16.254, p < .001
CPT-IP Mean	1.56 (\pm 0.79)	2.50 (\pm 0.74)	t(857) = 16.707, p < .001
Estimated IQ	86.38 (\pm 13.81)	104.85 (\pm 12.14)	t(483) = 13.742, p < .001

Supplementary Table 1. Countries demographic characteristics

Country	Population (2018, in thousands)	Gross National Income (GNI) per capita, 2018 (2011 PPP \$)	Gini coefficient (2010-2017)	HDI (2018)	HDI rank (2018)
Argentina	44,495	17,611	40.6	0.830	48
Brazil	209,469	14,068	53.3	0.761	79
Chile	18,729	21,972	46.6	0.847	42
Colombia	49,649	12,896	49.7	0.761	80
México	126,191	17,628	43.4	0.767	76

GNI per capita is measured using the 2011 Purchasing Power Parity exchange from local currencies into USD; this measure of per capita income uses the price of a common basket of goods to match different currencies purchasing power. A larger GNI per capita would indicate higher purchasing power. The Gini coefficient measures income distribution ranging from 0 to 100, with 0 being absolute equality and 100 the theoretical maximum inequality. The HDI is a composite score calculated using a life expectancy index, educational index, as well as a GNI index, and it is meant to measure overall development in different countries.

Supplementary Table 2. Sociodemographic and clinical data by subgroups of cognitive performance

Variables	Subgroup 1 (n = 374)	Subgroup 2 (n = 133)	Group comparisons
Sociodemographic			
Age	26.82 (± 9.34)	31.36 (± 11.62)	$t(491) = -4.459, p < .001$
Sex [n, male/female]	232/82	79/45	$\chi^2(1) = 4.471, p = .034$
Occupational Status [n]			$\chi^2(2) = 8.046, p = .018$
No work, no study	82	37	
Work	36	10	
Study	38	4	
Retirement or government aid	0	0	
Years of Education	12.34 (± 2.67)	10.03 (± 3.27)	$t(352) = 6.678, p < .001$
Parent's Years of Education	11.90 (± 4.17)	9.29 (± 4.20)	$t(202) = 3.812, p < .001$
Income	663.61 (± 415.27)	540;87 (± 242.53)	$t(82) = 1.379, p = .172$
Clinical			
Age at Onset	21.95 (± 6.09)	23.24 (± 8.05)	$t(235) = -1.349, p = .179$
Illness Duration	4.65 (± 6.67)	7.55 (± 10.68)	$t(317) = -2.936, p = .004$
Number of hospitalizations	0.96 (± 1.22)	2.22 (± 3.98)	$t(286) = -4.11, p < .001$
PANSS Positive	18.93 (± 7.88)	22.44 (± 9.26)	$t(306) = -3.365, p < .001$
PANSS Negative	21.38 (± 7.47)	26.23 (± 9.18)	$t(306) = -4.819, p < .001$
PANSS General	39.44 (± 13.14)	45.82 (± 15.19)	$t(306) = -3.69, p < .001$
PANSS Total	79.63 (± 24.80)	94.48 (± 30.57)	$t(305) = -4.439, p < .001$
Estimated IQ	93.82 (± 10.63)	85.70 (± 9.54)	$t(196) = 4.565, p < .001$

Figure 1

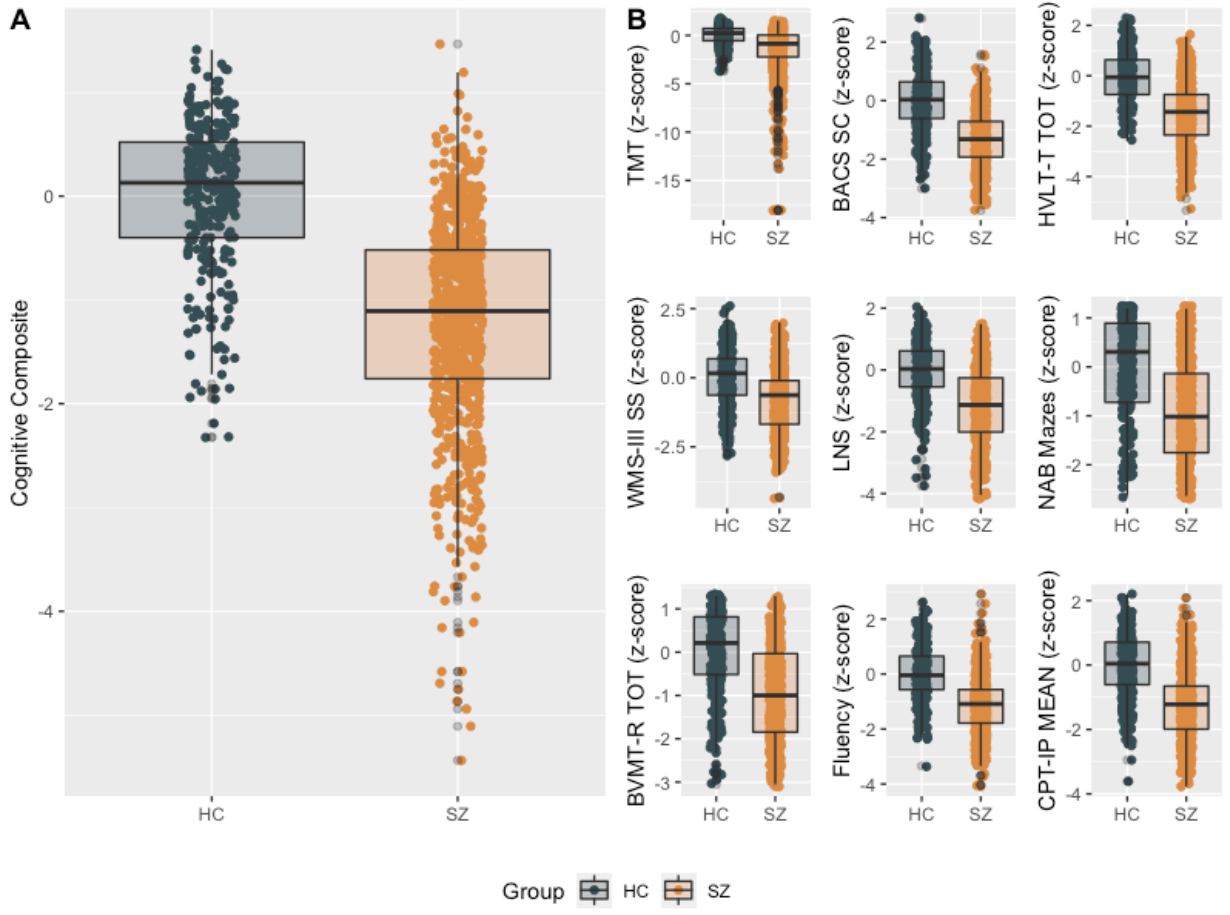


Figure 2

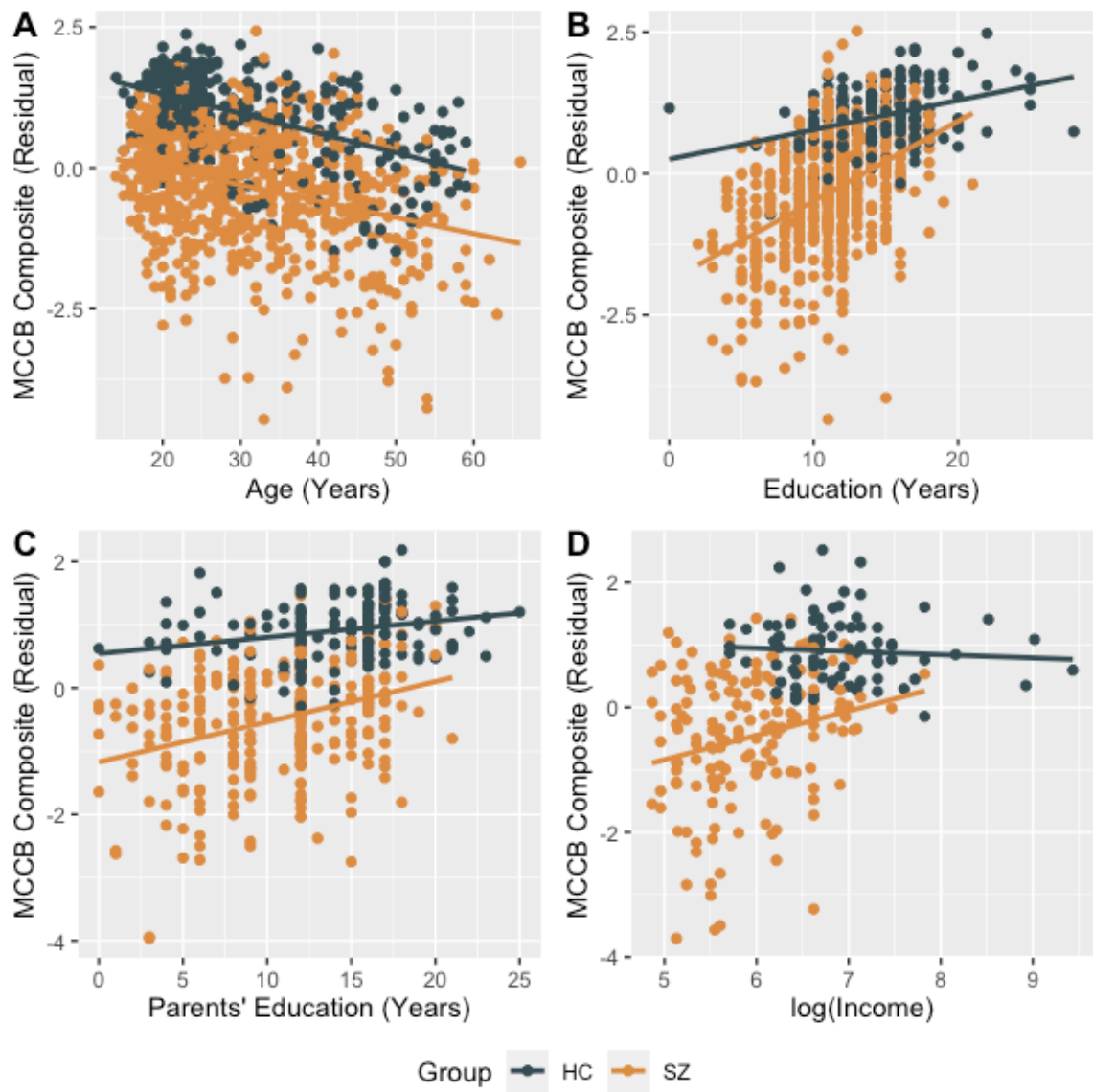
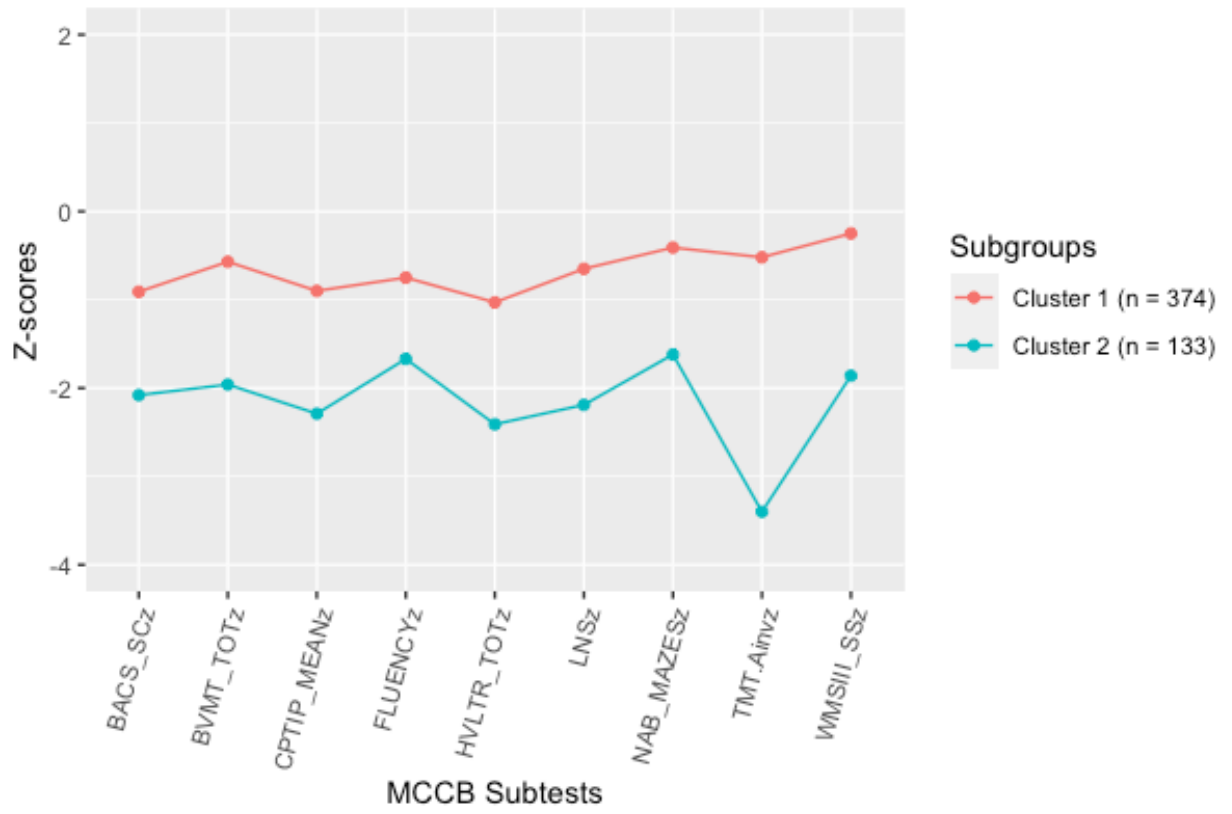


Figure 3



Supplementary Figure 1

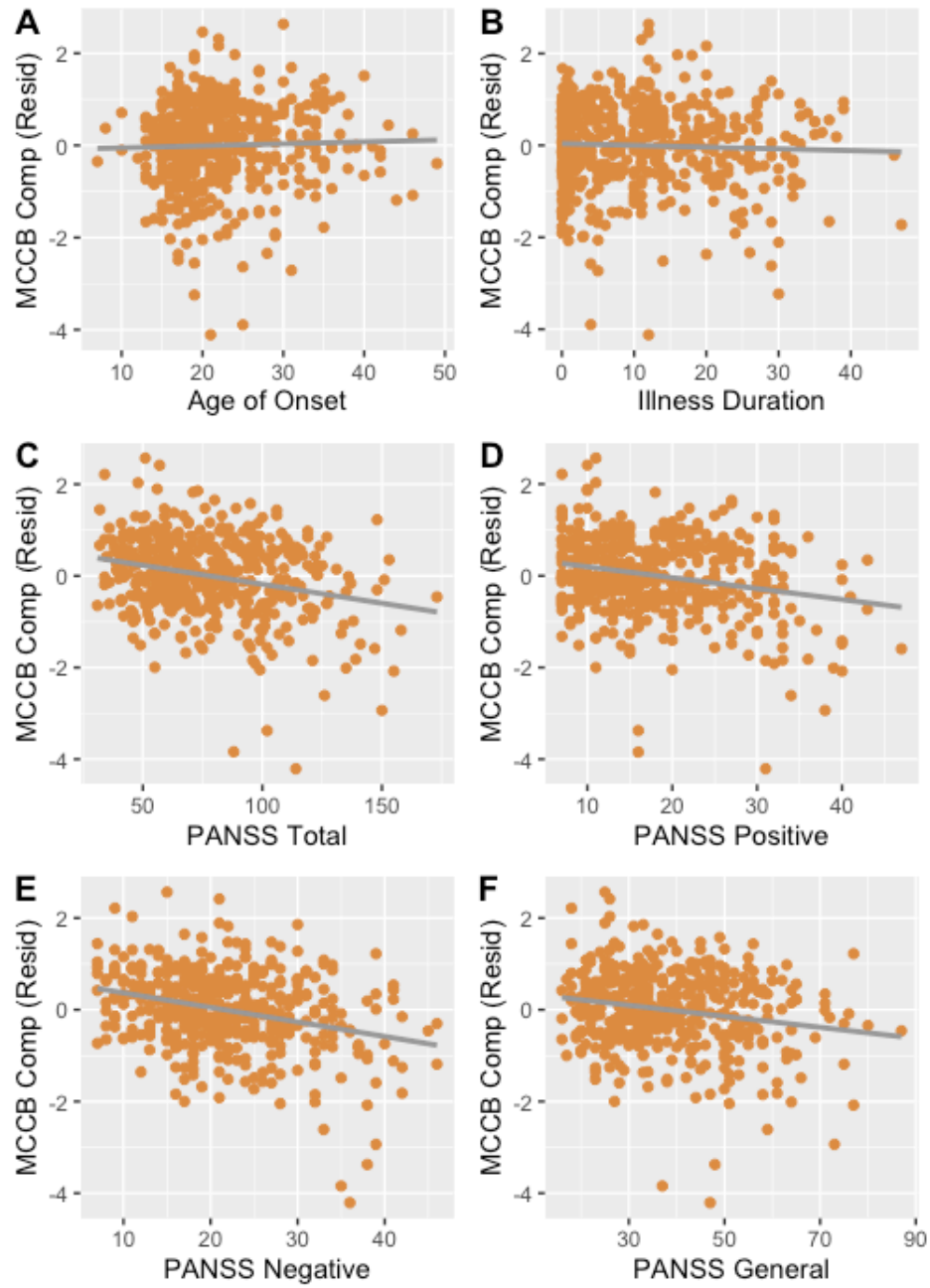


Figure Legend: Relationship between clinical variables and MCCB cognitive composite (z-score) in individuals with schizophrenia (SZ), controlling for age, gender and education.

Supplementary Figure 2.

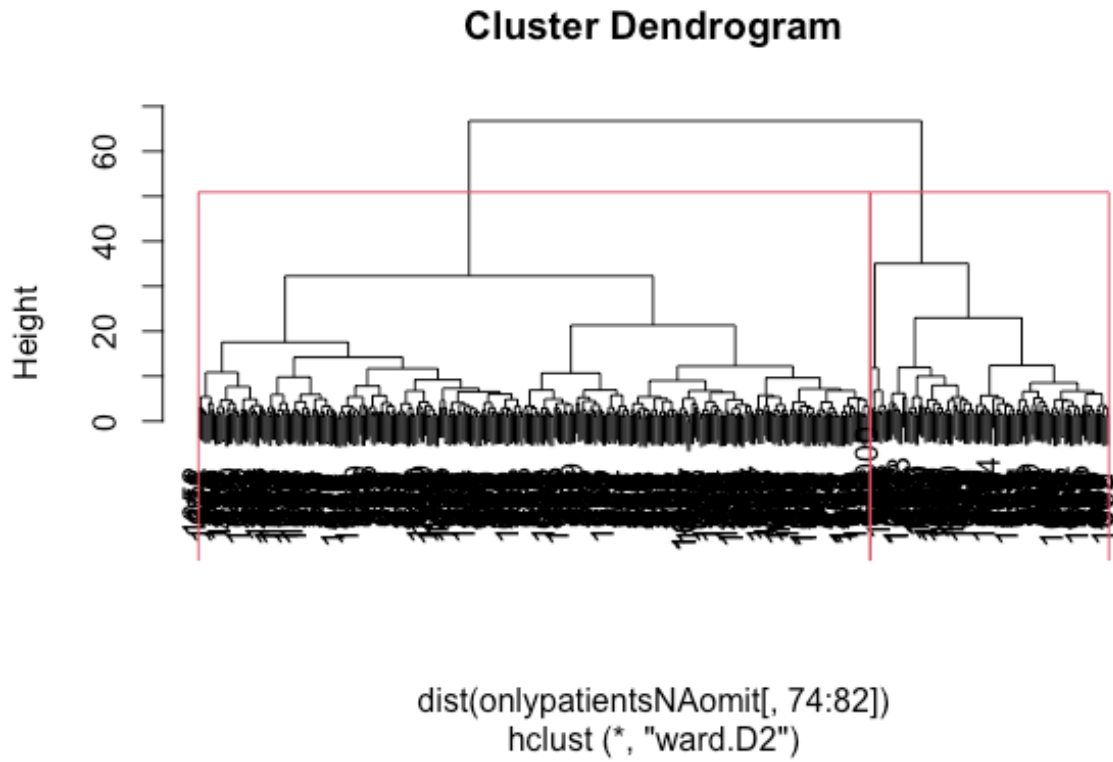


Figure Legend: Dendrogram of individuals with schizophrenia produced by Hierarchical Cluster Analysis, illustrating the arrangement of the cognitive clusters.

5 CONSIDERAÇÕES FINAIS

Este trabalho teve como objetivo ampliar a compreensão dos mecanismos relacionados aos processos cognitivos de indivíduos com esquizofrenia a partir da análise de uma grande amostra da América Latina, trazendo, desta forma, diversidade e representatividade à literatura. A partir dos achados desta Dissertação, podemos sugerir que existem semelhanças e diferenças no desempenho cognitivo de pessoas com esquizofrenia da América Latina se comparadas a outros estudos incluindo populações de países desenvolvidos.

Indivíduos com esquizofrenia apresentam prejuízos cognitivos quando comparados a controles saudáveis nos diversos domínios, contudo apenas uma minoria apresenta desempenho considerado clinicamente como déficit cognitivo. O efeito da idade nos processos cognitivos dos pacientes foi semelhante ao dos controles, indicando trajetórias de envelhecimento cognitivo similares. No entanto, o nível educacional dos indivíduos com esquizofrenia foi associado a ganhos maiores na cognição dos pacientes. Além disso, percebeu-se um impacto maior dos fatores sociais nos pacientes, uma vez que renda familiar e nível educacional dos pais estava mais relacionado ao desempenho cognitivo em indivíduos com esquizofrenia que aos controles saudáveis. Com isso, é possível se hipotetizar que os pacientes poderiam ser mais vulneráveis aos efeitos crônicos de ambiente desfavoráveis, como é o contexto de países da América Latina.

Desta forma, os presentes achados indicam a necessidade da criação de políticas públicas para proteção do desenvolvimento da infância, especialmente em indivíduos em alto risco para desenvolver esquizofrenia e outros transtornos mentais graves, uma vez que ambientes menos desfavoráveis potencialmente levam a melhores desfechos de saúde nessas populações. Estudos futuros devem focar em um maior aprofundamento dos impactos sociais nos desfechos da esquizofrenia, buscando esclarecer os mecanismos envolvidos nesses processos.

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