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References

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Structural Brain Markers Are Differentially Associated With Neurocognitive Profiles in Socially Marginalized People With Multimorbid Illness

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Persons who are homeless or marginally housed comprise a heterogeneous, socially impoverished population. Marginal housing is a common solution in concentrated urban centers, providing basic shelter to people of low socioeconomic status who are considered to be on the brink of homelessness. These housing solutions, however, are often characterized by precarious and substandard living conditions ([Vlahov et al., 2007](#)). Although marginally housed persons face imminent risk for being homeless, many have previously experienced homelessness and will experience additional transitions between housing statuses in the future ([Hwang et al., 2011](#); [Vila-Rodriguez et al., 2013](#)). Moreover, the overall health status of homeless and marginally housed persons is reported to be equally poor ([Hwang et al., 2011](#)) and they experience similar levels of unmet health care needs ([Argintaru et al., 2013](#)). Together this suggests that the margins between these two populations are highly dynamic with no clear demarcations.

Marginalized persons face extensive exposure to adversities, with elevated rates of substance dependence, viral infection, and major psychiatric illness ([Fazel, Khosla, Doll, & Geddes, 2008](#); [Robertson et al., 2004](#); [Shannon, Ishida, Lai, & Tyndall, 2006](#); [Vila-Rodriguez et al., 2013](#)). Further, these features are frequently comorbid, with rates exceeding 50% ([Krausz et al., 2013](#)). They also experience greater severity of psychiatric illness when compared to persons of low socioeconomic status with stable housing ([Eyrich-Garg, Cacciola, Carise, Lynch, & McLellan, 2008](#)). The deleterious impact of multimorbidity is further compounded by high rates of reported unmet health care needs, despite the fact that health care is

universally available in Canada ([Argintaru et al., 2013](#)). Although established treatments exist for illnesses such as Hepatitis C and psychosis, actual treatment rates in marginalized persons are remarkably low ([Jones et al., 2015](#)). Indeed, health disparities are becoming increasingly prevalent in high-income countries ([Fazel, Geddes, & Kushel, 2014](#)). Consequently, this population suffers poor outcomes, including decreased psychosocial functioning ([Vila-Rodriguez et al., 2013](#)) and an eightfold increase in mortality risk compared to age- and gender-matched Canadian adults ([Jones et al., 2015](#)).

Strikingly, little is known about neurocognitive outcomes and the associated risk factors in marginally housed and homeless persons; yet, the prevalence of neurocognitive impairment appears to be very high as demonstrated by only a handful of relevant reports. For example, in a large Canadian cohort of homeless adults, 72% were reportedly impaired, with the most prominent deficits in verbal learning and memory ([Stergiopoulos et al., 2015](#)). These findings correspond to our work investigating the marginally housed ([Gicas et al., 2014](#)), as well as with few additional existing studies suggesting the presence of broad impairments in the core domains of memory, attention, processing speed, and executive functioning ([Burra, Stergiopoulos, & Rourke, 2009](#); [Pluck, Lee, David, Spence, & Parks, 2012](#)).

Characterizing neurocognition in this population is important because these skills are instrumental for engagement in complex real-world activities such as medication adherence, financial management, driving ability, and interpersonal communications ([Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009](#)), all of which are especially relevant in persons who face numerous socioeconomic and psychosocial barriers that impede functioning. In marginalized persons neurocognition appears to have a unique contribution to real-world functioning even when other factors such as housing status and psychiatric symptoms are taken into account ([Stergiopoulos, Burra, Rourke, & Hwang, 2011](#)). Further, establishing the links between brain integrity and neurocognition is a crucial target for systematical investigation, given the multimorbid burden that is apt to negatively impact brain structure in marginalized persons. Investigating variation in divergent dimensions of brain structure may provide a framework for appreciating some of the key determinants of, or markers for, neurocognitive impairment, including those related to developmental and environmental sources. Ultimately, this information may be useful for prevention and in optimizing strategic health care delivery for the benefit of individuals and the community.

In an extension of our previous investigation ([Gicas et al., 2014](#)), the aim of the present study was to examine the association between distinct neurocognitive profiles and structural brain measures. This represents a novel investigation that aims to provide a foundational characterization of brain-behavior associations in a marginalized population. We used a surface-based method of imaging analysis to parse complementary aspects of cortical structure (thickness, gyrification; [Hogstrom, Westlye, Walhovd, & Fjell, 2013](#)) that could provide insight into factors that may contribute to neurocognitive impairment. With novel advances in imaging analysis, cortical folding can now be measured in 3-dimensional space using the local gyrification index (LGI), which represents a ratio between the surface area buried within sulci to the surface area of the exposed cortex within a selected region of interest ([Schaer et al., 2008](#)). Gross gyrification of the brain is largely established at birth and undergoes minimal change into adolescence ([Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995](#); [White, Su, Schmidt, Kao, & Sapiro, 2010](#)). Thus, deviations in basic neurodevelopmental processes in utero, as a result of genetic or environmental influences, can lead to hypo- or hyper-gyrification. Focal alterations in gyrification have been identified in neurodevelopmental disorders such as schizophrenia ([Harris et al., 2007](#); [Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011](#)), autism spectrum disorders ([Libero, DeRamus, Deshpande, & Kana, 2014](#); [Wallace et al., 2013](#)), fetal

alcohol spectrum disorders ([Infante et al., 2015](#)), and Williams syndrome ([Fahim et al., 2012](#)). However, gyrification represents a novel area of literature and findings are mixed, with reports of gyrification being increased, decreased, or variable by cortical subregion.

In contrast, cortical thickness, which is measured as the distance (in millimeters) between the pial surface and the gray-white matter boundary ([Fischl & Dale, 2000](#)), is highly dynamic across the life span ([Hogstrom et al., 2013](#); [Schnack et al., 2015](#); [Storsve et al., 2014](#)). The frontal and temporal cortices are especially susceptible to thinning with normal age-related changes ([Fjell et al., 2009](#); [Lemaitre et al., 2012](#); [McGinnis, Brickhouse, Pascual, & Dickerson, 2011](#); [Raz & Rodrigue, 2006](#); [Thambisetty et al., 2010](#)) and with risk exposure, such as comorbid substance use disorders ([Lawyer et al., 2010](#); [Momenan et al., 2012](#)), HIV infection ([Holt, Kraft-Terry, & Chang, 2012](#)), progression of psychiatric illness ([Assunção Leme et al., 2013](#); [Goldman et al., 2009](#); [van Haren et al., 2011](#)), and histories of concussion ([Tremblay et al., 2013](#)) or childhood abuse ([Kelly et al., 2013](#)). Together, gyrification and cortical thickness represent complementary cortical parameters that can be used to shed light on the extent to which structural brain integrity, with its presumed underpinnings (neurodevelopmental vs. environmental risk exposure), contributes to neurocognition in heterogeneous populations.

In this study, we linked neurocognition in marginalized persons to key brain regions known to regulate inhibitory control, decision-making (anterior cingulate and orbitofrontal cortices; [Miller & Cohen, 2001](#); [Pujara & Koenigs, 2014](#)), and memory (entorhinal cortex; [Fjell et al., 2014](#); hippocampus; [Van Petten, 2004](#)). These neurocognitive functions are represented in profiles derived from our previous work using cluster analysis to optimally group individuals on the basis of neurocognitive similarities ([Gicas et al., 2014](#)). This statistical approach is ideally suited to managing the natural heterogeneity within our multimorbid sample by facilitating examination of within- and between-groups patterns ([Lange, Iverson, Senior, & Chelune, 2002](#)).

In our prior report ([Gicas et al., 2014](#)), we statistically characterized three clusters with unique neurocognitive profiles as follows: (a) a higher functioning subgroup with generally intact abilities (Cluster 1); (b) a lower functioning subgroup with generally impaired abilities, but with a relative strength in decision-making (Cluster 3); and (c) a subgroup that fell intermediate to the others, with a selective and pronounced weakness in decision-making (Cluster 2). Further, these subgroups were meaningfully differentiated on numerous external variables, including sociodemographics, substance use, viral infection, negative symptoms, neurological soft signs, and risk-taking behavior.

Given the distinct neurocognitive patterns, we hypothesized that decreased regional frontal and temporal cortical thickness and decreased hippocampal volume would be associated with Cluster 3, the lowest functioning subgroup. We further hypothesized that regional gyrification indices of Cluster 3 would significantly differ from Clusters 1 and 2, in alignment with a neurodevelopmental interpretation. However, the heterogeneity of findings within the gyrification literature precludes a directional hypothesis. We also anticipated that decreased cortical thickness in the orbitofrontal cortex would be associated with Cluster 2, given the circumscribed decision-making deficit in this subgroup. In addition, given the malleability of cortical thickness across the life span, we anticipated that age would modulate the relationship between cortical thickness and neurocognitive clusters, with stronger associations in older individuals ([Burzynska et al., 2012](#)). To complement our investigation of structural brain integrity, we examined cluster differences on behavioral and diagnostic proxy measures of developmental difficulties and acquired brain insult/risk exposure.

Method

Participants

As part of a 10-year longitudinal investigation, a total of 371 participants were enrolled in the study between November 2008 and November 2014. Participants were recruited from four different single-room occupancy hotels (SROs; $N = 306$) located in the Downtown Eastside (DTES) of Vancouver, British Columbia (see details in [Vila-Rodriguez et al., 2013](#)). To better capture the population of individuals living in this highly impoverished neighborhood, we recruited an additional 65 participants from outside the community courthouse, which is located in the DTES neighborhood. All persons living in one of the four target SROs or persons dwelling in the DTES who had a community court date assigned within the previous 6 months were approached to participate in the study. Within the combined sample, the mean number of years spent on the DTES was 8.53 (median = 6.87; $SD = 7.53$) with 71.6% of individuals reporting ever being homeless. The marginalization of this sample is further reflected in the high rates of unemployment (87%) and low mean monthly income in CAD ($M = \$859.13$; Median = \$825.00; $SD = \$396.98$). It is important to highlight that the definition of homelessness is multifaceted, and for the purpose of the current study, we focus on those who are conventionally defined as either marginally housed (accommodations barely meet minimum standards and there is imminent risk for loss of accommodations) or characterized by tertiary homelessness (living in single-room accommodations that fail to meet minimum community standards; [Chamberlain & Mackenzie, 1992](#)).

The inclusion criteria for the larger study were English fluency and either living in a SRO hotel or having contact with the community court within the previous 6 months. A flow diagram is presented in [Figure 1](#) to outline participants retained for inclusion in the current study. To summarize, a total of 299 (of 371 recruited) had valid neurocognitive data and were included in our initial cluster analysis. Of the 299 clustered subjects, 211 had complete multivariate data and were included in our primary regression analysis. All participants provided written informed consent and received small honoraria for each assessment completed (clinical, neurocognitive, MRI). Ethics approvals were obtained from the Clinical Research Ethics Board of the University of British Columbia in accordance with Tri-Council Policy, and the Simon Fraser University Office of Research Ethics. Additional details regarding study design and recruitment are provided in our previous work ([Vila-Rodriguez et al., 2013](#); [Jones et al., 2015](#)). A description of the sample is provided in [Table 1](#).

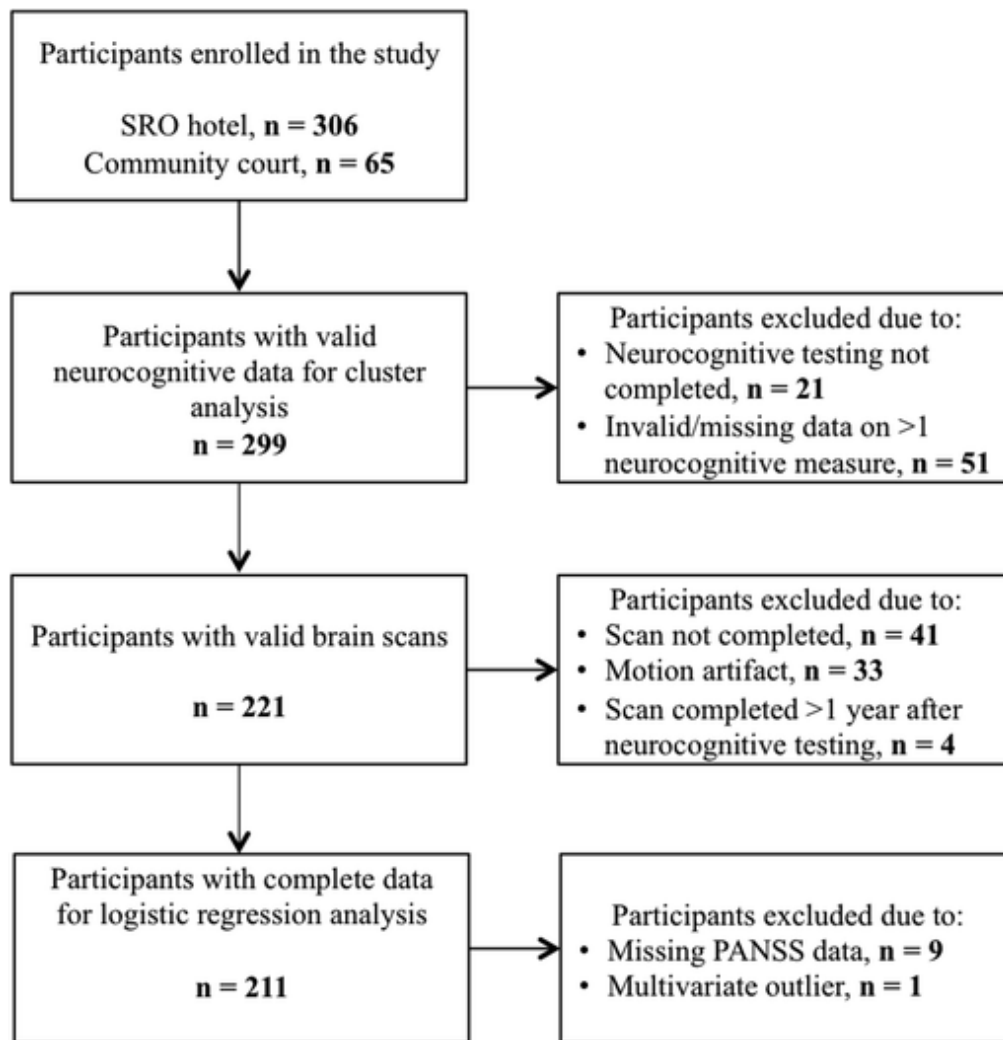


Figure 1. Flow diagram of participant inclusion.

Table 1
Sample Characteristics of Clustered Participants (*N* = 299)

Characteristic	%	<i>M</i> (<i>SD</i>)	Mdn	Range
Age (years)		43.3 (9.5)	44	23–68
Education (years)		10.4 (2.2)	10	3–16
Premorbid IQ (WTAR)		97.5 (8.8)	97	77–122
Symptoms of psychosis (PANSS) ^a				
Positive		15.3 (5.6)	14	7–36
Negative		16.2 (5.8)	15	7–39
General		36.0 (8.2)	35	19–59
Total		67.5 (16.6)	65	33–129
Gender (male)	78.6			
Ethnicity				
White	62.5			
First Nations	26.8			
Black	2.7			
Latino	.7			
Other/mixed/unknown	7.3			
Psychiatric diagnosis				
Psychotic illness, any	46.2			
Mood disorder, any	28.1			
Anxiety disorder, any	26.8			
Substance dependence disorder				
Alcohol	15.7			
Cannabis	34.1			
Stimulant	83.9			
Opioid	43.5			
Viral infection				
HIV ^c	16.2			
Hepatitis C ^d	68.8			
Hepatitis B ^e	39.8			
Herpes simplex ^c	90.5			
Cytomegalovirus ^e	67.3			
Traumatic brain injury				
Possible	39.1			
Probable	14.7			
Definite	9.7			

Note. WTAR = Wechsler Test of Adult Reading; PANSS = Positive and Negative Syndrome Scale; BDI = Beck Depression Inventory; SOFAS = Social and Occupational Functioning Assessment Scale; RFS = Role Functioning Scale; NOS = Not otherwise specified.

^a*n* = 283. ^b*n* = 285. ^c*n* = 296. ^d*n* = 295. ^e*n* = 294.

Sample Characteristics of Clustered Participants (*N* = 299)

Material and Procedures

Neurocognitive assessment

Details regarding the neurocognitive assessment used to derive the clusters are reported elsewhere (Gicas et al., 2014). Assessments were conducted by research assistants who were trained and supervised by a registered psychologist. Participants completed a battery of tests that included measures of premorbid IQ (Wechsler Test of Adult Reading; Wechsler, 2001), verbal learning and memory (Hopkins Verbal Learning Test Revised [HVLT]; Brandt & Benedict, 2001), color-word inhibition (Stroop Color-Word Test), sustained attention (Rapid Visual Information Processing subtest [RVIP]; Fray, Robbins, & Sahakian, 1996), mental flexibility (Intra-Dimensional Extra-Dimensional subtest (IDED); Fray et al., 1996), and decision-making (Iowa Gambling Task (IGT); Bechara, Damasio, Damasio, & Anderson, 1994). These represent reliable and valid neuropsychological measures that are sensitive to impairments in a diverse range of clinical populations.

Following completion of the neurocognitive assessment, the examiner subjectively rated the validity of each measure on a scale ranging from 1 (*clearly invalid*) to 5 (*clearly valid*). Data rated as 4 (*most likely valid*) or

higher were retained for analyses, and all other ratings were individually inspected to verify rating accuracy. Reasons for invalid ratings could include, but are not limited to, participant intoxication, extreme fatigue, inability to adequately comply with test instructions, frustration, or equipment failures. Approximately 93% of the total sample that completed at least some of the neurocognitive battery had overall validity ratings of 4 or higher.

To assure English language fluency, we administered the English Language Acculturation Questionnaire. This measure includes 12 items which uses a 5-point scale to assess the degree to which an individual prefers to speak, think, read, and write primarily in English. Scores range from 12 (*very fluent in English*) to 60 (*not at all fluent in English*). A score of 12 was automatically assigned to participants who reported being born in Canada and having learned English as their first language. We used a cut-off of 24 for the current study, which means participants were, on average, “much fluent in English”. In the current sample ($N = 299$), 92.6% reported being born in Canada and having learned English as their first language. Of the remaining participants, mean length of time residing in North America was 30.94 years ($SD = 11.21$), and mean age at immigration to North America was 14.41 years ($SD = 10.45$).

Clinical assessment

Trained research assistants, psychiatrists, and/or neurologists conducted clinical assessments. These sessions were scheduled at times that were independent from the neurocognitive assessments. Full details of the assessments are reported by [Vila-Rodriguez et al. \(2013\)](#).

Developmental variables

Diagnosis of schizophrenia (and other psychiatric diagnoses, see [Table 1](#)) were rendered via consensus using the Best Estimate Clinical Evaluation and Diagnosis ([Endicott, 1988](#)), the Mini-International Neuropsychiatric Interview ([Sheehan et al., 1998](#)), and a mental status examination, in accordance with criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; [American Psychiatric Association, 2000](#)). A history of special education or a modified curriculum in school was self-reported during a structured baseline interview. To assess neurological soft signs (NSS), a selection of items from the Cambridge Neurological Inventory was administered ([Chen et al., 1995](#); see Table A1). All ratings were summed to yield a total NSS score, with higher scores representing worse neurological status. To assess extrapyramidal symptoms (EPS), the Extrapyramidal Symptom Rating Scale was administered ([Chouinard & Margoless, 2005](#)). A total EPS score was derived by summing scores across the dimensions of dystonia, dyskinetic movements, and Parkinsonism, with higher scores reflecting worse neurological status.

Acquired brain insult

Diagnoses of MRI pathology (stroke, hemorrhage, aneurysm) were made by a neuroradiologist according to definitions provided by [Vernooij and colleagues \(2007\)](#). Further, traumatic brain injury (TBI) was defined as follows: none (no reported history of a head injury); possible (reported loss of consciousness less than 5 min AND confusion less than one day); probable (loss of consciousness at least 5 min or greater OR confusion for at least one day or greater); and definite (visible signs on MRI OR classified as probable with persistent symptoms attributable to TBI).

Risk exposure

Diagnoses of substance dependence (see [Table 1](#)) were made following the procedure used for psychiatric diagnoses summarized above. To index a history of childhood physical and/or sexual abuse (up to age 12), the Trauma History Questionnaire was administered ([Mueser et al., 2001](#)). To measure virus exposure, blood samples were drawn for serological assays of five viruses—HIV, hepatitis B, hepatitis C, herpes simplex virus, and cytomegalovirus. Seropositivity indicates having ever been exposed to a virus, except for HIV in which it indicates active infection. A sum of all positive results was computed and used to operationalize total virus exposure.

Other variables

Demographic variables, including age, years of education, gender, and ethnicity were self-reported during a structured baseline interview. To facilitate our investigation of age as a potential moderator, we grouped participants as 50 years and older (75th percentile and above; 50–68 years) and under 50 years (23–49 years). To assess psychiatric symptoms, the Positive and Negative Syndrome Scale (PANSS; [Kay, Fiszbein, & Opler, 1987](#)) was administered. The total scores, as well as positive, negative, and general subscale scores were computed, with higher scores indicating more severe psychiatric symptoms.

Neuroimaging acquisition and processing

Structural imaging was conducted proximal to the neurocognitive testing session (89% within one day, 10% within one month, 1% within one year). Whole brain MRIs were acquired on a Philips Achieva 3.0T scanner equipped with an eight-channel SENSE-Head coil and using a 3D FFE T1 weighted structural sequence applied in the sagittal plane with 190 1-mm thick slices (TR/TE = 7.6/3.5 ms; acquisition matrix = 256 × 250; field of view = 256 mm; flip angle = 8°; total acquisition time = 7:23 min). Images were visually inspected for significant motion artifact by trained raters (Donna J. Lang, Wayne Su, and A. Talia Vertinsky). Additionally, all pial and white matter surfaces were visually inspected for segmentation failures and manually corrected where necessary. Automatic cortical parcellation was performed using the publically available FreeSurfer 5.1 software (available for download at <https://www.nmr.mgh.harvard.edu/>) to generate values for local gyrification index (IGI) and cortical thickness (CT; details in [Fischl et al., 2004](#)) using the Desikan-Killiany atlas ([Desikan et al., 2006](#)). Left and right hemisphere cortical parameters were generated from the parcellation procedure and summed to create a bilateral index for the following regions: medial orbitofrontal cortex (mOFC), lateral orbitofrontal cortex (lOFC), anterior cingulate cortex (ACC; average of rostral and caudal subregions), and entorhinal cortex (ERC). The correlations between hemispheres for each region ranged from .48 to .81, suggesting these measures could be reasonably combined for the purpose of conducting more parsimonious statistical models. Whole brain averages for gyrification and cortical thickness were also computed.

To segment the hippocampus, we implemented an alternative approach to the automatic procedure offered by FreeSurfer due to the high rates of visible hippocampal neuropathology in our sample (large hippocampal infarcts, significant atrophy, dilation of perivascular channels), which could lead to automatic segmentation bias. Manual segmentation of the hippocampus was performed on 20 participants selected from our sample whose MRI's did not have obvious imaging artifact to create a set of custom templates. Images were registered to the templates using the SyN method ([Avants, Epstein, Grossman, & Gee, 2008](#)), followed by joint label fusion and corrective learning using the PICS Multiatlas segmentation tool from the Advanced Normalization Tools (ANTs) program (available for download at <http://stnava.github.io/ANTs/>).

Statistical Analysis

Cluster analysis

All analyses were conducted using the SPSS 22.0. First, a k-means cluster analysis was employed to cluster the original 249 participants with the additional community court participants, following procedures outlined in our earlier study of a subset of these participants ([Gicas et al., 2014](#)). Participants with invalid and/or missing data on two or more neurocognitive measures were excluded from the cluster analysis. Because of significant positive skew, the IDED adjusted error score was log transformed and subsequently multiplied by -1 so lower scores reflected poorer performance in accordance with the other measures. Age and education were regressed on HVLt, Stroop, RVIP, IDED, and IGT scores to control for variance associated with these demographic factors (see [Manly et al., 2011](#)). Standardized residuals generated from this procedure were used in the cluster analysis ($N = 299$). A kappa coefficient was used to determine whether participants from the original clusters were consistently reassigned to the same clusters in the current analysis.

Logistic regression analysis

A series of sequential multinomial logistic regression analyses were conducted to examine the associations between each brain region of interest (ROI) and clusters. The assumption of linearity in the logit was evaluated using the Box-Tidwell approach ([Hosmer & Lemeshow, 2000](#)) and models were inspected for multivariate outliers. One case was deemed a multivariate outlier and excluded from subsequent analyses, as it exceeded acceptable thresholds for influence and fit statistics according to standard cut-offs outlined in [Cohen et al. \(2003, p. 410\)](#). The results were unchanged with this case excluded from the models.

Independent variables of interest for the regression analyses included regional gyrification indices and cortical thicknesses (IOFC, mOFC, ERC, ACC), the corresponding ROI Thickness \times Age interaction terms, and hippocampal volume. The three neurocognitive clusters served as the dependent variable. Gender, age (under 50 years, 50+ years), total years of education, total brain volume, and PANSS negative symptoms were included as covariates in each model. These covariates were selected based upon their known associations with neurocognitive functioning, which is our primary outcome measure. Moreover, all of these covariates (except age) differed between the clusters. Therefore, we wished to model any variability in neurocognition attributable to these factors. Of further note, although intracranial volume is often used in imaging studies, we have elected to use total brain volume because this is more conceptually related to neurocognition than head size. Regardless, these variables are very strongly correlated in our sample ($r = .987$). All continuous variables were converted to standard z-score units to ease interpretation. A Bonferroni correction was applied to the four cortical ROI analyses to control for error inflation ($p = .0125$). The critical alpha value was set to $p = .05$ for all other independent variables.

A multinomial logistic regression model was run with only covariates included. Next, five separate full models were tested (one per ROI), each including the covariates plus the gyrification index, thickness, and the corresponding interaction term. The differences between the covariate-only model and the full models were calculated to determine whether the brain measures were significantly associated with the clusters after controlling for demographic factors and negative symptoms. Model differences were calculated using the following equation with 6 degrees of freedom: $\chi^2 = 2(LL[\text{full model}] - LL[\text{covariate only model}])$; [Tabachnik & Fidell, 2013](#)). Pairwise comparisons were examined for all brain measures that were significant in the omnibus models (log-likelihood ratio tests).

Analysis of proxy variables

To evaluate cluster differences on proxy variables, analyses of variance and chi-square tests were conducted. Clusters were compared on proxy measures of possible developmental difficulties, which included a diagnosis of schizophrenia and a history of ever having received special education. In addition, total NSS were used to represent subtle nonlocalizable motor and sensory abnormalities with putative neurodevelopmental origins. Total EPS were used as a measure to rule out the possibility that observed motor and sensory abnormalities (NSS) could be attributed to neuroleptic side effects rather than microstructural brain integrity (see [Gicas et al., 2014](#)).

To index acquired brain insult, clusters were compared for differences in diagnosed MRI pathology and TBI. Proxies of risk exposure included substance dependence diagnosis, history of childhood physical and/or sexual abuse, and total virus exposure.

Results

Cluster Analysis

The profiles of the original clusters in [Gicas et al. \(2014\)](#) were regenerated with a larger sample ($N = 299$) in the current analysis. Agreement between the original clusters and the current clusters was found to be excellent ($\kappa = .84$). The three-cluster solution is depicted in [Figure 2](#). Briefly, Cluster 1 ($n = 87$; 29.1%) was characterized by the highest neurocognitive functioning across all domains. In contrast, Cluster 2 ($n = 109$; 36.5%) demonstrated abilities that generally fall intermediate to Clusters 1 and 3, but with pronounced weakness in decision-making. Finally, Cluster 3 ($n = 103$; 34.4%) was characterized by the overall lowest functioning, with the exception of relative strength in decision-making. The overall cluster patterns in the current sample were the same as previously reported ([Gicas et al., 2014](#)). For descriptive purposes, cluster profiles were constructed with demographically corrected T scores (age and/or education) using the normative databases of the respective tests (see [Figure 3](#)).

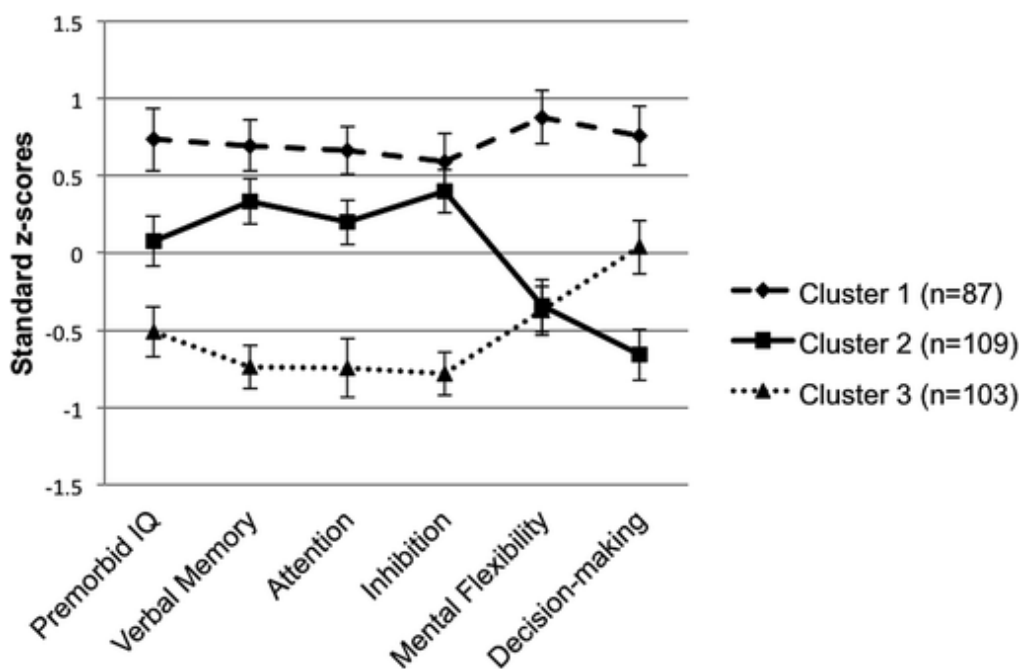


Figure 2. Profiles of mean neurocognitive scores by cluster membership. Error bars represent 95% confidence intervals.

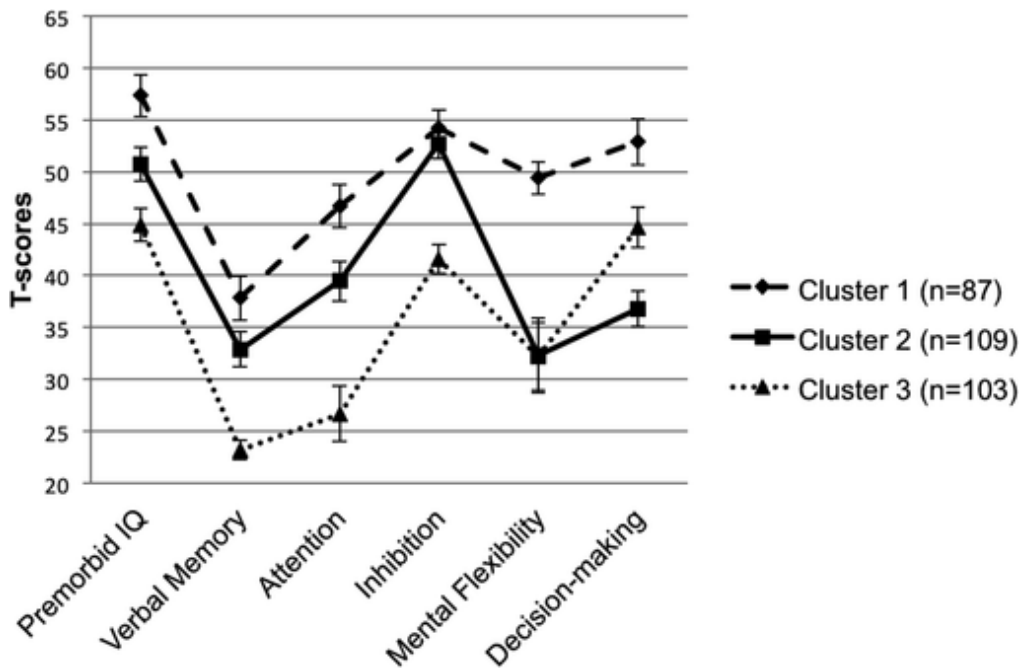


Figure 3. Profiles of demographically corrected mean neurocognitive scores by cluster membership. Error bars represent 95% confidence intervals.

Logistic Regression

Based on the sample of individuals retained for cluster analysis ($N = 299$), no demographic differences (age, education, gender) were observed between individuals included ($n = 211$) versus excluded ($n = 88$) from regression analyses due to missing or invalid data ($p > .05$). Further, excluded cases showed a relatively even distribution across the three clusters.

In line with our hypotheses, omnibus testing revealed that ERC IGI ($\chi^2 = 13.35$, $p = .001$), mOFC IGI ($\chi^2 = 11.57$, $p = .003$), and IOFC IGI ($\chi^2 = 9.03$, $p = .011$) were differentially associated with the clusters. Further as predicted, we found that age was a significant moderator of brain-cluster associations. Specifically, the mOFC Thickness \times Age interaction term was significant ($\chi^2 = 16.73$, $p < .001$), with a trend toward significance noted for the ACC Thickness \times Age interaction term ($\chi^2 = 5.74$, $p = .057$). The difference between the log-likelihood ratios for the covariate-only model and the full models revealed that brain measures were significantly associated with clusters above and beyond the effects of gender, age, total brain volume, education, and negative symptoms (ERC: $\chi^2 = 15.32$, $p < .025$; IOFC: $\chi^2 = 13.69$, $p < .05$; mOFC: $\chi^2 = 25.88$, $p < .001$). No associations were found between the clusters and hippocampal volume, whole brain gyrification, or whole brain thickness ($p > .05$).

Parameter estimates were examined to determine which of the three clusters the brain measures differentiated. Table 2 lists the regression coefficients of significant pairwise comparisons, whereas Table 3 provides descriptive statistics (raw data), organized by cluster membership, for all independent variables included in the models. Briefly, for every SD unit increase in gyrification of the IOFC, mOFC, and ERC regions, there was an approximately 50% decreased likelihood of being in Cluster 1 (highest functioning), compared to Cluster 3 (lowest functioning, decision-making strength). Likewise, with each SD unit increase in ERC and mOFC gyrification, there was a 34% and 38% decreased likelihood of being in Cluster 2 (intermediate functioning, decision-making weakness), compared to Cluster 3. In other words, greater

gyrification in frontal and temporal regions was associated with a greater likelihood of being in Cluster 3.

Table 2

Significant Associations Between Brain Measures and Neurocognitive Clusters (N = 211)

Group comparison	Region of interest	B (SE)	Wald χ^2 test (p value)	Odds ratio (95% CI)	Odds ^a of being in target cluster
C1 vs. <u>C3</u>	IOFC IGI	-.67 (.23)	8.41 (.004)	.51 (.32-.80)	49% ↓
	mOFC IGI	-.78 (.25)	9.64 (.002)	.46 (.28-.75)	54% ↓
	ERC IGI	-.78 (.23)	11.91 (.001)	.46 (.30-.72)	54% ↓
	mOFC CT × Age				
	Under 50 years	-.80 (.30)	7.27 (.007)	.45 (.25-.80)	55% ↓
	50+ years	1.22 (.46)	6.92 (.009)	3.37 (1.36-8.35)	237% ↑
	ACC CT × Age ^b				
	Under 50 years	-.05 (.26)	.04 (.842)	.95 (.58-1.57)	5% ↓
C2 vs. <u>C3</u>	50+ years	.91 (.42)	4.58 (.032)	2.48 (1.08-5.69)	148% ↑
	ERC IGI	-.42 (.19)	4.80 (.028)	.66 (.45-.96)	34% ↓
	mOFC IGI	-.49 (.20)	5.86 (.016)	.62 (.42-.91)	38% ↓
C1 vs. <u>C2</u>	mOFC CT × Age				
	Under 50 years	-.44 (.28)	2.50 (.114)	.65 (.38-1.11)	35% ↓
	50+ years	1.00 (.43)	5.34 (.021)	2.72 (1.16-6.34)	172% ↑
	ACC CT × Age ^b				
	Under 50 years	.09 (.25)	.15 (.702)	1.10 (.68-1.78)	10% ↑
	50+ years	1.07 (.41)	6.91 (.009)	2.91 (1.31-6.45)	191% ↑

Note. Brain measures were available for 211 participants. Underline indicates reference group and non-underline is the target group. CI = confidence interval; C1 = Cluster 1; C2 = Cluster 2; C3 = Cluster 3. IOFC = lateral orbitofrontal cortex; mOFC = medial orbitofrontal cortex; ERC = entorhinal cortex; IGI = local gyrification index; CT = cortical thickness; ACC = anterior cingulate cortex.

^a Percent change in odds ratio (OR) = $(1 - OR) \times 100$. ^b Not significant in the omnibus model.

Significant Associations Between Brain Measures and Neurocognitive Clusters (N = 211)

Table 3

Descriptive Statistics For Independent Variables by Cluster Membership (N = 211)

Independent variable	Cluster 1, n = 59 M (SD)	Cluster 2, n = 82 M (SD)	Cluster 3, n = 70 M (SD)
Medial orbitofrontal CT (mm)	4.64 (.25)	4.61 (.26)	4.63 (.29)
Lateral orbitofrontal CT (mm)	5.04 (.31)	5.02 (.29)	4.99 (.32)
Anterior cingulate CT (mm)	5.43 (.27)	5.36 (.31)	5.39 (.40)
Entorhinal CT (mm)	6.75 (.50)	6.81 (.59)	6.70 (.72)
Average whole brain CT (mm)	2.40 (.11)	2.40 (.11)	2.38 (.13)
Medial orbitofrontal IGI	4.08 (.14)	4.07 (.14)	4.11 (.20)
Lateral orbitofrontal IGI	4.93 (.20)	4.97 (.22)	5.02 (.28)
Anterior cingulate IGI	3.92 (.16)	3.90 (.18)	3.93 (.22)
Entorhinal IGI	4.89 (.18)	4.91 (.19)	4.98 (.27)
Average whole brain IGI	2.94 (.10)	2.93 (.11)	2.95 (.13)
Hippocampal Volume (mm ³)	7406.86 (891.58)	7129.34 (746.37)	7028.53 (773.87)
Total Brain Volume (mm ³)	1501009.71 (120980.79)	1429579.44 (106811.72)	1435146.06 (111064.03)
Negative PANSS	13.58 (3.65)	16.24 (6.26)	17.51 (5.77)
Age (years) ^a	44.10 (9.03)	43.07 (9.39)	42.94 (9.80)
Education (years)	11.00 (2.41)	10.13 (2.47)	9.96 (1.90)

Note. Brain measures were available for 211 participants. This data has not been corrected for covariates. CT = cortical thickness; IGI = local gyrification index; PANSS = Positive and Negative Syndrome Scale.

^a Age was included as a dichotomous variable in the regression analysis but reported in this table as a continuous variable for descriptive purposes.

Descriptive Statistics For Independent Variables by Cluster Membership (N = 211)

Close inspection of the mOFC Thickness × Age interaction revealed that, in participants under age 50 ($n = 151$), for every SD unit increase in mOFC thickness there was a 55% decreased likelihood of being in Cluster 1, compared to Cluster 3. Conversely, in participants who were aged 50 or older ($n = 60$), with every SD unit increase in mOFC thickness there was a 237% increased likelihood of being in Cluster 1 versus 3, and a 172% increased likelihood of being in Cluster 1 versus 2. These associations are depicted in [Figures](#)

4 and 5. A trend toward significance was seen in the ACC Thickness \times Age interaction term in the omnibus model. Therefore, we further explored whether pairwise comparisons would reveal statistically significant differences. For every *SD* unit increase in ACC thickness in individuals 50 years and older, there was a 148% increased likelihood of being in Cluster 1 versus Cluster 3, and a 191% increased likelihood of being in Cluster 1 versus Cluster 2 (see Figures 6 and 7). In essence, greater thickness in select frontal regions was associated with a greater likelihood of being in Cluster 1 (higher profile of neurocognitive functioning) for older individuals only. There was no association between ACC thickness and clusters for individuals under age 50.

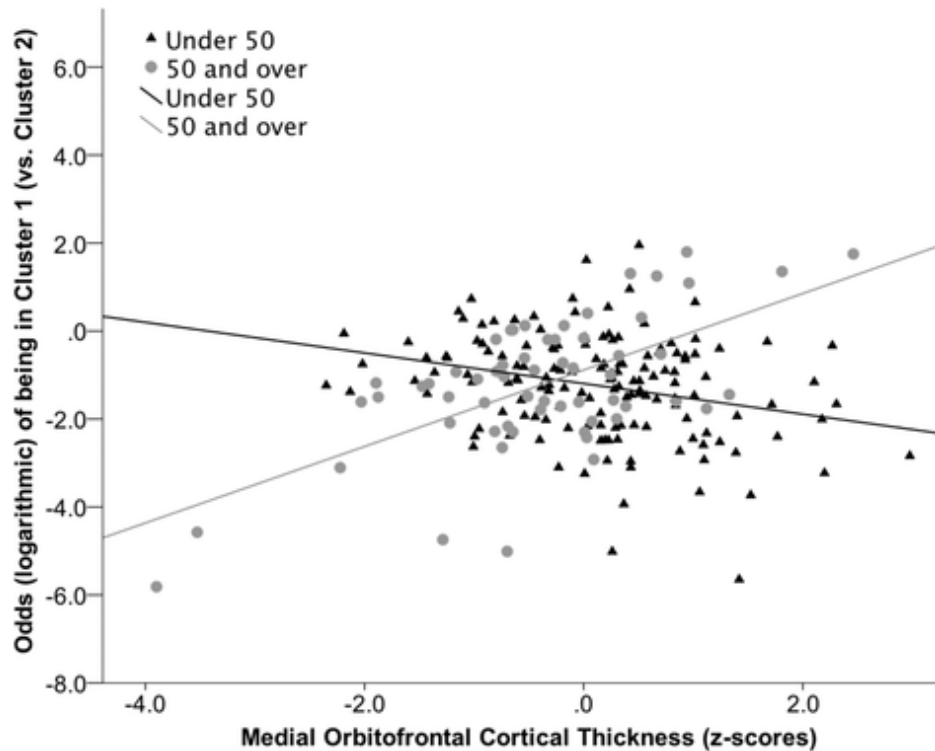


Figure 4. Odds (in logarithmic units) of being in Cluster 1 (vs. Cluster 2) as a function of medial orbitofrontal cortical thickness and age.

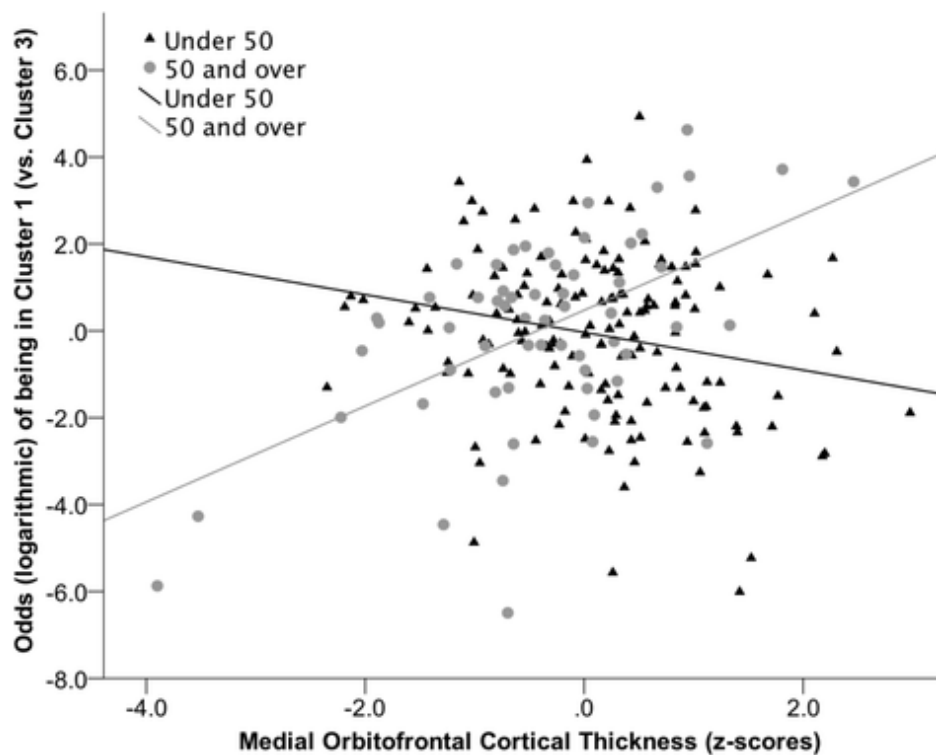


Figure 5. Odds (in logarithmic units) of being in Cluster 1 (vs. Cluster 3) as a function of medial orbitofrontal cortical thickness and age.

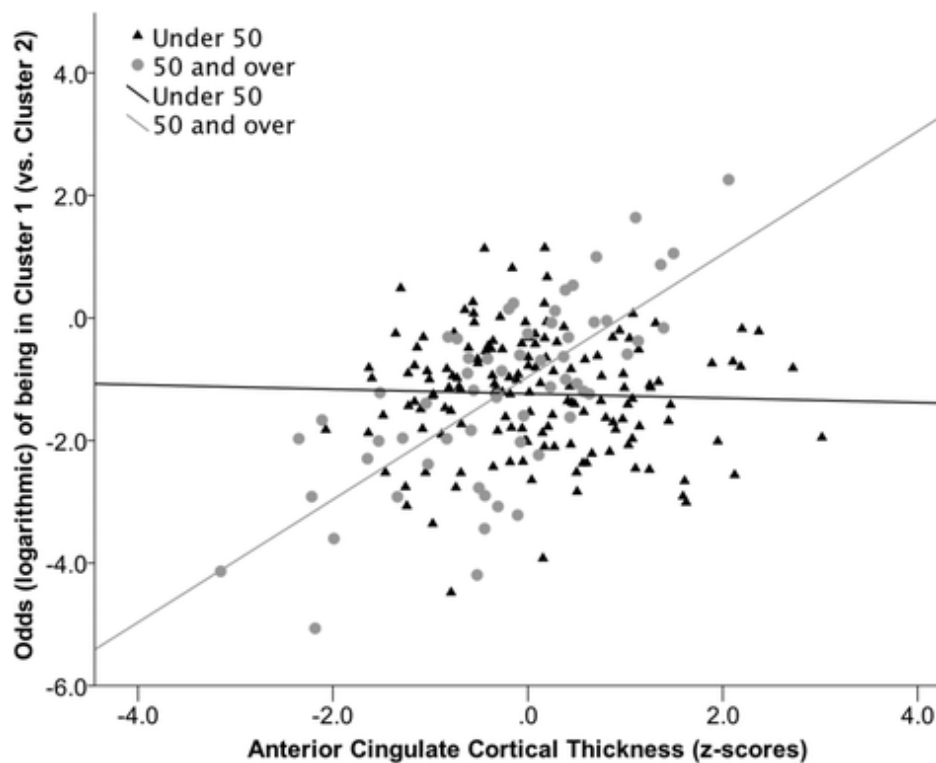


Figure 6. Odds (in logarithmic units) of being in Cluster 1 (vs. Cluster 2) as a function of anterior cingulate cortical thickness and age.

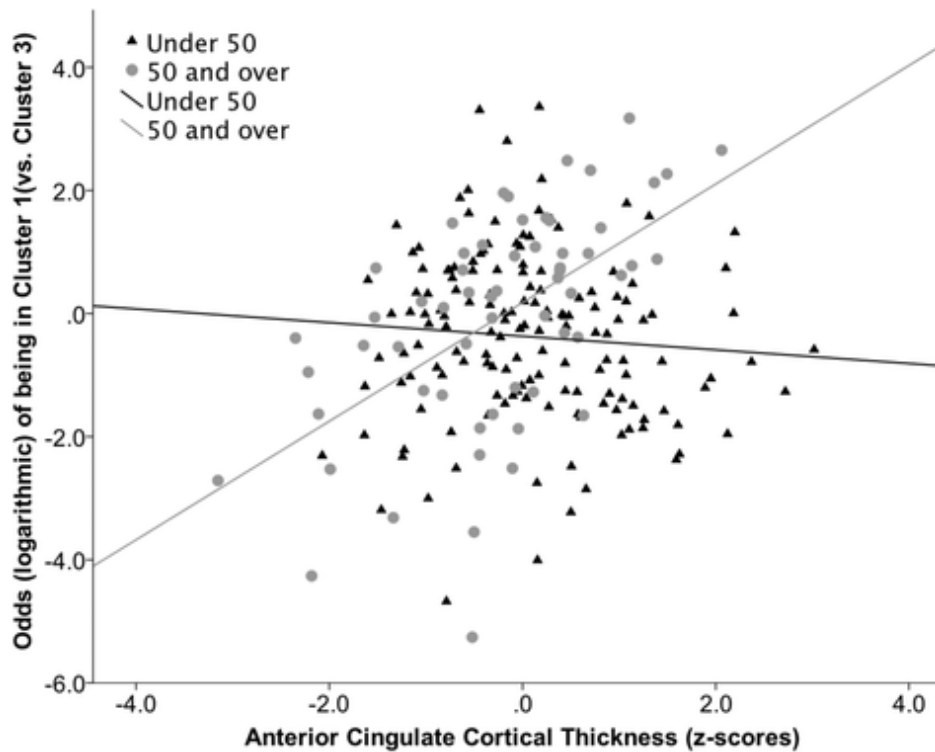


Figure 7. Odds (in logarithmic units) of being in Cluster 1 (vs. Cluster 3) as a function of anterior cingulate cortical thickness and age.

Regression analyses were repeated excluding those with a diagnosis of schizophrenia or schizoaffective disorder ($n = 33$) to rule out the possibility that these are solely explanatory of the structural brain differences observed between clusters. The findings were essentially unchanged. Likewise, when left and right hemispheres were analyzed separately in the regression models, the pattern of findings remained the same. We also repeated regression analyses excluding two older participants that appeared to have outlying mOFC thickness points (z-scores less than -3) evident in [Figures 4 and 5](#). Our results were similar, thus we opted to retain the cases given that they did not emerge as influential points in our check for multivariate outliers. Lastly, we conducted the regression analyses excluding the two participants who had their MRI scans completed more distal to the baseline neurocognitive testing (282 days, 322 days). Again, our findings did not change with these cases omitted; therefore we opted to include them to maintain the sample size and the representativeness of this sample. Follow-up inspection of these cases using qualitative notes from neuroradiological reviews did not reveal any evidence of overt progressive illness that might influence the structure-function associations for these two cases.

Proxy Variables

On developmental proxy variables, Cluster 3 was characterized by a higher rate of schizophrenia ($\chi^2 = 6.91$, $p = .009$), and a higher incidence of ever having received special education ($\chi^2 = 4.10$, $p = .043$), compared to Cluster 1. Further, higher mean total NSS, $F = 12.96$, $p < .001$ were observed in Cluster 3 compared to Clusters 1, $t = 4.77$, $p < .001$ and 2, $t = 4.19$, $p < .001$, in alignment with our previous findings ([Gicas et al., 2014](#)). No differences were observed for total EPS ($p > .05$).

Regarding acquired brain insult/risk exposure proxies, higher rates of any MRI pathology were observed in Cluster 2 ($\chi^2 = 7.84$, $p = .005$) and Cluster 3 ($\chi^2 = 5.46$, $p = .019$) relative to Cluster 1. When further inspected, the rates of stroke and aneurysm appeared to drive the group differences on MRI pathology. A higher prevalence of stroke was observed in Cluster 2 ($\chi^2 = 9.95$, $p = .002$), and Cluster 3 ($\chi^2 = 7.33$, $p =$

.007) compared to Cluster 1, with the same pattern of higher aneurysm prevalence in Cluster 2 ($\chi^2 = 4.14$, $p = .042$) and Cluster 3 ($\chi^2 = 4.81$, $p = .028$) compared to Cluster 1. In addition, Cluster 2 exhibited significantly higher rates of opioid dependence ($\chi^2 = 4.74$, $p = .029$) and stimulant dependence ($\chi^2 = 5.12$, $p = .024$) relative to Cluster 3. Likewise, the rate of opioid dependence was significantly higher in Cluster 1 compared to Cluster 3 ($\chi^2 = 6.01$, $p = .014$). Cluster differences on substance dependence are consistent with our previous report (Gicas et al., 2014). The rate of reported childhood abuse was significantly higher in Cluster 1 ($\chi^2 = 5.90$, $p = .015$), and marginally higher in Cluster 2 ($\chi^2 = 3.53$, $p = .060$) compared to Cluster 3. No cluster differences were found for total virus exposure, $F = 2.10$, $p = .124$.

When the clusters were compared on basic sociodemographics, the findings were consistent with our previous report with more years of education, $F = 4.06$, $p = .018$ in Cluster 1 compared to Cluster 2, $t = 2.50$, $p = .013$ and Cluster 3, $t = 2.50$, $p = .013$. Likewise, there were a greater proportion of females in Cluster 2 compared to Cluster 1 ($\chi^2 = 10.48$, $p = .001$) and Cluster 3 ($\chi^2 = 10.75$, $p = .001$). No age differences were observed ($p > .05$). Descriptive statistics for the proxy variables by cluster membership are provided in Table 4.

Table 4
Descriptive Statistics of Proxy Measures by Cluster Membership (N = 299)

Proxy measure	Cluster 1	Cluster 2	Cluster 3	Comparisons
Developmental				
Schizophrenia diagnosis ^a , <i>n</i> (%)	2 (2.3)	9 (8.3)	13 (12.6)	C3 > C1**
Special education ^b , <i>n</i> (%)	19 (22.4)	30 (27.5)	37 (35.9)	C3 > C1*
Total NSS ^c , <i>M</i> (<i>SD</i>)	10.1 (7.5)	11.1 (7.4)	15.7 (6.6)	C3 > C1****, C3 > C2****
Total EPS ^d , <i>M</i> (<i>SD</i>)	9.6 (8.3)	12.1 (11.4)	11.8 (10.2)	ns
Acquired brain insult/risk exposure				
MRI pathology ^e , <i>n</i> (%)				
Any pathology	9 (12.2)	29 (30.2)	23 (27.1)	C2 > C1**, C3 > C1*
Stroke	0 (.0)	12 (12.5)	8 (9.4)	C2 > C1***, C3 > C1**
Hemorrhage	1 (1.4)	1 (1.0)	0 (.0)	ns
Aneurysm ^f	1 (1.4)	8 (8.4)	8 (9.4)	C2 > C1*, C3 > C1*
TBI ^g				
Possible	38 (43.7)	37 (33.9)	42 (40.8)	ns
Probable	16 (18.4)	17 (15.6)	11 (10.7)	ns
Definite	6 (6.9)	12 (11.0)	11 (10.7)	ns
Drug dependence^h, <i>n</i> (%)				
Stimulant	72 (82.8)	98 (89.9)	81 (78.6)	C2 > C3*
Opioid	44 (50.6)	52 (47.7)	34 (33.0)	C1 > C3*, C2 > C3*
Alcohol	14 (16.1)	17 (15.6)	16 (15.5)	ns
Cannabis	30 (35.4)	39 (35.8)	33 (32.0)	ns
Childhood abuse ^g , <i>n</i> (%)	14 (20.3)	13 (16.5)	6 (7.1)	C1 > C3*, C2 > C3†
Total virus exposure ^h , <i>M</i> (<i>SD</i>)	2.6 (1.1)	2.8 (1.2)	3.0 (1.3)	ns
Demographics				
Age (years), <i>M</i> (<i>SD</i>)	43.2 (9.1)	43.3 (9.7)	43.4 (9.8)	ns
Education (years), <i>M</i> (<i>SD</i>)	10.9 (2.2)	10.1 (2.5)	10.2 (2.0)	C1 > C2*, C1 > C3*
Gender, <i>n</i> (% female)	12 (13.8)	37 (33.9)	15 (14.6)	C2 > C1***, C2 > C3***

Note. Reflects data for 299 participants included in the cluster analysis. NSS = neurological soft signs; EPS = extrapyramidal symptoms; TBI = traumatic brain injury.

^a *n* = 299. ^b *n* = 297. ^c *n* = 229. ^d *n* = 271. ^e *n* = 255. ^f *n* = 254. ^g *n* = 233. ^h *n* = 290.

† $p = .060$. * $p < .05$. ** $p < .01$. *** $p < .005$. **** $p < .001$.

Descriptive Statistics of Proxy Measures by Cluster Membership (N = 299)

Secondary Analyses

To further understand the nature of the Age \times Cortical thickness interactions, we examined differences between the younger (<50 years) and older (50+ years) age groups on key proxy measures described above. Independent samples *t* tests and chi-square tests were used for continuous and categorical variables respectively. Given the exploratory nature of these analyses, we did not apply a Bonferroni

correction. To summarize, older participants demonstrated a significantly higher rate of MRI pathology ($\chi^2 = 4.73$, $p = .030$) and TBI ($\chi^2 = 4.77$, $p = .029$) compared to younger participants. Conversely, in younger participants, there was a higher instance of a history of special education ($\chi^2 = 7.27$, $p = .007$) and a trend toward a higher proportion of individuals with a schizophrenia diagnosis ($\chi^2 = 3.69$, $p = .055$). Results are further reported in Table 5. Importantly, the interaction term remains significant when we exclude select subsets of participants with definite TBI, schizophrenia diagnosis, history of special education, or any MRI pathology (as defined in the Method section; stroke, hemorrhage, aneurysm). This demonstrates the robustness of the effect and that confounds of the age groups are not the primary drivers of the interactive effect.

Table 5
Proxy Measure Differences by Age Group (N = 211)

Proxy measure	Younger (<50 years), n = 151	Older (50+ years), n = 60	Test statistic (p value)
Developmental			
Schizophrenia diagnosis, n (%)	18 (11.9)	2 (3.3)	$\chi^2 = 3.69$ (.055 [†])
Special education, n (%)	50 (33.6)	9 (15.0)	$\chi^2 = 7.27$ (.007)
Total NSS, M (SD)	11.67 (7.30)	12.40 (7.49)	$t = -.59$ (.554)
Total EPS, M (SD)	11.35 (9.96)	9.10 (7.30)	$t = 1.59$ (.114)
Acquired brain insult/risk exposure			
Any MRI pathology, n (%)	31 (20.7)	21 (35.0)	$\chi^2 = 4.73$ (.030)
Definite TBI, n (%)	12 (7.9)	11 (18.3)	$\chi^2 = 4.77$ (.029)
Stimulant dependence, n (%)	128 (84.8)	52 (86.7)	$\chi^2 = .12$ (.725)
Opioid dependence, n (%)	64 (42.4)	24 (40.0)	$\chi^2 = .10$ (.751)
Alcohol dependence, n (%)	24 (15.9)	10 (16.7)	$\chi^2 = .02$ (.890)
Cannabis dependence, n (%)	60 (39.7)	16 (26.7)	$\chi^2 = 3.18$ (.074)
Childhood abuse, n (%)	15 (13.0)	5 (9.4)	$\chi^2 = .45$ (.502)
Total virus exposure, M (SD)	2.74 (1.24)	3.07 (1.20)	$t = -1.74$ (.084)
Demographics			
Education, M (SD)	10.12 (2.06)	10.82 (2.80)	$t = -1.75$ (.083)
Gender, n (% female)	31 (20.5)	9 (15.0)	$\chi^2 = .86$ (.355)

Note. Reflects data for 211 participants used in logistic regression analyses. Bold *p* values denotes statistically significant findings.

[†] Trend towards significance.

Proxy Measure Differences by Age Group (N = 211)

Discussion

We established that structural brain measures are differentially associated with distinct neurocognitive profiles in a multimorbid marginalized sample. Greater gyrification in frontal and temporal regions was associated with Cluster 3 (overall lowest neurocognitive functioning, relative decision-making strength) compared to the other clusters. Further, regional frontal cortical thicknesses differentiated clusters, but this effect was moderated by age. Specifically, for older persons, greater mOFC thickness was associated with an increased likelihood of being in Cluster 1 (overall highest neurocognitive functioning) compared to Cluster 2 (intermediate neurocognitive capacities, prominent decision-making weakness) and Cluster 3. This same pattern was observed for ACC thickness, though the effect in the overall regression model only trended toward statistical significance. The reverse pattern was selectively observed for younger individuals in that greater mOFC thickness predicted membership in Cluster 3 versus Cluster 1. With respect to developmental proxy measures, Cluster 3 exhibited the highest rates of schizophrenia, a history of having received special education, and greater NSS. With respect to proxy measures of acquired brain insult, Cluster 2 exhibited the highest rate of MRI pathology. For indices of risk exposure, Cluster 1 and Cluster 2 demonstrated higher rates of substance dependence and childhood abuse, relative to Cluster 3.

Our findings support the contention that etiologies of neurocognitive impairments are relatively different between groups. The pattern of greater frontal and medial temporal gyrification being associated with Cluster 3 may be reflective of early neurodevelopmental aberrations. Indeed, a number of schizophrenia studies have reported increased gyrification in select regions of the frontal (Falkai et al., 2007; Palaniyappan et al., 2011; Vogeley et al., 2000) and temporal cortices (Harris et al., 2004; Schultz et al., 2010) in patients, in individuals at-risk for schizophrenia (Harris et al., 2007; Stanfield et al., 2008), and in unaffected first-degree relatives (Falkai et al., 2007). Regional increases in gyrification have also been observed in autism spectrum disorders (Liberio, DeRamus, Deshpande, & Kana, 2014; Wallace et al., 2013) and Williams syndrome (Fahim et al., 2012). However, a number of these studies have also reported regional decreases in gyrification relative to healthy controls. Such findings simultaneously highlight the heterogeneity of cortical alterations that can result from early deviations in neurodevelopment and the need for further studies on gyrification abnormalities in clinical populations. Although we ruled out the possibility of global group differences in gyrification, we selectively focused on key fronto-temporal regions. Therefore, we may not have captured the full spectrum of gyrification differences that exists across groups, which could have also included regions of decreased gyrification in Cluster 3 relative to the others. Our interpretations should be further tempered by the fact that we do not have a healthy comparison group to determine the actual direction and extent of gyrification differences.

Although we observed that Cluster 3 was associated with greater regional gyrification, it was also differentiated from Cluster 1 by frontal cortical thickness. More specifically, and what emerged as most interesting, is that our hypothesized pattern of “bigger is better” only held true for older individuals. Follow-up analyses revealed that there are higher rates of MRI pathology and traumatic brain injury in older individuals compared to their younger counterparts. We conjecture that, as these older individuals face diminishing brain reserve as a result of biological and/or environmental insults, there is a greater reliance on remaining brain structure to maintain adequate neurocognitive functioning (Burzynska et al., 2012). On the other hand, in younger individuals, the reverse was true whereby greater OFC thickness was associated with a poorer profile of neurocognitive functioning (Cluster 3). Although this latter finding was unexpected, it remains consistent with typical life span developmental patterns in which thinner cortices are associated with better intellectual functioning up until early adulthood, but the association reverses in middle-age such that there is a positive association between regional thicknesses and function (Schnack et al., 2015). In young psychiatric samples, thicker cortices may reflect aberrant neurodevelopmental pruning processes (Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Lacerda et al., 2007). Such an interpretation is consistent with our finding that there is a higher rate of schizophrenia diagnoses in younger individuals within this sample. We also observed a higher proportion of younger individuals with a history of special education. Although this may be reduced to cohort effects, it is also plausible that it may signal the greater degree of neurodevelopmental difficulties in this age group, consistent with the higher rates of schizophrenia.

While our neurodevelopmental hypothesis of Cluster 3 is limited by the parameters of our study design, our interpretation is bolstered by the fact that Cluster 3 exhibited higher rates of schizophrenia and special education, in addition to greater negative symptoms and NSS (also see Gicas et al., 2014). Both negative symptoms and NSS are considered to be relatively stable, trait markers of schizophrenia (Ventura et al., 2015; Chan & Gottesman, 2008), but have also been observed in other psychiatric populations (Foussias, Agid, Fervaha, & Remington, 2014; Kaiser, Heekeren, & Simon, 2011; Chen et al., 1995) and in clinical at-risk samples (Lyne et al., 2014; Piskulic et al., 2012). These markers may be considered as reflective of

diffuse cerebral dysfunction related to aberrant development of neurocognitive systems.

The neuroanatomic and proxy variable differences between Cluster 3 and the other clusters persisted despite exclusion of participants with a schizophrenia or schizoaffective diagnosis. This suggests that the findings of elevated psychiatric and neurological symptoms, along with greater gyrification, in Cluster 3 might ultimately reflect a continuum of putative neurodevelopmental psychopathology, rather than markers of a categorical disease entity. This lends further support to the hypothesis that the observed neurocognitive deficits of Cluster 3 are apt to have been longstanding, and may serve as a vulnerability marker for further brain and neurocognitive degradation with a lifetime of accumulating risk exposures.

In contrast to Cluster 3, the neurocognitive deficits associated with Cluster 2 are more circumscribed and thus may be more aptly characterized as acquired impairment as a function of exposure to various environmental insults. Cluster 2 exhibited the most pronounced impairment in, and poorest overall, decision-making ability. Affective decision-making processes are thought to be subserved by the ventromedial prefrontal cortex ([Bechara, 2003](#); [Stuss & Levine, 2002](#)), which supports our finding that cortical thinning in the mOFC was associated with a greater likelihood of being in Cluster 2, compared to Cluster 1, albeit only for individuals aged 50 years and older. Cortical thinning in this subgroup may be extensively related to environmental risk exposures. Indeed, Cluster 2 had elevated rates of MRI pathology, substance dependence, and childhood abuse (compared to Cluster 3), all of which are likely to make a unique contribution to brain integrity in this group. For example, frontal thinning has been observed in polysubstance users ([Lawyer et al., 2010](#); [Momenan et al., 2012](#)) and in those exposed to early life adversities, such as childhood abuse ([Kelly et al., 2013](#)) and low socioeconomic status ([Noble et al., 2015](#)). Cortical thinning may also be exacerbated with aging under certain conditions, such as HIV infection ([Holt et al., 2012](#); [Pfefferbaum et al., 2014](#)) and history of concussion ([Goswami et al., 2016](#); [Tremblay et al., 2013](#)). Although cortical thickness is much more vulnerable to degradation over the life span than gyrification, it is important to note that there is some evidence suggesting reductions in gyrification with early life risk exposures, including childhood abuse ([Kelly et al., 2013](#)) and cannabis use ([Shollenbarger, Price, Wieser, & Lisdahl, 2015](#)). Maturation of tertiary aspects of cortical folding continues through adolescence ([White et al., 2010](#)), and environmental insults during this highly dynamic period could plausibly result in focal gyrification abnormalities in persons with otherwise normal neurodevelopmental trajectories. The interaction between early risk exposures and brain maturation, as well as the degree to which multiple co-occurring conditions exert a cumulative or synergistic impact on cortical brain integrity are matters ripe for future investigation.

Our findings that regional frontal thicknesses, but not medial temporal thickness or hippocampal volume, differentiated the clusters may reflect the vulnerability of the prefrontal structures and fronto-striatal neural circuitry that subserves decision-making and inhibitory control processes in a substance dependent population. Structural ([Ersche et al., 2011, 2012](#)) and functional ([Ersche et al., 2005](#); [Hester & Garavan, 2004](#); [Luo et al., 2013](#)) abnormalities in the OFC and ACC have been consistently reported in persons with substance dependence disorders compared to healthy controls. These regions both receive primary inputs from the ventral portion of the striatum ([O'Callaghan, Bertoux, & Hornberger, 2014](#)), and dysfunction in this network has been strongly implicated in the development and maintenance of drug addiction ([Everitt & Robbins, 2013](#)), and to a lesser extent in other psychiatric illnesses ([Pujara & Koenigs, 2014](#)). For instance, poorer white matter tract integrity in the fronto-subcortical circuitry has been linked with longer durations of stimulant use ([Ersche et al., 2012](#)) and opioid use ([Upadhyay et al., 2010](#)). Frontal structures are also

exceptionally vulnerable to normal aging processes. A clear anterior-posterior gradient of cortical degradation exists in which the prefrontal cortex is affected earliest, followed by relatively milder effects in temporal regions, consistent with the “last in, first out” hypothesis (Fjell et al., 2009; Raz & Rodrigue, 2006; Thambisetty et al., 2010). Moreover, these effects are already observed by middle age (McGinnis et al., 2011). Together, this may indicate heightened risk for premature or accelerated aging in a middle aged, multimorbid population.

Relatedly, the degradation of frontal structures may also help to explain the lack of association between hippocampal volume and neurocognitive clusters despite substantial memory impairment across all three groups (see Figure 3). Indeed, successful verbal recall is dependent on one’s ability to initially attend to and process relevant stimuli, which is regulated by dorsolateral prefrontal structures (Stuss & Levine, 2002). Thus, in our sample, memory performance may be more reflective of a generalized impairment in lower level attentional and processing speed abilities and associated neural circuitry, rather than true memory impairment.

The current findings should be interpreted in light of certain limitations. First, the cross-sectional nature of this study limits our understanding of the extent to which the cluster differences are truly representative of neurodevelopmental and/or aging processes. When directly compared to a longitudinal approach, a cross-sectional design has demonstrated to underestimate age-related changes in cortical thickness (Fjell et al., 2014). Second, we focused exclusively on cortical brain structure, but there are likely to be important differences between the clusters on other brain measures. For example, the ventromedial prefrontal cortex and ventral striatum must work in concert to mediate complex decision-making and inhibitory control processes, and it is likely that degradation in key cortical regions is also associated with decreased subcortical volumes and/or decreased white matter tract integrity in the relevant circuitry. Explorations of these brain structures in future studies will help to further elucidate the drivers of neurocognitive impairment. In addition, we were not able to evaluate how brain integrity in this multimorbid sample compares to healthy persons, although our within sample comparisons are still highly informative to our understanding of the unique vulnerabilities confronted by different subgroups. It is also noteworthy that the clusters represent profiles of relative strengths and weaknesses across several core neurocognitive domains, but the associations between cortical parameters and individual neurocognitive measures may reveal a unique and complementary pattern of structure-function associations, which should be addressed in follow-up investigations.

Although we attempted to corroborate self-report data whenever possible (verifying self-report of TBI against imaging data), some measures relied solely on self-report (childhood trauma, history of special education, years of education) and this data may be less reliable as a function of memory impairment and/or selective reporting. Further, we studied an inherently heterogeneous population and the drivers of degradation in brain structure and neurocognitive functioning is apt to be multifactorial. It is likely that there are both independent and cumulative impacts on neurocognition, as a consequence of neurodevelopmental disorders and environmental risk exposures, including childhood trauma, substance use, viral infection, psychiatric illness, traumatic brain injury, and neurodegenerative diseases associated with aging. The current cross-sectional design and available data preclude our ability to make any definitive conclusions about causal associations. Future longitudinal research investigating the extent to which risk exposures are differentially associated with changes in brain and neurocognition over time will help contribute to our understanding. Indeed, lower socioeconomic status in childhood (Noble et al., 2015) and stressful childhood

events (Kelly et al., 2013; Luby et al., 2013) negatively impact numerous cortical and subcortical brain structures. These “hidden” factors limit our interpretation in the current study as we are not able to directly observe the effects of childhood events on this adult sample.

To the best of our knowledge, this is the first study to examine structural brain integrity and neurocognition in a socially marginalized sample. We present comprehensive data from a large cohort, with minimal exclusion criteria, thereby providing a rich representation of the inherent complexity that exists in this population. These findings stand as a significant contribution to our understanding of the multiple pathways to neurocognitive impairment in marginalized persons. Ultimately, this is of importance for the optimization of health service delivery. Centering efforts on identifying the specific factors that result in acute neurocognitive losses for select subgroups with high rates of risk exposures could inform early interventions that help to mitigate future impairments. This is especially critical for younger persons who are likely to have had less lifetime risk exposure. In contrast, those who appear to have a longstanding history of lower neurocognitive functioning, with putative neurodevelopmental origins, and who may have an increased risk for further structural and neurocognitive losses in older age represent a particularly vulnerable subgroup. Such individuals may require more intensive supports at all stages during their lifetime to preserve brain health and maintain optimum neurocognitive functioning. For example, persons with psychiatric illness and substantial impairments in executive functioning and memory may benefit most from a supportive group home environment as oppose to living alone to maximize everyday functioning (Schutt et al., 2006). A practical recommendation moving forward would be to screen for cognitive impairment given the central role of neurocognition in performing complex everyday activities (Gorman et al., 2009). Moreover, screening should be considered especially important in older adults given that neurocognition is more strongly tied to brain integrity at this stage in life (Burzynska et al., 2012). In conclusion, our study has laid the foundation for future explorations of brain–behavior relationships within the growing literature on socially marginalized populations. Examining longitudinal brain changes and the impact on neurocognition will be an important next step in understanding the risks and challenges marginalized individuals face.

Footnotes

¹ The cluster profiles were reconstructed in the reduced sample ($n = 211$) and correlated with the profiles of the full sample ($n = 299$). Corresponding profiles correlated well with each other, demonstrating good internal validity. Visual inspection of the graphs revealed no differences in magnitude or shape between the full and reduced sample profiles.

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APPENDIX

APPENDIX A: Items Administered from the Cambridge Neurological Inventory

Item	Scoring criteria
Snout reflex	0, .5, 1, 9
Grasp reflex	0, .5, 1, 2, 9
Palmomental reflex	0, .5, 1, 9
Finger-nose test (left)	0, .5, 1, 2, 9
Finger-nose test (right)	0, .5, 1, 2, 9
Finger-thumb tapping (left)	0, .5, 1, 2, 9
Finger-thumb tapping (right)	0, .5, 1, 2, 9
Finger-thumb opposition (left)	0, .5, 1, 2, 9
Finger-thumb opposition (right)	0, .5, 1, 2, 9
Mirror movements 1 (left)	0, .5, 1, 2, 9
Mirror movements 1 (right)	0, .5, 1, 2, 9
Diadochokinesia (left)	0, .5, 1, 2, 9
Diadochokinesia (right)	0, .5, 1, 2, 9
Mirror movements 2 (left)	0, .5, 1, 2, 9

Mirror movements 2 (right)	0, .5, 1, 2, 9
Fist-edge-palm test (left)	0, .5, 1, 2, 9
Fist-edge-palm test (right)	0, .5, 1, 2, 9
Oseretsky (left)	0, .5, 1, 2, 9
Oseretsky (right)	0, .5, 1, 2, 9
Rhythm tapping test	0, .5, 1, 2, 9
Go/no-go test	0, .5, 1, 2, 9
Extinction	0, .5, 1, 2, 9
Finger agnosia (left)	0, .5, 1, 2, 9
Finger agnosia (right)	0, .5, 1, 2, 9
Stereognosia (left)	0, .5, 1, 2, 9
Stereognosia (right)	0, .5, 1, 2, 9
Graphesthesia (left)	0, .5, 1, 2, 9
Graphesthesia (right)	0, .5, 1, 2, 9
Left-right orientation	0, .5, 1, 2, 9

Note. See Chen et al. (1995) for full item description and definition of scoring criteria.

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