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Cognitive reserve attenuates age-related cognitive decline in the context of putatively accelerated brain ageing in schizophrenia-spectrum disorders

Original Article

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Abstract

Background. In schizophrenia, relative stability in the magnitude of cognitive deficits across age and illness duration is inconsistent with the evidence of accelerated deterioration in brain regions known to support these functions. These discrepant brain–cognition outcomes may be explained by variability in cognitive reserve (CR), which in neurological disorders has been shown to buffer against brain pathology and minimize its impact on cognitive or clinical indicators of illness.

Methods. Age-related change in fluid reasoning, working memory and frontal brain volume, area and thickness were mapped using regression analysis in 214 individuals with schizophrenia or schizoaffective disorder and 168 healthy controls. In patients, these changes were modelled as a function of CR.

Results. Patients showed exaggerated age-related decline in brain structure, but not fluid reasoning compared to controls. In the patient group, no moderation of age-related *brain* structural change by CR was evident. However, age-related *cognitive* change was moderated by CR, such that only patients with low CR showed evidence of exaggerated fluid reasoning decline that paralleled the exaggerated age-related deterioration of underpinning brain structures seen in *all patients*.

Conclusions. In schizophrenia-spectrum illness, CR may negate ageing effects on fluid reasoning by buffering against pathologically exaggerated structural brain deterioration through some form of compensation. CR may represent an important modifier that could explain inconsistencies in brain structure – cognition outcomes in the extant literature.

Introduction

Accelerated brain ageing has been implicated in schizophrenia, where an increase in the rate of grey matter loss at certain timepoints throughout the lifespan – and by proxy, the illness course – translates to the pronounced morphological differences seen in patients *v.* controls (Hulshoff Pol *et al.*, 2002; Schnack *et al.*, 2016; Cropley *et al.*, 2017). Current evidence suggests that while the most extensive brain changes occur in early illness stages (Schnack *et al.*, 2016), there is a pattern of exaggerated brain tissue loss, particularly in frontal regions, extending into the sixth decade and corresponding to ~15–20 years post illness onset (Pol and Kahn, 2008; Cropley *et al.*, 2017).

The frontal cortex is highly susceptible to the effects of ageing (Raz and Rodrigue, 2006), and its integrity important for *fluid* cognitive processes that are vulnerable to age-related change (Ryan *et al.*, 2000; Kievit *et al.*, 2014; Harvey and Rosenthal, 2018). These include reasoning and working memory, which are executive processes that interact to allow for novel problem solving independent of past knowledge or experiences; and can be considered relative

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to *crystallized* intelligence which is acquired with experience and intellectual stimulation (e.g. education) and is relatively resistant to age-related decline (Ryan *et al.*, 2000; Lindenberger, 2001). Pronounced deficits in fluid cognition is evident in schizophrenia irrespective of age and across all illness stages; and can be so severe that patients as young as 40 have been shown to perform at the level of healthy adults as much as 30 years older (Pantelis *et al.*, 1997; Loewenstein *et al.*, 2012; Harvey and Rosenthal, 2018). There is *some* evidence to suggest a greater burden of increasing age on certain executive functions in patients relative to controls (Loewenstein *et al.*, 2012). However, generally, studies show a proportionate decline in fluid cognitive performance, such that the relative magnitude of deficits in schizophrenia appears to remain stable over time (Heaton *et al.*, 1994; Heaton *et al.*, 2001; Harvey and Rosenthal, 2018). This is inconsistent with the evidence of progressive age-related deterioration in brain regions known to support these functions (Hulshoff Pol *et al.*, 2002; Cropley *et al.*, 2017). In addition, there appears to be a subgroup of patients with significant brain structural and functional deficits who have normal levels of fluid cognition despite being of an equivalent age to controls or schizophrenia patients with compromised cognition, which further complicates interpretation of pertinent findings (Heinrichs *et al.*, 2017; Lewandowski *et al.*, 2019; Van Rheenen *et al.*, 2018).

These discrepant brain–cognition outcomes may be partially reconciled by the concept of cognitive reserve (CR), which was proposed to account for individual differences in the cognitive or clinical manifestations of age or illness-related brain pathology (e.g. accelerated brain ageing) (Stern, 2002). CR has been studied extensively in the context of neurological illness, where patients with the same disease burden (brain pathology) show marked variability in the expression of disease symptoms as a function of high or low levels of crystallized intelligence (Sumowski *et al.*, 2010*a*; Stern, 2012). Better outcomes are taken to reflect the manifestation of some form of active *compensation* – possibly involving plastic neural reorganization – by which crystallized intelligence builds CR to enable *resilience* to brain pathology by minimizing its impact on cognitive or clinical indicators of illness (Stern, 2002, 2009, 2012). This is in contrast to evidence from healthy cohorts showing that greater CR is associated with both better cognition (Opdebeeck *et al.*, 2016) *and* preserved brain volume (Solé-Padullés *et al.*, 2009; Bartrés-Faz and Arenaza-Urquijo, 2011), which suggests a more preventative or *neuroprotective* effect of CR on neuroanatomy and manifest behaviour in health as opposed to disease.

Proxies of CR include measures of reading or vocabulary knowledge, which are commonly used to estimate premorbid (crystallized) intellectual functioning (Stern, 2009; Sumowski *et al.*, 2010*b*). Schizophrenia studies tend to show lower estimated premorbid intelligence in patients compared to controls (Nelson *et al.*, 1990). However, the magnitude of this deficit is typically less than that of fluid cognitive domains. Moreover, an overlap in the distribution of scores on direct and proxy measures of premorbid intelligence across patients and controls – as much as 67% (Woodberry *et al.*, 2008) – indicates that a sizeable proportion of those with a schizophrenia diagnosis perform within the range of most healthy individuals (Weickert *et al.*, 2000; Woodward and Heckers, 2015; Weinberg *et al.*, 2016; Van Rheenen *et al.*, 2018). Notably, schizophrenia patients with better estimated premorbid intelligence have been found to have less severe symptoms and better clinical and occupational outcomes (Leeson *et al.*, 2011; Wells *et al.*, 2015). They also have better fluid cognition and more positive generalizability effects of cognitive remediation therapy than those with low premorbid intelligence (Weickert *et al.*, 2000; Holthausen *et al.*, 2002; Fiszdon *et al.*, 2006; Kontis *et al.*, 2013; Van Rheenen *et al.*, 2017). In the absence of brain imaging data, however, it is not clear whether these better behavioural outcomes reflect a greater capacity to tolerate brain pathology (resilience), or simply less brain pathology itself (neuroprotection) (Christensen *et al.*, 2007; Vuoksimaa *et al.*, 2013).

Certainly, a resilience effect of CR could explain findings of discrepant brain and behaviour change. In this context, only patients with low CR would show pathological age-related cognitive changes that parallel exaggerated age-related changes seen in the brain. In contrast, patients with higher CR would be resilient to these detrimental brain changes, as demonstrated by an absence/attenuation of age-related *cognitive* decline. In this case, correlations between the brain and behaviour would vary as a function of CR.

Here, we present the first study to examine CR in schizophrenia-spectrum illness using indices of both the brain and behaviour in the context of age. Use of these indices in combination is needed to establish whether CR confers neuroprotective or resilience effects in individuals on the schizophrenia spectrum (Christensen *et al.*, 2007). Hence, we used a large, age-diverse, cross-sectional dataset comprising structural neuroimaging and cognitive data, to identify the circumstances whereby fluid cognitive functions in schizophrenia-spectrum illness parallel the putative trajectory of exaggerated age-related deterioration in brain structure. In line with past research, we hypothesized that effects consistent with accelerated ageing would only be evident in analyses of brain structure but not fluid cognition when controls were compared to *all patients*. However, within the patient group, we expected that the putative rate of age-related *cognitive* change would be moderated by CR, such that only those patients with low levels of CR would show evidence of exaggerated age-related decline. No moderation of putative age-related *brain* structural change by CR was predicted for the patient group, as the overall pattern of findings was expected to correspond to a resilience effect of CR (as opposed to neuroprotection) in those with schizophrenia-spectrum illness.

Given the evidence of more pronounced age-related changes in the frontal cortex (Raz and Rodrigue, 2006; Cropley *et al.*, 2017), we focused our analyses *a-priori* on this region and the fluid cognitive functions that it is known to impact. Here, we extend previous work by focusing not only on putative changes in grey matter volume, but also on its morphological drivers – cortical thickness and surface area.

Method

Neuroimaging, cognitive and clinical data from 214 individuals with schizophrenia and schizoaffective disorder and 168 controls was obtained from the Australian Schizophrenia Research Bank (ASRB). All participants provided informed consent for the analysis of their stored data. Study procedures were approved by the Melbourne Health Human Research Ethics Committee. The Diagnostic Interview for Psychosis (Castle *et al.*, 2006) was used to obtain clinical symptom ratings and confirm patient diagnoses according to ICD-10 or DSM-IV criteria. The Scale for the Assessment of Negative Symptoms (Andreasen, 1983) was used to assess negative symptoms. Further details regarding participant characterization are given in the Supplementary material.

Measures

CR was assessed through a composite score of two measures available in the ASRB; the Wechsler Test of Adult Reading and the Wechsler Adult Intelligence Scale – Vocabulary Test. These measures assess either reading of irregularly pronounced words or the depth and breadth of vocabulary knowledge (Wechsler, 1997*a*; Holdnack, 2001). Performance on them is considered to be resistant to age or illness-related performance decline in adulthood (Ryan *et al.*, 2000), and may even improve with age (Ben-David *et al.*, 2015). This was supported in our data by a very small *positive* correlation between age and the composite measure ($r = 0.11$, $p = 0.03$). These measures are associated with crystallized intelligence – which is partially heritable (Plomin and Deary, 2015), but they are also uniquely predicted by intellectually enriching activities such as education and reading even after controlling for general intellectual functioning (Stine-Morrow *et al.*, 2015). Raw scores on both measures were standardized and summed, where patients with composite scores below the 10th percentile of the healthy control sample were classified as having below-average CR (low CR group) and those above this considered to have CR within the normal range (average CR group). We elected to classify patients using this method because scores on these tests correlate highly with verbal and full-scale intelligence quotient (IQ) scores, where performance in the 10th percentile or lower corresponds closely to the cut-off between 'low average' and 'borderline' IQ ranges; the 10th percentile cut-point is a landmark neuropsychological percentile rank frequently used to define the lowest scoring individuals in a sample (Wechsler, 1997*a*; Wechsler, 1997*b*; Crawford and Garthwaite, 2009; Brooks *et al.*, 2011; de Zeeuw *et al.*, 2012; Woodward and Heckers, 2015; Czepielewski *et al.*, 2016).

Cognitive tests were selected from those in the ASRB if they met two criteria based on available evidence; performance on the test is known to deteriorate with age across the range of the sample (18–65 years) and is clearly linked to frontal brain functioning. The Letter Number Sequencing Test (LNS) and Matrix Reasoning Test met these criteria (Ryan *et al.*, 2000; Barbey *et al.*, 2014; Kievit *et al.*, 2014)[1]†. The LNS requires participants to verbally reorder a series of numbers and letters according to a specific rule set (e.g. numbers followed by letters). The Matrix Reasoning Test requires that participants complete a visual pattern by selecting the missing pattern piece from an array of possibilities. These tests assess working memory and fluid reasoning and provide prototypical estimates of both verbal and performance-based fluid cognition respectively. Higher scores on both tests indicate better performance. Details are provided elsewhere (Randolph *et al.*, 1998; Wechsler, 1999).

MRI image acquisition and processing

T1-weighted (MPRAGE) structural scans were acquired using Siemens Avanto 1.5 Tesla scanners. T1-weighted images comprised 176 sagittal slices/brain of 1 mm thickness without gap; field of view = 250 × 250 mm^2; repetition time/echo time = 1980/4.3 ms; data matrix size = 256 × 256; voxel dimensions = 1.0 mm × 1.0 mm × 1.0 mm. The same acquisition sequence was acquired at all ASRB sites. Image processing was conducted using the Freesurfer software package (version 5.1.0, http://surfer.nmr.mgh.harvard.edu/), which consists of a volume-based and a surface-based stream (Dale *et al.*, 1999; Fischl *et al.*, 1999, 2002; Fischl and Dale, 2000). The former was used to extract volume estimates (including intracranial volume), while the latter was used to extract cortical thickness and surface area estimates by reconstructing a three-dimensional cortical surface model. This includes segmentation of the pial surface and the grey/white matter boundaries for each hemisphere, using image intensity and continuity information from the MRI volume. Surfaces were initially inspected for skull stripping and surface boundary defects. Inaccuracies in outlining cortical surfaces and brain structures were manually corrected with Freesurfer's editing tools in accordance with an internal, standardized quality control and editing protocol. Edited images were then reprocessed through the Freesurfer pipeline and the output visually inspected again. This process was repeated until all surface errors were corrected, and any images that failed this process were excluded from the analysis. Four trained raters performed the Freesurfer processing and manual correction, blind to participant diagnosis. Inter-rater reliability of the final volume estimates (after correction) was calculated for 34 brain regions from a subset of 20 volumes. The intra-class coefficient was >0.90 for all regions except for the left (0.72) and right (0.59) temporal pole and the left (0.81) and right (0.82) frontal pole.

Thickness measures were obtained by calculating the shortest distance between the grey/white matter boundary and the pial surface at vertices on a uniform triangular grid with 1 mm spacing across the cortex. The surface area was obtained using the shortest distance between vertices on the white surface.

Statistical analysis

Intracranial volume and cortical volume, thickness and surface area estimates for each of the frontal regions delineated by the Desikan–Killiany Atlas (Desikan *et al.*, 2006) (online Supplementary Fig. S1) were imported into the Statistical Package for the Social Sciences (SPSS) version 24. Given that fluid reasoning and working memory index frontal brain systems bilaterally (Petrides *et al.*, 1993; Prabhakaran *et al.*, 1997; Christoff *et al.*, 2001), the left and right hemispheres for each frontal region were summed to create total volume, thickness or surface area scores. This also served to constrain the number of comparisons required. Global frontal scores were also generated for each imaging measure by summing each region within the frontal cortex bilaterally.

Moderation analyses were implemented using the Preacher and Hayes PROCESS plugin for SPSS. Data were analysed in sequential steps (Supplementary Fig. S1) and modelled linearly given evidence that age-related grey matter change in the frontal cortex is linear (Raz *et al.*, 2005; Hutton *et al.*, 2009; Giorgio *et al.*, 2010). Initially, we regressed age, diagnosis and their interaction on each of the cognitive tests of interest, as well as on each of the frontal cortical *volume* scores (Step 1). In brain regions in which an interaction effect was evident, we further explored whether the effect was driven by differential age-related changes in surface area or thickness by diagnostic group (Step 2). Once the regions of volume, thickness or area showing pathological variation in putative age-related decline in patients *v.* controls were established, we ascertained whether their association with the cognitive tests of interest differed between patients with low or average CR (Step 3). We did not examine variation by CR in controls given the limited number of cases in the low CR group ($n = 17$). For brain and cognitive measures whose association in patients was moderated by CR, we tested whether the effect of age on these measures was also moderated by CR (Step 4). Finally, in cases in which age-related

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†The notes appear after the main text.

change in cognition and/or brain structure differed in those with low *v.* average CR, the age-related slopes of each patient subgroup were modelled relative to controls (Step 5). Comparison of simple slopes was performed for significant interaction effects. A False Discovery Rate (FDR) of 5% was set to correct for multiple testing. This correction was applied to the interaction effects of each of Steps 1–4 *separately* (13, 8, 16, 8 tests, respectively) as well as the corresponding post-hoc simple slopes for each group (2 per interaction Step 1–4, 3 per Step 5).

In diagnostic comparisons, gender and site were entered as covariates in the analyses of cognitive tests, while site and intracranial volume[2] were covaried in the analyses of brain measures. Intracranial volume[3] was included as a covariate alongside site in the within-schizophrenia brain measures analysis *a-priori*, in order to link our findings to CR independent of brain reserve. Gender did not differ between the patient subgroups and was therefore not controlled in the within-schizophrenia analyses. Age, group (diagnostic or CR) and covariates were always entered into each model at Block 1, while the interaction term was entered at Block 2 to ascertain R^2 change. Standard errors were estimated with the Davidson–McKinnon Heteroskedasticity consistent inference. Five-thousand bootstrap samples were drawn with replacement from the original sample to calculate the 95% bias-corrected (BCa) confidence intervals (Cl) for the unstandardized regression (b) coefficients for each model; the effects were considered statistically significant if the 95% BCa CI did not overlap zero.

Results

Descriptives

There were minimal age differences between patients and controls, but patients had a slightly increased intracranial volume and were overrepresented by males (Table 1a). Patients with average CR were slightly older than those with below-average CR. They also had longer illness durations and less severe negative symptoms[4]. There were no CR subgroup differences in gender distribution, diagnostic categorization, onset age, positive symptoms or medication usage (Table 1b).

Diagnostic differences in age-related cognitive and brain structural decline (Steps 1 and 2)

Diagnostic differences in age-related cognitive and brain structural decline are shown in Table 2. As expected, no significant age×diagnosis interaction effects were evident for either of the cognitive tests of interest. Significant interactions effects were evident for global frontal, caudal middle frontal, pars orbitalis and pars triangularis volume, such that patients showed greater age-related volume loss in these regions compared to controls (Step 1). Subsequent analyses (Step 2) indicated significant age-related contraction of the cortical area in these regions in patients but not controls, with no significant age×diagnosis interaction effects evident for cortical thickness. Online Supplementary Fig. S2 presents the regions in which there were significant differences in age-related brain structural change in patients relative to controls.

Moderation of pathological brain morphology on cognition by CR in patients (Step 3)

Of the brain measures showing a pathological age-related change in patients at Step 1 or 2, no main or interaction effects of caudal middle frontal volume or area on Matrix Reasoning or LNS scores were evident, nor were effects of global frontal volume and area on LNS. However, the effect of global frontal volume and area, pars triangularis and pars orbitalis volume and area on Matrix Reasoning scores differed between patients with average and low CR, as did the effect of pars orbitalis and triangularis volume and area on LNS scores (Fig. 1). In patients with low CR, significant brain–cognition relationships of moderate effect were evident, such that lower brain volume or area predicted worse cognitive performance. Those with average CR either showed much weaker, or non-significant relationships (online Supplementary Table S1).

Moderation of age-related change in cognition and brain structure by CR in patients (Step 4)

No main effects or age×CR interactions were evident for any of the brain measures whose association with cognition was moderated by CR at Step 3. However, age-related change in Matrix Reasoning performance *did* differ significantly between CR subgroups, with a much sharper age-related decline in performance evident in those with low CR (Table 3; online Supplementary Fig. S3a). While the LNS interaction term only trended towards significance ($p = 0.08$ uncorrected), post-hoc conditional effects analysis (produced automatically in PROCESS) showed age-related decline in the performance in only the patients with low CR (online Supplementary Table S2 and online Supplementary Fig. S3b). [5]

Diagnostic differences in age-related cognitive decline as a function of CR subgroup (Step 5)

Figure 2 shows age-related cognitive decline in Matrix Reasoning performance in controls and patients with either low or average CR. *Relative to controls*, a significant exaggeration of age-related change in Matrix Reasoning scores was evident for only the patients with low CR (online Supplementary Table S3a). CR subgroup – control differences are not reported for the LNS given the interaction term only trended towards significance.

Discussion

We aimed to reconcile the inconsistencies regarding brain–cognition relationships in a large sample of schizophrenia-spectrum patients and healthy controls. Consistent with the accelerated brain ageing hypothesis of schizophrenia (Harvey and Rosenthal, 2018; Nguyen *et al.*, 2018), our results showed greater frontal cortex volume reductions in patients with increasing age, particularly in lateral middle and rostral segments of the inferior frontal gyrus. This pattern was reminiscent of a declining structural brain trajectory, did not vary as a function of CR, and was largely explained by contraction of the cortical surface with age.

As predicted, an absence of age-related changes in fluid reasoning and working memory were inconsistent with these results. While this superficially suggests a lack of direct association between brain structure and cognition, further analysis revealed that this was only the case for those characterized by CR in a range equivalent to most controls. Patients with below-average CR, however, showed significant and/or stronger negative relationships between these cognitive functions and frontal brain structure, likely owing to more pronounced putative age-related decline in performance than for patients with average CR. Indeed, only patients with low CR showed putative age-related

Table 1. Demographic and clinical characteristics of the sample

(**a**)

	Schizophrenia-spectrum patients (*n* = 214)			Healthy controls (*n* = 168)			
	%	*M*	S.D.	%	*M*	S.D.	Group comparison
Gender (% male)	72	–	–	48	–	–	$\chi^2(1) = 22.42$, $p = 0.00$
Age	–	37.54	9.78	-	39.74	14.00	$F_{(1380)} = 3.27$, $p = 0.07$
Illness duration (years)	–	14.25	9.23	–	–	–	–
Illness onset age	–	23.29	6.07	–	–	–	–
Current positive symptoms	–	1.79	2.56	–	–	–	–
Lifetime positive symptoms	–	7.49	3.35	–	–	–	–
Negative symptoms	–	24.61	16.82	–	–	–	–
Diagnosis (% schizophrenia)	82.7	–	–	–	–	–	–
Medications (% taking)		–	–	–	–	–	–
Antipsychotics	86.9	–	–	–	–	–	–
Typical	8.4	–	–	–	–	–	–
Atypical	83.6	–	–	–	–	–	–
Anti-cholinergics	6.5	–	–	–	–	–	–
Mood stabilizers	15	–	–	–	–	–	–
Antidepressants	33.6	–	–	–	–	–	–
Anxiolytics	12.1	–	–	–	–	–	–
Lithium	4.2	–	–	–	–	–	–
Intracranial volume (mm^3)	–	1 623 474.18	143 732.27	–	1 589 665.39	156 384.32	$F_{(1380)} = 4.82$, $p = .03$

(**b**)

	Low CR (*n* = 77)			Average CR (*n* = 137)			
	%	*M*	S.D.	%	*M*	S.D.	Group comparison
Gender	72.7	–	–	71.5	–	–	$\chi^2(1) = 0.04$, $p = 0.85$
Age	–	35.40	8.93	–	38.74	10.06	$F_{(1212)} = 0.5.89$, $p = 0.02$
Illness duration	–	12.52	8.77	–	15.22	9.37	$F_{(1212)} = 4.28$, $p = 0.04$
Illness onset age	–	22.88	7.07	–	23.53	5.43	$F_{(1212)} = 0.55$, $p = 0.46$
Current positive symptoms	–	2.09	2.77	–	1.62	2.42	$F_{(1190)} = 1.46$, $p = 0.23$
Lifetime positive symptoms	–	6.97	3.20	–	7.79	3.40	$F_{(1190)} = 2.66$, $p = 0.10$
Negative symptoms	–	29.91	18.75	–	21.50	14.80	$F_{(1201)} = 12.48$, $p = 0.00$

(*Continued*)

Table 1. (*Continued.*)

(b)

	Low CR (n =77)			Average CR (n = 137)			Group comparison
	%	*M*	S.D.	%	*M*	S.D.	
Diagnosis (% schizophrenia)	–	85.71	81.02	–	–	–	$\chi^2(1) = 0.76$, $p = 0.38$
Medications (% taking)	–	–	–	–	–	–	
Antipsychotics	87	–	–	86.9	–	–	$\chi^2(1) = 0.00$, $p = 0.98$
Typical	9.1	–	–	8.0	–	–	$\chi^2(1) = 0.07$, $p = 0.79$
Atypical	83.1	–	–	83.9	–	–	$\chi^2(1) = 0.03$, $p = 0.88$
Anti-cholinergics	9.1	–	–	5.1	–	–	$\chi^2(1) = 1.29$, $p = 0.26$
Mood stabilizers	11.7	–	–	16.8	–	–	$\chi^2(1) = 0.1.01$, $p = 0.32$
Antidepressants	35.1	–	–	32.8	–	–	$\chi^2(1) = 0.11$, $p = 0.74$
Anxiolytics	9.1	–	–	13.9	–	–	$\chi^2(1) = 1.05$, $p = 0.31$
Lithium	3.9	–	–	4.4	–	–	$\chi^2(1) = 0.03$, $p = 0.87$
Intracranial volume	–	1 620 822.79	144 617.01	–	1 624 964.37	143 743.13	$F_{(1212)} = 0.04$, $p = 0.84$

CR, cognitive reserve.

fluid reasoning decline that mirrored the pervasive age-related frontal volume and surface area changes evident in *all* patients both globally and regionally in the ventral inferior frontal gyrus. Thus, the burden of frontal brain pathology on fluid cognition varied as a function of CR.

This is the first study to integrate measures of both cognition and brain imaging in the context of age, to explicitly determine whether patients with below-average CR are less cognitively *resilient* to pathological brain change. Although existing studies explicitly focussed on CR in schizophrenia-spectrum samples have shown that patients with higher CR have better behavioural outcomes (Holthausen *et al.*, 2002; Leeson *et al.*, 2011; Wells *et al.*, 2015), the mechanism by which this occurs remained unknown in the absence of concurrent analysis of brain pathology or age-related change. That is, in past studies it was not clear whether more positive patient outcomes in those with higher CR reflected (1) a neuroprotective effect on both the brain and behaviour regardless of ones point in the lifespan/illness course, where a larger gap needed to be crossed to reach the threshold of significant impairment relative to those with lower CR, or (2) manifestation of a greater tolerance of age/illness-related pathology of the brain than those with lower CR. Our findings are supportive of the latter, where schizophrenia-spectrum patients showed an equivalent level of brain pathology irrespective of CR, but their cognitive outcomes varied by CR in the context of putative age-related decline. These findings are consistent with the effects of CR seen in neurological illnesses such as multiple sclerosis, where CR appears to protect against cognitive decline that is secondary to illness effects rather than confer gains to cognition itself (Sumowski *et al.*, 2009; Sumowski *et al.*, 2010*b*).

Relevantly, despite the average CR patient subgroup being older and having been exposed to the deleterious effects of the illness for longer, they exhibited less age-related cognitive deficits and less severe negative symptoms than the low CR patients. This further supports our hypothesis of a resilience effect of CR. Crucially, these findings shed light on seemingly discrepant results in past schizophrenia research showing a pathological change in the brain, but not cognition, as a function of age and illness progression. They also point to CR as an important modifier that could explain the inconsistent brain structure – cognition correlations that are seen across schizophrenia studies (Karantonis *et al.*, In preparation).

Our finding suggesting an absence of exaggerated frontal thickness reductions alongside exaggerated age-related frontal volume reductions in the whole patient group is also of interest, particularly in the context of marked frontal areal contraction with age that was entirely absent in healthy controls. This is contrary to the work in healthy individuals showing that exaggerated age-related volume loss of frontal regions is explained by cortical thinning, while age-related surface area changes in these regions are minimal (Lemaitre *et al.*, 2012; Storsve *et al.*, 2014). In our data, the main effect of surface area was *absent* while a pattern of increased surface area in younger patients and decreased surface area in older patients was *present* (online Supplementary Fig. S1). This suggests that absolute diagnostic differences in surface area are age-dependent in schizophrenia-spectrum illness and that the *trajectory* of surface area is highly relevant to its neuroanatomical and cognitive characterization.

Our findings should be considered in the context of the strengths of the study, which include the large sample of individuals diagnosed with a schizophrenia-spectrum illness with both cognitive and neuroimaging data; and the multi-site nature

Table 2. Diagnostic differences in age-related cognitive and brain structural change

	DV	Moderator IV Interaction	*b*	S.E.	*t*	*p*	95% Lower bound CI	95% Upper bound CI	Model summary	Model summary after addition of interaction term
Cognitive test[a]	*LNS*								$F_{(8373)} = 13.29$, $p = 0.00$, $R^2 = 0.23$	$F_{(1373)} = 2.62$, $p = 0.11$, R^2 change = 0.01
		Dx	2.73	0.30	9.22	0.00	2.16	3.31		
		Age	−0.03	0.01	−2.45	0.02	−0.05	−0.01		
		Age×Dx	−0.04	0.02	−1.61	0.11	−0.10	0.33		
	Matrix Reasoning								$F_{(8373)} = 10.52$, $p = 0.00$, $R^2 = 0.18$	$F_{(1373)} = 0.36$, $p = 0.55$, R^2 change = 0.00
		Dx	3.15	0.52	6.04	0.00	2.23	4.42		
		Age	−0.12	0.03	−4.79	0.00	−0.17	−0.07		
		Age×Dx	0.03	0.05	0.60	0.55	−0.06	0.12		
Volume[b]	*Global Frontal*								$F_{(8373)} = 148.23$, $p = 0.00$, $R^2 = 0.75$	$F_{(1373)} = 7.37$, $p = 0.01$, R^2 change = 0.01
		Dx	4116.20	1004.71	4.10	0.00	2168.85	6075.25		
		Age	−643.86	47.3828	−13.59	0.00	−736.49	−553.15		
		Age×Dx	248.90	91.66	2.72	0.01	76.22	423.71		
		Conditional effect of IV for Sz-spectrum patients	−753.32	72.09	10.45	0.00	−895.08	−611.57		
		Conditional effect of IV for HC	504.42	56.49	8.93	00	−615.50	−393.34		
	Caudal Middle Frontal								$F_{(8373)} = 26.73$, $p = 0.00$, $R^2 = 0.35$	$F_{(1373)} = 7.65$, $p = 0.01$, R^2 change = 0.01
		Dx	−54.62	7.79	−7.01	0.00	−86.95	593.32		
		Age	244.60	179.15	1.37	0.17	−69.79	−39.16		
		Age×Dx	41.73	15.09	2.77	0.01	13.22	71.18		
		Conditional effect of IV for Sz-spectrum patients	−72.97	11.75	−6.21	0.00	−96.08	−49.87		
		Conditional effect of IV for HC	−31.24	9.47	−3.30	0.00	−49.85	−12.63		
	Pars Orbitalis								$F_{(8373)} = 34.80$, $p = 0.00$, $R^2 = 0.44$	$F_{(1373)} = 7.54$, $p = 0.01$ R^2 change = 0.01
		Dx	210.12	58.01	3.62	0.00	96.07	323.11		
		Age	−21.05	2.52	−8.35	0.00	−26.08	−16.10		
		Age×Dx	13.28	4.83	2.75	0.01	3.95	22.86		
		Conditional effect of IV for Sz-spectrum patients	−26.89	3.80	−7.09	0.00	−34.36	−19.43		
		Conditional effect of IV for HC	−13.61	3.03	−4.49	0.00	−19.58	−7.65		

(*Continued*)

Table 2. (*Continued.*)

DV	Moderator IV Interaction	*b*	s.e.	*t*	*p*	95% Lower bound CI	95% Upper bound CI	Model summary	Model summary after addition of interaction term
Pars Triangularis								$F_{(8373)} = 28.63$ $p = 0.00$, $R^2 = 0.39$	$F_{(1373)} = 7.44$, $p = 0.01$, R^2 change = 0.01
	Dx	340.28	108.59	3.13	0.00	126.78	549.18		
	Age	−37.56	4.98	−7.54	0.00	−47.31	−27.72		
	Age×Dx	25.94	9.50	2.73	0.01	7.18	44.18		
	Conditional effect of IV for Sz-spectrum patients	−48.96	7.41	−6.61	0.00	−63.53	−34.39		
	Conditional effect of IV for HC	−23.03	6.09	−3.781	0.00	−35.00	−11.05		
Rostral Middle Frontal								$F_{(8373)} = 65.69$ $p = 0.00$, $R^2 = 0.63$	$F_{(1373)} = 4.78$, $p = 0.03$, R^2 change = 0.01
	Dx	983.83	306.26	3.21	0.00	392.68	1575.56		
	Age	−137.72	13.20	−10.43	0.00	−163.07	−112.43		
	Age×Dx	55.95	25.58	2.19	0.03	6.20	105.01		
Lateral Orbitofrontal								$F_{(8373)} = 56.04$, $p = 0.00$, $R^2 = 0.58$	$F_{(1373)} = 3.30$, $p = 0.07$, R^2 change = 0.00
	Dx	370.42	122.40	3.03	0.00	139.87	612.63		
	Age	−49.94	5.89	−8.47	0.00	−61.11	−39.18		
	Age×Dx	20.78	11.44	1.82	0.07	−1.37	43.12		
Superior Frontal								$F_{(8373)} = 91.26$, $p = 0.00$, $R^2 = 0.66$	$F_{(1373)} = 2.79$, $p = 0.10$, R^2 change = 0.00
	Dx	928.11	353.75	2.62	0.01	243.84	1633.18		
	Age	−168.4	15.92	−10.58	0.00	−198.86	−138.53		
	Age×Dx	52.16	31.18	1.67	0.10	−4.35	112.42		
Precentral								$F_{(8373)} = 48.63$ $p = 0.00$, $R^2 = 0.52$	$F_{(1373)} = 0.03$, $p = 0.86$, R^2 change = 0.00
	Dx	420.26	232.15	1.81	0.07	−3.59	851.64		
	Age	−83.90	9.39	−8.93	0.00	−102.58	−66.20		
	Age×Dx	3.21	18.39	0.17	0.86	−31.61	39.82		
Paracentral								$F_{(8373)} = 22.21$ $p = 0.00$, $R^2 = 0.30$	$F_{(1373)} = 2.76$, $p = 0.10$, R^2 change = 0.01
	Dx	−135.93	92.91	−1.46	0.14	−320.93	43.98		
	Age	−14.83	4.16	−3.57	0.00	−22.79	−6.95		
	Age×Dx	12.95	7.80	1.66	0.10	−1.96	28.17		

	Frontal Pole								$F_{(8373)} = 16.40$ $p = 0.00$, $R^2 = 0.23$	$F_{(1373)} = 2.36$ $p = 0.13$, R^2 change $= 0.01$
		Dx	100.82	29.73	3.39	0.00	42.07	158.16		
		Age	−10.26	1.29	−7.95	0.00	−12.74	−7.74		
		Age×Dx	3.95	2.57	1.54	0.13	−1.00	8.80		
	Pars Opercularis								$F_{(8373)} = 22.82$ $p = .00$, $R^2 = 0.37$	$F_{(1373)} = 1.16$, $p = 0.28$, R^2 change $= 0.00$
		Dx	391.46	120.24	3.26	0.00	155.67	625.07		
		Age	−37.70	5.46	−6.90	0.00	−48.43	−26.88		
		Age×Dx	11.39	10.56	1.08	0.28	−8.47	32.58		
	Medial Orbitofrontal								$F_{(8373)} = 57.04$ $p = 0.00$, $R^2 = 0.54$	$F_{(1373)} = .83$, $p = 0.36$, R^2 change $= 0.00$
		Dx	262.22	92.90	2.82	0.01	79.80	446.69		
		Age	−27.86	4.39	−6.34	0.00	−36.51	−19.32		
		Age×Dx	7.56	8.32	.91	0.36	−8.41	23.64		
Area[b]	*Global Frontal*								$F_{(8373)} = 171.47$ $p = 0.00$, $R^2 = 0.79$	$F_{(1373)} = 10.97$, $p = 0.00$, R^2 change $= 0.01$
		Dx	−314.00	310.37	−1.01	0.31	−931.38	271.27		
		Age	−67.99	13.84	−4.91	0.00	−94.65	−40.68		
		Age×Dx	85.87	25.93	3.31	0.00	38.26	138.49		
		Conditional effect of IV for Sz-spectrum patients	−105.75	21.2607	−4.97	0.00	−147.56	−63.95		
		Conditional effect of IV for HC	−19.89	15.38	−1.29	0.20	−50.12	10.35		
	Caudal Middle Frontal								$F_{(8373)} = 26.73$ $p = 0.00$, $R^2 = 0.36$	$F_{(1373)} = 8.73$, $p = 0.00$, R^2 change $= 0.01$
		Dx	−31.29	58.64	−0.53	0.59	−149.66	80.85		
		Age	−7.81	2.47	−3.16	0.00	−12.51	−3.16		
		Age×Dx	13.99	4.74	2.95	0.00	5.13	23.55		
		Conditional effect of IV for Sz-spectrum patients	−13.96	3.75	−3.72	0.00	−21.33	−6.58		
		Conditional effect of IV for HC	0.03	2.9185	0.01	0.99	−5.71	5.77		
	Pars Orbitalis								$F_{(8373)} = 61.04$ $p = 0.00$, $R^2 = 0.55$	$F_{(1373)} = 9.63$, $p = .00$, R^2 change $= 0.01$
		Dx	−1.36	13.23	−0.10	0.92	−27.32	24.50		
		Age	−1.82	0.57	−3.20	0.00	−2.96	−0.74		
		Age×Dx	3.43	1.11	3.10	0.00	1.27	5.54		
		Conditional effect of IV for Sz-spectrum patients	−3.33	0.85	−3.92	0.00	−5.0	−1.66		
		Conditional effect of IV for HC	0.10	0.71	0.14	0.89	−1.30	1.50		

(*Continued*)

Table 2. (*Continued.*)

	DV	Moderator IV Interaction	*b*	S.E.	*t*	*p*	95% Lower bound CI	95% Upper bound CI	Model summary	Model summary after addition of interaction term
	Pars Triangularis								$F_{(8373)} = 25.31$ $p = 0.00$, $R^2 = 0.39$	$F_{(1373)} = 7.91$, $p = 0.00$, R^2 change = 0.01
		Dx	24.68	35.2604	0.70	0.49	−41.91	95.71		
		Age	−4.67	1.48	−3.15	0.00	−7.55	−1.81		
		Age×Dx	8.00	2.84	2.81	0.01	2.54	13.45		
		Conditional effect of IV for Sz-spectrum patients	−8.19	2.15	−3.80	0.00	−12.42	−3.95		
		Conditional effect of IV for HC	−0.19	1.90	−0.10	0.92	−3.92	3.54		
Thickness[b]	*Global Frontal*								$F_{(8373)} = 21.26$ $p = 0.00$, $R^2 = 0.27$	$F_{(1373)} = 0.03$, $p = 0.86$, R^2 change = 0.00
		Dx	1.56	0.25	6.32	0.00	1.07	2.04		
		Age	−0.10	0.01	−9.17	0.00	−0.12	−0.08		
		Age×Dx	−0.00	0.02	−0.18	0.86	−0.05	0.04		
	Caudal Middle Frontal								$F_{(8373)} = 16.74$ $p = 0.00$, $R^2 = 0.22$	$F_{(1373)} = 0.05$, $p = 0.83$, R^2 change = 0.00
		Dx	0.1281	0.0250	5.12	0.00	0.08	0.18		
		Age	−0.0095	0.0010	−9.08	0.00	−0.01	−0.01		
		Age×Dx	−0.0004	0.0020	−0.22	0.83	−0.00	0.00		
	Pars Orbitalis								$F_{(8373)} = 11.41$ $p = 0.00$, $R^2 = 0.20$	$F_{(1373)} = 0.02$, $p = 0.90$, R^2 change = 0.00
		Dx	0.23	0.04	6.38	0.00	0.16	0.30		
		Age	−0.01	0.00	−6.58	0.00	−0.01	−0.01		
		Age×Dx	0.00	0.00	0.13	0.90	−0.01	0.01		
	Pars Triangularis								F (8373) = 16.23 $p = 0.00$, $R^2 = .25$	$F_{(1373)} = 0.00$, $p = 0.95$, R^2 change = 0.00
		Dx	0.16	0.03	5.65	0.00	0.10	0.21		
		Age	−0.01	0.00	−8.74	0.00	−0.01	−0.01		
		Age×Dx	0.00	0.00	0.07	0.95	−0.01	0.01		

Dx, diagnosis; HC, healthy control; Sz, schizophrenia.

Note that values for covariates are not displayed for brevity. Covariates, age and Dx were entered at block 1, and the interaction term was entered at block 2. Conditional effects of age on the DV for each group are only reported for those interactions surviving False Discovery Rate (FDR) correction. Confidence intervals for all but the conditional effects of age for each group are bias corrected.

[a] Controlling for site, gender.

[b] Controlling for site, intracranial volume.

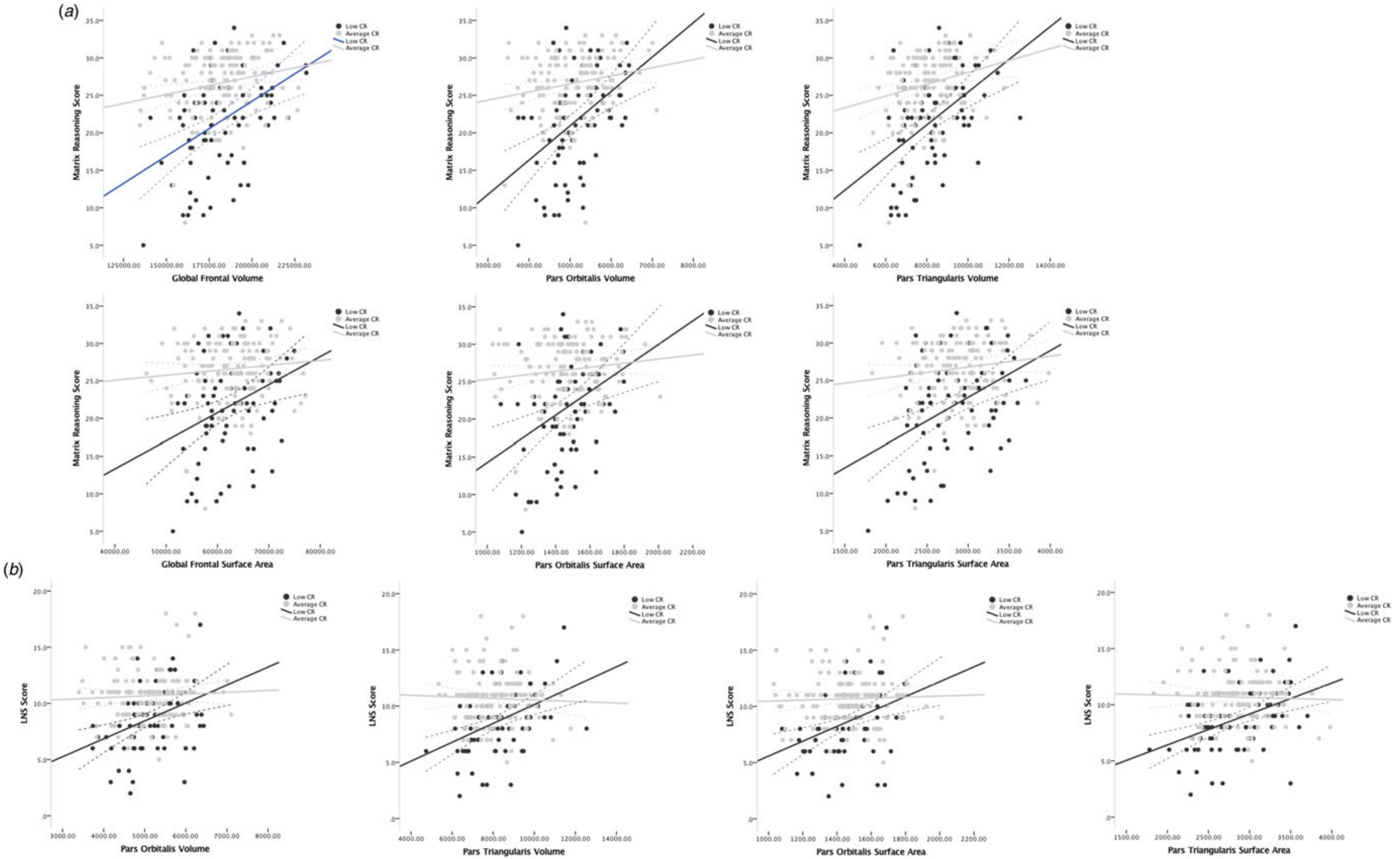

Fig. 1. Correlations between brain volume or surface area and cognitive performance for schizophrenia-spectrum patients with average or below average (low) cognitive reserve (CR). Panel A = fluid reasoning; panel B = working memory. Letter Number Sequencing = LNS. Volume is in mm^3, surface area in mm^2. Graphs depict cognitive tests for which brain region×CR interactions survived FDR correction.

Table 3. Moderation of age-related change in cognition fluid reasoning by CR in schizophrenia-spectrum patients

DV:	IV Moderator interction	*b*	s.e.	*t*	*p*	BC 95% Lower bound CI	BC 95% Upper bound CI	Model summary	Model summary after addition of highest order unconditional interaction term
Matrix Reasoning[a]								$F_{(7206)} = 12.30$, $p = 0.00$, $R^2 = 0.35$	$F_{(1206)} = 13.93$ $p = 0.00$, R^2 change = 0.05
	Age	−0.20	0.03	−6.04	0.00	−0.26	−0.13		
	CR subgroup	0 5.68	0.74	7.65	0.00	4.26	7.10		
	Age×CR subgroup	0.29	0.08	3.73	0.00	0.13	0.42		
	Conditional effect of age for low CR subgroup	−0.38	0.07	−5.46	0.00	−0.52	−0.24		
	Conditional effect of age for average CR subgroup	−0.10	0.03	−2.97	0.00	−0.16	−0.03		

CR, cognitive reserve; HC, healthy controls.

Note that values for covariates are not displayed for brevity. Confidence intervals for all but the conditional effects of age for each group are bias corrected.

[a] Controlling for site.

of the sample that speaks to geographic generalizability. Several limitations should also be considered, including the use of a cross-sectional experimental design to infer age-related change. Thus, it is possible that these findings may be partially attributable to the factors including cohort effects, or psychotropic medication use in the case of the schizophrenia-control comparisons. While longitudinal experimental designs are undoubtedly preferable in the exploration of this research question, they are also economically unfeasible and impractical owing to high attrition rates in psychiatric samples. In order to explore our hypotheses, the benefits of a large cross-sectional sample spanning key periods of adulthood was weighted against this and considered in the context of evidence showing that cross-sectional trends provide reliable estimates for longitudinally assessed age-related change within the frontal cortex specifically (Raz *et al.*, 2005; Raz and Lindenberger, 2011).

Other limitations include (1) the use of bilateral composite brain measures, such that CR moderation effects of left or right frontal regions were not explored. While this was done for conceptual and statistical reasons, it is possible that different effects for each hemisphere exist; (2) the use of different medications in the sample. The absence of distribution differences in the percentage of patients using different medication classes between CR subgroups suggests that medication may not have a key role in our findings; however, no dosing information was available which impeded our ability to clearly tease apart medication effects; (3) restriction of fluid cognition measures to the only two tests available in the ASRB that met our criteria, making it unclear whether different effects occur with other fluid tests sensitive to age-related decline (Ryan *et al.*, 2000); (4) use of data collected on a 1.5 Tesla MR scanner, which may have affected the signal to noise ratio and subsequent analysis outcomes; and (5) analysis of CR effects in only the schizophrenia-spectrum diagnosed individuals, leaving questions open about whether different CR effects would be evident in patients *v.* controls. Finally, CR is a broad construct that was operationalized by a composite proxy measure of crystallized intellectual functioning in this study. While this approach is justified and well-recognized in the literature, it is possible that different moderation effects may be seen with other proxy measures of CR that were not considered here, such as education or occupational functioning. Future research will do well to build on our work using several indices of CR and by following participants over the lifespan.

In sum, our findings indicate that associations between fluid cognition and brain volume and area are moderated by CR in schizophrenia-spectrum illness. As CR does not moderate pathological age-related increases in the magnitude of structural brain abnormalities as it does age-related increases in fluid reasoning deficits, it appears to confer resilience to the latter by negating the influence of the former through some form of compensation. While not tested in these data, it is possible that this compensation involves adaptive engagement of alternative neural regions and/or networks to maintain fluid cognitive performance when the usual structural neural resources are deteriorated (Stern, 2009).

Our findings thus suggest that CR, as proxied by crystallized intelligence, is a key factor in explaining individual differences in ageing effects on fluid reasoning in schizophrenia-spectrum illness. While genetic and neurodevelopmental influences on schizophrenia may affect the accumulation of CR in terms of such intelligence (Barnett *et al.*, 2006), evidence also shows that intellectual enrichment through education and early life reading

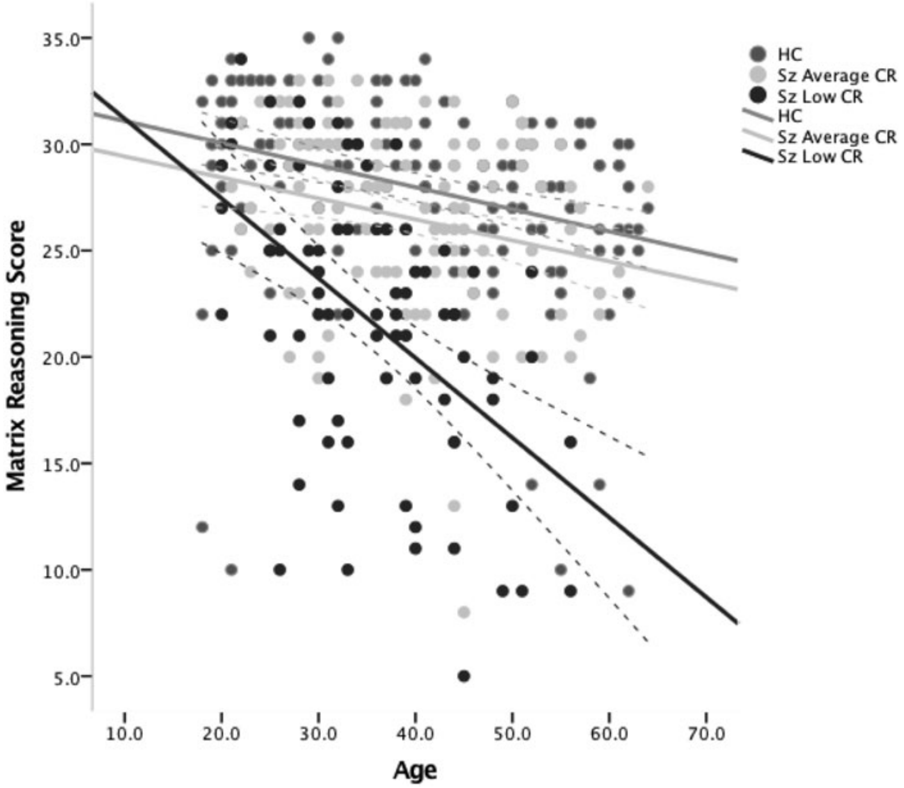

Fig. 2. Age-related decline in fluid reasoning in schizophrenia-spectrum (Sz) subgroups with low or average cognitive reserve (CR) *v.* healthy controls (HC). Age is reported in years.

engagement can boost later intelligence even after controlling for underlying genetic influences (Ramsden *et al.*, 2013; Ritchie *et al.*, 2015; Ritchie and Tucker-Drob, 2018). Thus, CR may represent a clinically important target that is amenable to change.

Notes

[1] Available ASRB cognitive data included the Repeatable Battery for Assessment of Neuropsychological Status (RBANS), LNS, Matrix Reasoning Test and Controlled Oral Word Association Test (COWAT) (Loughland *et al.*, 2010). Note that although the COWAT is an executive measure associated with frontal brain functioning, evidence suggests that age-related performance decline on this measure is evident in late life, at ages beyond those captured in the ASRB (Rodríguez-Aranda and Martinussen, 2006). Thus, it was not selected as a measure of interest in the current study.

[2] To avoid overcorrecting, gender was not used as a covariate for brain structure analyses since it was highly correlated with intracranial volume.

[3] Brain reserve and CR are not consistently related in schizophrenia and may not be synonymous (Van Rheenen *et al.*, 2018), hence we aimed to remove the effects of the former given our focus on the latter.

[4] Subsequent within schizophrenia-spectrum subgroup analyses were conducted with and without negative symptoms as a covariate. As findings remained unchanged, for brevity the results without negative symptoms as a covariate are presented.

[5] As a secondary check of the significant findings, we re-analysed the data using the CR variable as a continuous measure. The general pattern of interaction effects was the same, where significant and/or stronger relationships between brain measures and the cognitive tests; and between age and the cognitive measures were evident when CR was at 1SD below the mean, and sometimes at the mean, *v.* at 1SD above the mean. Similar to the dichotomous variable analysis, the relationship between age and the brain measures did not differ by CR. Given the similarity in the interaction effects across the two methods, for brevity these findings are not reported, although examples of the outcomes of some analyses are presented in online Supplementary Fig. S4 for demonstrative purposes.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719001417.

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