Title: Copy number deletion burden is associated with cognitive, structural, and resting-state network differences in patients with schizophrenia

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Total burden of copy number deletions has been implicated in schizophrenia risk and has been associated with reduced cognitive functioning. The current study aims to replicate the cognitive findings and investigate regional grey and white matter volumes. Moreover, it will explore resting-state networks for correlations between functional connectivity and total deletion burden. All imaging differences will be investigated for correlations with cognitive differences. Seventy-eight patients with chronic schizophrenia, who formed a subset of a large genome-wide association study (GWAS), were assessed for intelligence, 34 had structural magnetic resonance imaging, 33 had resting-state functional magnetic resonance imaging, and 32 had diffusion tensor imaging (DTI). Total deletion burden was negatively associated with IQ performance and positively associated with regional volumes in the striatum bilaterally and in the right superior temporal gyrus and white-matter in the corpus callosum. Correlations were identified between deletion burden and both hyper and hypoconnectivity within the default-mode network and hypoconnectivity within the cognitive control network. The functional connectivity correlations with deletion burden were also correlated with the IQ differences identified. Total deletion burden affects regional volumes and resting-state functional connectivity in key brain networks in patients with schizophrenia. Moreover, effects of deletions on cognitive functioning in may be due to inefficiency of key brain networks as identified by dysconnectivity in resting-state networks.

Schizophrenia is a highly heritable disorder with estimates of heritability as high as 80% [1]. Although recent studies have made considerable ground in explaining these genetic factors, much is left unexplained. The emerging picture is of a complex genetic architecture including both common and rare variants [2]. Of these rare variants, copy number variants (CNVs), especially rare (<1% frequency) deletions have been identified to a greater extent in schizophrenia compared with healthy controls [3]. Recently, several studies have looked to characterize these deletions in schizophrenia. Using a liberal definition of uncommon deletions (<3% frequency), a recent study [4] found cognitive ability to be inversely correlated with deletion burden in patients but not healthy controls, suggesting an interaction between deletions and other schizophrenia associated genetic and environmental risk variants, affecting cognitive functioning. They also found deletion burden to be positively correlated with ventricle size offering evidence that deletions may be impacting structural phenotypes relevant for disease risk. Another study [5] also found a higher rate of deletions that affect genes in patients with schizophrenia compared with healthy controls but found no evidence for an effect of global CNV burden or global deletion burden on total brain volume or grey and white matter volumes. A further study by the same group [6] found no link between total deletion burden and intelligence as measured by the Wechsler Adult Intelligence Scale (WAIS). However, this may be due to the inclusion of all deletions regardless of

frequency and could explain the discrepancy between their findings and the findings of Yeo et al [4].

Although current evidence suggests that total brain volume does not correlate with deletion burden, specific regional effects have not been explored. Regional grey-matter differences in patients with schizophrenia are diffuse and inconsistent between studies [7]. However, a meta-analytical approach of voxel-based morphometry (VBM) studies allowed the comparison of a large number of patients and controls to find regions consistently and robustly associated with disease. A large meta-analysis of 31 studies with 1195 schizophrenia patients and 1262 healthy controls found regional decreases in GM in the insula, anterior cingulate, left parahippocampal gyrus, left middle frontal gyrus, postcentral gyrus, and thalamus. Grey-matter increases were identified in the striatum [8]. Grey-matter volumes are heritable [9], although evidence for their potential as endophenotypes is inconsistent [10, 11].

In addition to volume differences, functional and structural connectivity may also provide clues as to how deletions influence the schizophrenia phenotype. Studies of resting-state functional connectivity have primarily identified global hypoconnectivity in patients compared with controls [12] although some studies have provided evidence for distinct patterns of hypo and hyperconnectivity in certain networks, including between striatal and prefrontal regions [13]. Evidence suggests that resting state networks are heritable [14, 15] and may be excellent candidates for endophenotypic research [16, 17]. Likewise, studies into structural white-matter integrity as measured by diffusion-weighted tensor

imaging (DTI) have found differences between patients with schizophrenia and healthy controls [18] and intermediate effects in well family members [19]. Fractional anisotropy (FA) differences are heritable [20] and mutations, especially rare deletions, may influence the connectivity between distinct brain regions rendering the brain less efficient, resulting in risk for psychosis.

In the following study, using a relatively conservative definition of rare deletions (occurring in <1% of our sample), we investigate the relationship between rare deletion burden and IQ, grey-matter as measured by voxel-based morphometry (VBM), white-matter integrity as measured by FA, and resting-state functional connectivity within the cognitive control and default mode networks.

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78 patients with schizophrenia were recruited from the Australian subsample of a genome-wide association study [21]. Individuals were comprehensively ascertained by trained clinicians using: (i) the Diagnostic Interview for Genetic Studies (DIGS) [22] (ii) Family Interview for Genetic Studies (FIGS) [23, 24]; (iii) information extracted from all available medical records; (iv) Narrative summary prepared by the interviewer and based on all information obtained from the DIGS, FIGS and medical records. The narrative summary was invaluable in recording the first-hand impressions of the interviewer. This facilitated diagnostic assessment by augmenting the DIGS interview information, especially when the participant's responses lacked clarity; (v) Best Estimate Final

Diagnosis (BEFD) [25] was assigned by two experienced research psychiatrists independently reviewing all available information then conferring to assign a consensus diagnosis; one of us (BM) reviewed every Australian case. Diagnostic inter-rater reliability was assessed using standard procedures [26]. Of the 78 patients, 32 were recruited for structural and functional neuroimaging. Of the remaining patients, the loss to follow up was due to being either unwilling or medically incapable of undergoing MRI.

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Quality control, identification and analytic methods have been described previously [21]. Briefly, DNAs were assayed using Affymetrix 6.0 genotyping arrays, which included approximately 900,000 single-nucleotide polymorphisms (SNPs) and approximately 900,000 copy number probes. CNVs were detected with the Birdseye module of the Birdsuite software package [27]. Quality control steps for CNV calls included: duplicate assays to develop narrow and broad call criteria, exclusion of calls involving telomeres and centromeres, immunoglobulin genes, and occurrence on one/two plates only. DNA samples were also subject to quality control steps. Plots of “regions of interest” calls were visually inspected with confirmation by a second calling algorithm Quantitative polymerase chain reaction (qPCR) confirmed the presence of selected CNVs. PLINK [28] pointwise analyses were conducted for all rare CNVs (with <1% frequency) and those of more than 100,000 bp.

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Most MGS DNAs were extracted from Epstein-Barr virus transformed lymphoblastic cell lines, and because EB transformation can create CNVs [29] we sought fresh blood samples from Australian MGS participants and extracted DNA from whole blood for confirmation of the CNVs documented in MGS. A proportion of the CNVs were confirmed for the purposes of another study using TaqMan Copy Number assays (Applied Biosystems) following recommended protocols on a StepOnePlus real-time PCR instrument (Applied Biosystems). Target assays were run simultaneously with reference assays that detect sequence that is known to have two copies in viable diploid human cells. Copy number for the targets was determined using the comparative C_T ($\Delta\Delta C_T$) method in which the C_T difference (ΔC_T) between target and reference sequences for each individual is compared to the ΔC_T value for control individuals that are known to have two copies of the target sequence. All CNVs were confirmed. In order to calculate the frequency of an individual event, CNVs were deemed the same if the overlap was greater than or equal to 50% of the union of the two events. Only deletions occurring in less than 1% of the Australian sample were considered rare. To enable confidence in the deletion calls, only those greater than 10,000bp were included.

[illegible]

Three clinical factors (positive, negative, mood) were computed based on the factor analysis carried out by Fanous et al [30] using the Lifetime Dimensions of Psychosis Scale (LDPS) [31].

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The Weschler Abbreviated Scale of Intelligence (WASI) [32] was used to assess global cognitive functioning. It contains four subtests of the full Weschler Adult Intelligence Scale 3rd Edition (WAIS-III) [33] and yields scores for verbal IQ (vIQ), incorporating the vocabulary and similarities subtests, and performance IQ (pIQ) incorporating the block design and matrix reasoning subtests. All four subtests combined, yield a full-scale IQ (fsIQ) score.

[illegible]

The National Adult Reading Test (NART) – 2nd edition [34] was used to measure premorbid IQ. It requires the reading of 50 non-regular words and predicts the participant's IQ prior to onset of psychotic symptoms.

[illegible]

Neuroimaging was performed using a 3-T Siemens Magnetom TrioTim at the Centre for Advanced Imaging at the University of Queensland. High-resolution T1-weighted 192 slices were acquired with 0.9mm^3 resolution, with a TR= 1900ms, TE = 2.3ms, TI= 900ms. Acquisition time was 4 minutes and 26 seconds. A 5-minute resting-state echo-planar imaging (EPI) scan (33 axial slice, matrix = 64x64 in plane resolution, slice thickness = 3.0mm, 150 volumes, TR= 2100ms, TE= 32ms) was acquired for each subject. Subjects were instructed to keep their eyes closed for the duration of the scan and try to relax and not think of anything in particular. They were instructed not to fall asleep. DTI images were acquired using transverse multislice spin echo, single shot, echo planar imaging (EPI) sequences with a TR= 9500ms, TE= 116ms, slice thickness of 3mm with no gap.

A 300mm field of view (FOV) was used with a voxel size of 2.3x2.3x2.5mm. Diffusion was measured along 64 directions (number of b-value= 2, low b-value= 0 and high b-value= 3000sec/mm^2. Acquisition time was 10 minutes 48 seconds and 60 slices were acquired.

Voxel-based morphometry

Voxel-based morphometry (VBM) was carried out using the VBM8 toolbox within SPM8, operating in MATLAB 7.10.0 (R2010a). T1 images were normalized to the MNI152 standardized space and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Proportional scaling was employed in order to account for any global differences in GM volume. Following preprocessing, sample images were inspected for homogeneity of covariance and manually checked to ensure correct registration to standard space. Preprocessed images were then smoothed using an 8-mm isotropic FWHM kernel. Multiple regression was performed with total deletion burden as predictor and age and sex included as covariates of no interest. Only voxels surpassing the voxel-level threshold of 0.001 uncorrected were included in the cluster level analysis, which was corrected for multiple comparisons at $p<0.05$ family-wise error (FWE) rate..

Fractional anisotropy

Fractional anisotropy (FA) analysis was carried out using FSL version 5.0.4. All data were skull stripped using BET [35]. Using FDT [36], eddy currents and simple head motion were corrected for by registering all data to the first image (b=0) with affine transformation and FA maps were created using DTIfit. Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-

Based Spatial Statistics [37]. Briefly, all FA data were aligned into a common space using the nonlinear registration tool FNIRT [38, 39]. All transformed images were averaged to create a mean FA image, which was thinned to create a mean FA skeleton, taking only the centres of white matter tracts common to all subjects. Voxel values were projected onto the skeleton by searching the local maxima along the perpendicular direction of the skeleton. The Randomise tool [40] within FSL was used for voxelwise permutation-based nonparametric inference. Contrasts were tested using 5000 permutations. Multiple comparisons were corrected using threshold-free cluster enhancement (TFCE). Significance was set at $p<0.05$, corrected for FWE rate. Deletion burden was included as a predictor in a linear model. Age and sex were included in the analysis as covariates of no interest. All variables were demeaned.

[illegible]

Preprocessing of the resting state data consisted of motion correction, slice-timing correction, band-pass filtering (0.008-0.04) as recommended by Bahia [41], coregistration to structural scan, spatial normalization to standard MNI space, and spatial smoothing using a 8mm Gaussian kernel.

Resting state analysis was carried out using the Conn toolbox [42] on MATLAB 7.10.0 (R2010a). Regions of interest (ROI) were selected in both the left and right dorsolateral prefrontal cortex (DLPFC) as hubs for the cognitive control network [43, 44]. This network has been implicated in schizophrenia, especially concerning executive functioning [45] with evidence for its status as a relevant endophenotype [46, 47]. ROIs in the posterior cingulate cortex (PCC) and medial

prefrontal cortex (mPFC) were included as central hubs of the default mode network [48]. This network is widely studied, with differences identified in patients with schizophrenia [49] and with evidence as a valid endophenotype [16, 17]. Again, only voxels surpassing the voxel-level threshold of 0.001 uncorrected were included in the cluster level analysis, which was corrected at $p<0.05$ FWE corrected.

[illegible]

All analysis was carried out in SPSS version 20.0.0. Spearman's rho correlation was employed for all analyses involving the IQ variables as it reduces the effect of outliers by limiting the outlier to the value of its rank. Marsbar v0.43 [50] was used to extract the regions of interest for the correlation with the IQ variables

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Seventy-eight patients with chronic schizophrenia (53 male and 25 female) were included in the cognitive analysis. There was no difference in total deletion burden dependent on sex (Male= 411,399.89 bp v Female = 578, 991.20 bp, U= 695, p=0.727), 34 underwent structural MRI, 33 underwent resting-state fMRI, and 32 underwent DTI. There was no relationship between total deletion burden and clinical factors in the total sample or in the reduced neuroimaging samples; age $r_s(76)= -0.092$, ns, positive symptoms $r_s(76)= -0.058$, ns, negative symptoms $r_s(76)= -0.087$, ns, mood symptoms $r_s(76)= -0.051$, ns..

[illegible]

As predicted, full-scale IQ was negatively correlated with total deletion burden, as was verbal IQ but not performance IQ. Performance on the NART premorbid IQ test was also negatively correlated (see table 1). Figure 1 provides a scatterplot highlighting the negative relationship between total deletion burden and full-scale IQ. When premorbid IQ was included as a covariate in a partial correlation, the association between full-scale IQ and total deletion burden was no longer significant, r=-0.10, p=0.39.

*** table 1 and figure 1 approximately here ***

[illegible]

The correlation between total deletion burden and total grey matter volume, rs(32)=-0.02, p=0.91), white matter volume, rs(32)=-0.23, p=0.19, and cerebrospinal fluid, rs(32)=-0.21, p=0.22) were all non-significant.

[illegible]

VBM identified four clusters of grey-matter that significantly positively correlated with total deletion burden (see figure 2). The clusters had peaks located in the left (1228 voxels) and right putamen (1394 voxels), left caudate nucleus (648 voxels), and the right superior temporal gyrus (567 voxels) (see table 2). There were no regions negatively correlated with total deletion burden which were significant. The cluster with a peak in the left putamen also contained voxels in the left hippocampus and left amygdala. The cluster in the

right putamen stretched to include the right olfactory cortex. The cluster in the left caudate nucleus included voxels in the left putamen and left rectal gyrus.

*** table 2 and figure 2 approximately here ***

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FA analysis found white-matter integrity was positively correlated with total deletion burden in three clusters situated in the body of the corpus callosum (see table 3.)

*** table 3 and figure 3 approximately here ***

[illegible]

Whole-brain analysis found significant clusters of reduced connectivity in the cognitive control network and default mode network in relation to deletion burden (see figure 4). Functional connectivity between the right DLPFC and right putamen decreased as deletion burden increased. Likewise, functional connectivity between the mPFC and the associative visual cortex and the PCC with the orbitofrontal cortex decreased as deletion burden increased. A positive correlation between deletion burden and functional connectivity between the mPFC and left iPFC was identified (see table 4).

*** table 4 and figures 4 and 5 approximately here ***

3.4 IQ – Neuroimaging Correlations

In order to explore the potential relationship between regional grey matter volumes,

white-matter integrity, resting-state functional connectivity and IQ, all regions of difference were entered into correlation analyses (see table 5). No significant correlations were identified between the grey or white matter measures but several of the resting-state functional connectivity measures were significantly correlated with IQ measures. Connectivity between the right DLPFC and the right putamen was positively correlated with performance IQ ($R_{(s)}$ = 0.446, p=0.009), and medial PFC to anterior visual cortex was significantly positively correlated to verbal IQ ($R_{(s)}$ = 0.360, p= 0.040), and full-scale IQ ($R_{(s)}$ = 0.375, p= 0.032). Connectivity between the medial PFC and the left iPFC was negatively correlated with performance IQ ($R_{(s)}$ = -0.377, p= 0.030).

*** Table 5 approximately here ***

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The current study found a negative correlation between total deletion burden and IQ, specifically verbal IQ. Regional grey-matter volumes were positively correlated with total deletion burden in the striatum and right STG as was white-matter integrity in the body of the corpus callosum. Resting-state functional connectivity was also correlated with total deletion burden with an inverse relationship between connectivity in the cognitive control and default mode networks. A positive correlation between these two networks was positively correlated with total deletion burden. Greater functional connectivity in the cognitive control network was positively correlated with performance IQ as was connectivity in the default mode network with verbal IQ. Stronger functional

connectivity between the default mode and cognitive control networks was negatively associated with performance IQ.

The finding of a negative correlation between IQ and deletion burden is consistent with a previous study by Yeo et al. [4] but in the current study this was only significant for verbal IQ and not performance IQ. As performance IQ is more a measure of fluid intelligence and verbal IQ more a measure of crystallized intelligence, rare deletions may be affecting language capacity and ability to learn from experience to a greater extent than the capacity to understand and apply abstract non-verbal concepts in problem-solving. The negative correlation identified total deletion burden and premorbid intelligence suggests that the deficits are consistent across development rather than a greater reduction around the onset of psychosis. As the correlation between total deletion burden and current IQ is no longer significant when premorbid IQ is included in the model, it suggests that there is no further cognitive decline after the onset of psychosis attributable to total deletion burden. A further consistency with Yeo et al. (2013) is the absence of a relationship with total grey and white matter volume. However, by investigating regional differences using VBM, we were able to identify several brain regions with grey-matter volumes significantly correlated with total deletion burden. Grey-matter volumes were positively correlated with total deletion burden in two regions, three clusters in the striatum and one in the right STG. Increased grey-matter in the striatum, predominantly the putamen, has previously been identified in patients with schizophrenia [8]. Striatal dysfunction is thought to be a fundamental element of schizophrenia with evidence for elevated dopamine levels in both the prodromal

and actively psychotic stages [51, 52]. Although increased putaminal volume has been associated with antipsychotic medication use [53-56] this is not consistent in the literature [57, 58].

Grey-matter volume of the right superior temporal gyrus, towards the right temporoparietal junction, was also positively correlated with total deletion burden. This region has been identified as abnormal in patients with schizophrenia with reduced volume compared with healthy controls [59]. The finding of a positive correlation between total deletion burden and grey-matter volume suggests that reduction in STG associated with schizophrenia is not associated with total deletion burden and may be associated with other genetic or environmental factors not examined in the current study.

Schizophrenia has been described as a disorder characterized by dysconnectivity between distinct brain regions [12]. Reduced connectivity within the prefrontal cortex between the right DLPFC and the right iPFC in relation to increased deletion burden suggests deletions may be affecting local connectivity within the PFC and having a detrimental effect on the cognitive control network. The function of the right iPFC remains poorly understood, but appears to have a role in cognitive control, especially inhibition and reorienting [60-62]. Interestingly, functional connectivity between the right DLPFC region and a cluster predominantly in the right putamen was negatively correlated with total deletion burden. Altered prefrontal-striatal connectivity has been identified in schizophrenia in both the ventral and dorsal circuits during rest [13] and during a working memory task [63]. As grey-matter within the striatum (putamen and

left caudate nucleus) was also correlated with total deletion burden, the reduced connectivity between the right DLPFC and right putamen further implicates these structures in the role of deletions in schizophrenia risk.

Aberrant functional connectivity in the default mode network has also been identified in patients with schizophrenia [64, 65] as well as those at high genetic risk [66]. In the current study, using the mPFC and PCC as seed regions of the DMN, we identified negative correlations between total deletion burden and connectivity between the PCC and the orbitofrontal cortex and between the mPFC and the bilateral associative visual cortex. A positive correlation was identified between deletion burden and connectivity between the mPFC and the left iPFC. Reduced anticorrelation between the mPFC and prefrontal regions during rest and task has been suggested to contribute to disturbances of thought and risk for schizophrenia [67]. The increased connectivity between a hub of the DMN and a region predominantly considered part of a cognitive control network, particularly relevant for selection of semantic information [68-70], might help explain the role of deletions in increasing risk and their effects on cognition.

An exploratory analysis to investigate whether IQ was correlated with any of the regions identified as having a relationship with total deletion burden, failed to find any significant relationships. However, functional connectivity between the right DLPFC and the right putamen was significantly positively correlated with performance IQ and functional connectivity between the mPFC and the associative visual cortex was positively correlated with verbal IQ and full-scale IQ. There was a negative correlation between connectivity between the mPFC

and the left iPFC and performance IQ. Prefrontal striatal connectivity has been linked with cognitive functioning in schizophrenia [71, 72] as well as in other populations [73-75]. The striatum and cortex are anatomically and functionally linked through several cortico-striatal-thalamic-cortical circuits [76] and pathologies of the striatum affect cognition in a similar manner to pathologies of the prefrontal cortex [77]. Although it is unknown why this network may be susceptible to deletions, one hypothesis relevant to schizophrenia surrounds the dopaminergic system. D2 receptor activity appears to play a key role in the metabolic rate of the striatum [78, 79] and dopamine is important in the regulation of the striatum by the prefrontal cortex [80]. A significant number of gene variants associated with schizophrenia are implicated directly or indirectly in the dopaminergic system [81] and it is a possibility that the rare deletions included in the present study are disproportionately affecting this pathway. The striatum is also a key region in the interaction of the dopaminergic and glutamatergic systems [82] with a recent genetic pathway analysis strongly implicating the glutamatergic system in schizophrenia [83].

Inability to deactivate the default mode network has been implicated in cognitive performance in the normal population [84, 85] as well as in patients with schizophrenia [86]. The negative correlation between IQ and connectivity between the mPFC and the left iPFC suggests that the association between cognition and total deletion burden may be partly caused by a failure to deactivate the default mode network. Although speculative, mutations may be reducing the efficiency of neural networks causing an inability to direct resources to the required network whilst inhibiting others. A positive correlation

between cognition and functional connectivity between the mPFC and the associative visual cortex further implicates the DMN in cognitive performance.

A prominent theory for schizophrenia posits that rare mutations lead to developmental instability and result in in a reduced capability to buffer or protect against other genetic mutations or environmental insults [87]. The two-hit hypothesis [88] also argues that risk for schizophrenia is due to an additive effect of genetic risk variants, where two or more hits are required for the disease to manifest. As total deletion burden has no cognitive effect in healthy controls [4], it suggests that these deletions are affecting the phenotype only in the presence of other environmental or genetic variants. Although an in-depth examination of the deletions was beyond the scope of this study, the fact that disparate deletions converged on common endophenotypes suggests that they are likely having an effect on fundamental processes of neuronal functioning, Several neuronal models of schizophrenia have been proposed based on genetic findings, such as the dysfunctional synapse [89] or the NMDA glutamate receptor [90]. Deletions, in the presence of other schizophrenia genetic risk factors, may be directly interrupting one or more of these systems resulting in reduced neural efficiency and dysfunctional connectivity, leading to greater cognitive dysfunction. However, CNVs may also be affecting the expression and regulation of genes other than those directly affected by the CNV itself [91]. Further research is required in order to characterize the effects of CNVs and their effects on neurophysiological functioning and role in schizophrenia risk.

Although in the current study we have provided evidence that deletions scattered around the genome converge on common endophenotypes, future large studies may be able to refine results by looking at specific deletions or group them according to their effects on certain biological pathways. Also, although cognition is not associated with deletion burden in healthy controls [4], this may not be the case with the neuroimaging phenotypes and should be investigated in future studies. Larger samples are always encouraged in studies aiming to characterize phenotypic affects of genetic variants in psychiatric disease and future studies should aim for a better distribution of total deletion burden. That said, the current study suggests that localized grey and white-matter volumes and in particular functional connectivity of key networks may offer interesting avenues of research into the effects of rare deletions in schizophrenia.

In sum, the current study replicated previous findings concerning the relationship between rare deletions and general cognition and extended the findings, identifying grey-matter volume differences in the striatum and right superior temporal gyrus and functional connectivity differences in cognitive control and default mode resting state networks. Cognition was not related to structure, but was related to functional connectivity within key resting-state networks.

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IQ correlates of total rare (<1% of sample) deletion burden as measured using the WASI and NART in patients with schizophrenia

	N	Mean (sd)	Spearman's rho	sig
Full-scale IQ	78	90.04 (15.52)	-0.267	
Verbal IQ	78	89.69 (17.83)	-0.303	
Performance IQ	78	91.79 (14.78)	-0.187	0.102
Premorbid IQ	77	96.00 (12.16)	-0.249	

Table 3. Regions positively correlated with total deletion burden in schizophrenia patients (N=34)

Basal Ganglia	L Putamen	-32	-9	-2	1228	0.000	0.001
	+ L Hippocampus	-32	-15	-11			
	+ L Amygdala	-30	6	6			
	R Putamen	15	9	0	1394	0.000	0.001
	+ R Olfactory cortex	27	6	-9			
	L Caudate nucleus	-6	12	13	648	0.003	0.027
	+ L Putamen	-15	10	3			
	+ L Rectal gyrus	-14	14	-8			
Temp Cortex	R STG	58	-39	18	567	0.004	0.044

STG = Superior temporal gyrus

□□□□□□. Regions with positive correlation between total deletion burden and fractional anisotropy (N=32).

Regions	voxels	Talaraich coordinates			Voxels	p
		□	□	□		
Corpus Callosum	left body	14	-12	34	74	0.049
	left body	13	11	28	68	0.049
	left body	15	-16	35	5	<0.050

□□□□□□. Regions with a significant correlation between total deletion burden and resting state functional connectivity in cognitive control and default mode networks.

Source ROI	hypo/hyper	Region peak	voxels	unc p	FWE p
Right DLPFC	hypo	Right Putamen	908	0.000	0.000
	hypo	Right inferior prefrontal cortex	390	0.002	0.000
mPFC	hypo	Bilateral Associative Visual Cortex	1182	0.000	0.000
	hyper	Left inferior prefrontal cortex	690	0.001	0.002
PCC	hypo	Orbitofrontal cortex	597	0.000	0.004

DLPFC= Dorsolateral prefrontal cortex
mPFC= Medial prefrontal cortex
PCC= Posterior cingulate cortex

Table 5. Correlation between IQ measures and grey-matter volumes and functional connectivity across default mode and cognitive control network.

	vIQ		pIQ		fsIQ	
	sp rho	sig	sp rho	sig	sp rho	sig
VBM (N=34)						
Left caudate nucleus	-0.191	0.279	0.032	0.859	-0.061	0.731
Left putamen	-0.109	0.540	-0.042	0.813	-0.051	0.774
Right putamen	-0.182	0.302	-0.039	0.828	-0.094	0.597
Right STG	-0.239	0.173	-0.022	0.902	-0.157	0.376
DTI FA (N=32)						
Left body CC	-0.167	0.362	-0.082	0.655	-0.150	0.411
RS – functional connectivity (N=33)						
rDLPFC-rPutamen	0.079	0.662	***0.446***	***0.009***	0.237	0.185
rDLPFC-riPFC	0.006	0.974	0.164	0.361	0.093	0.606
mPFC-liPFC	-0.109	0.547	***-0.377***	***0.030***	-0.255	0.152
mPFC-aVC	***0.360***	***0.040***	0.267	0.133	***0.375***	***0.032***
PCC-OFC	-0.051	0.779	0.068	0.706	-0.025	0.892

VBM= Voxel-based morphometry; DTI= Diffusion tensor imaging; FA= Fractional anisotropy; CC= Corpus callosum; RS= resting-state; rDLPFC= Right dorsolateral prefrontal cortex; riPFC= Right inferior prefrontal cortex; mPFC= Medial prefrontal cortex; liPFC= Left inferior prefrontal cortex; aVC= Associative visual cortex; PCC= Posterior cingulate cortex; OFC= Orbitofrontal cortex

Research Highlights

- Negative correlation between total copy number deletion burden and IQ
- Grey-matter differences associated with total deletion burden
- White-matter differences associated with total deletion burden
- Functional connectivity in two key networks is associated with deletion burden
- Cognitive functioning correlates with functional connectivity

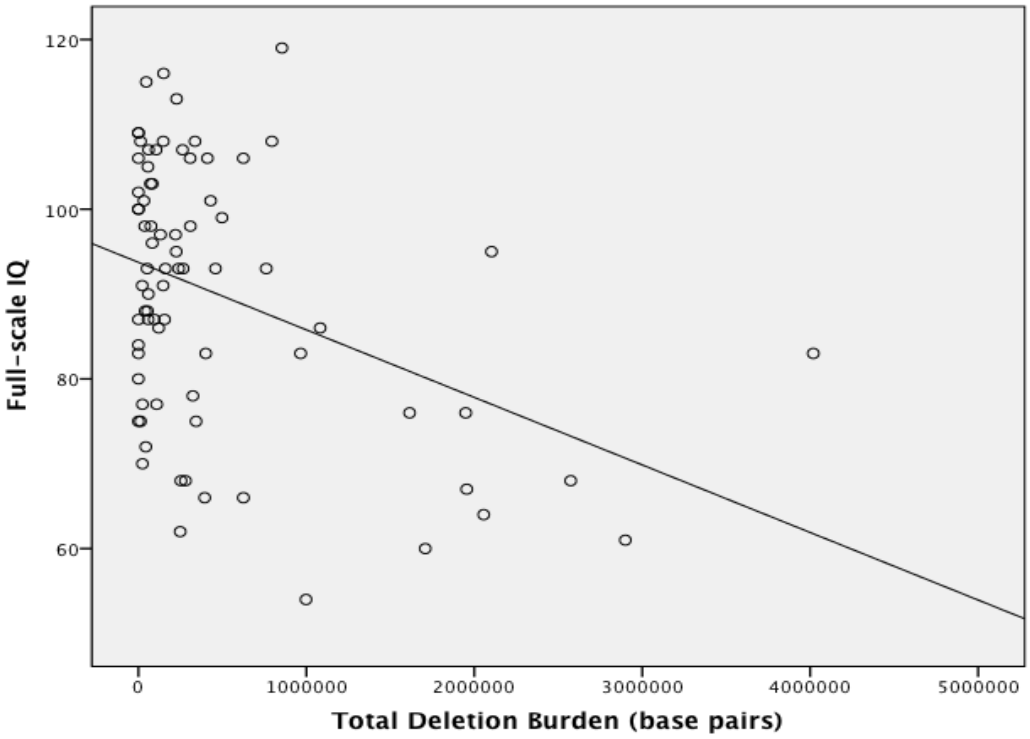

Figure 1. Scatterplot of the relationship between total rare (<1%) deletion burden (base pairs) and Full-scale IQ as measured by the WASI (N=78, rs(76)= -0.267, p=0.018)

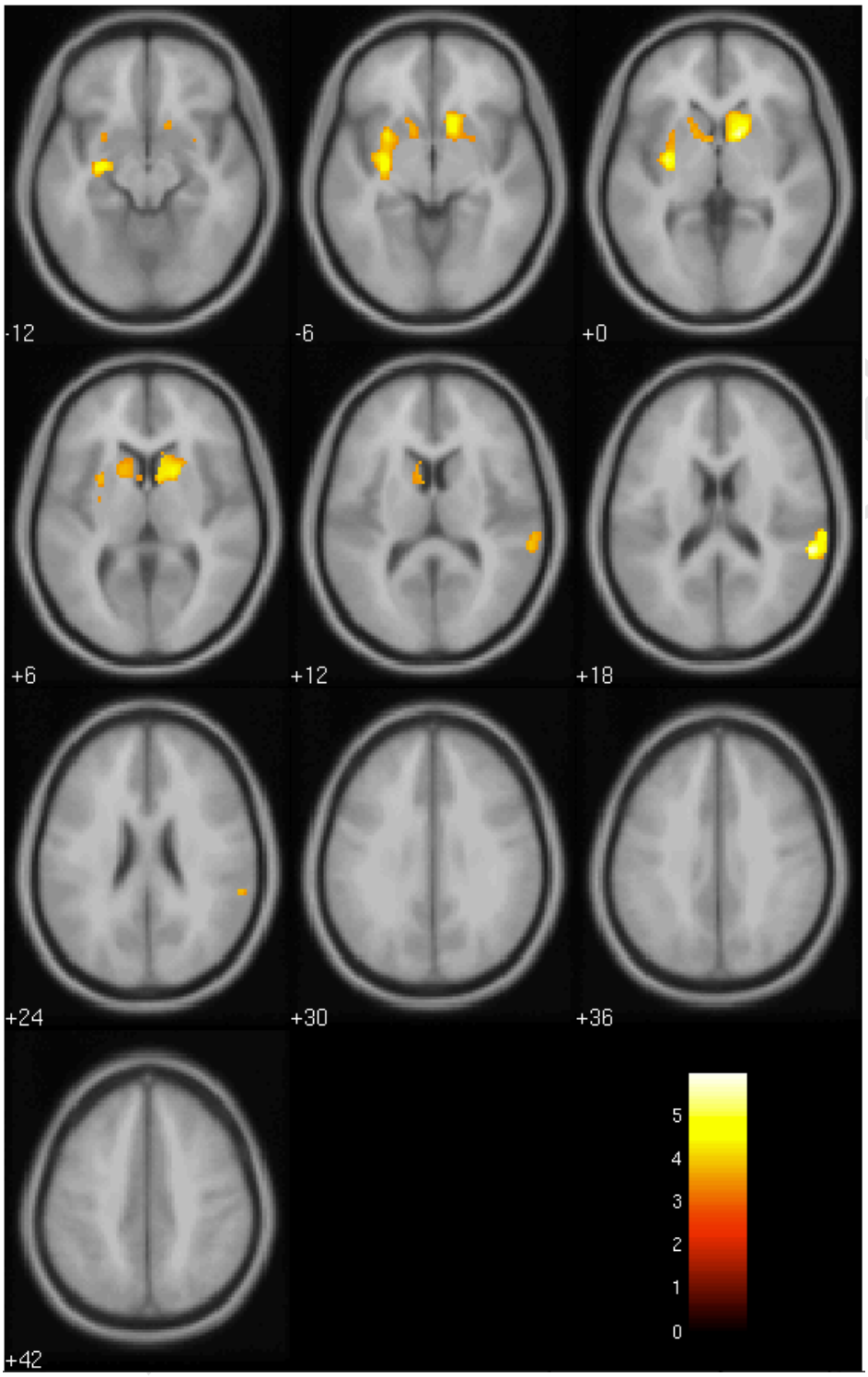

Figure 2. Regions with positive correlation between increased grey-matter volume and total rare (<1% of the sample) deletion burden. Clusters with peaks in the left and right putamen, left caudate nucleus, and superior temporal gyrus were identified (Numbers refer to axial slice number).

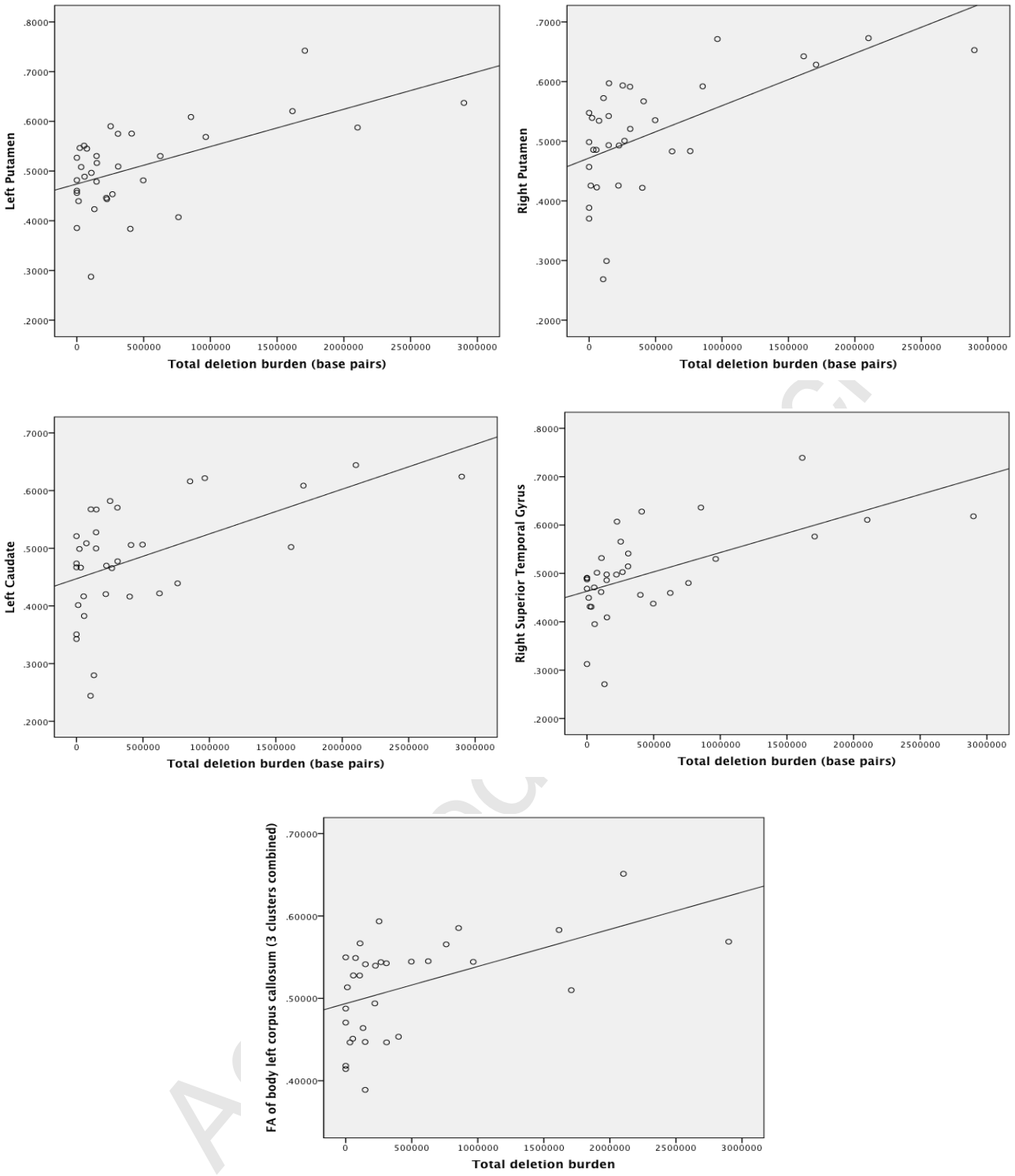

Figure 3. Scatterplots detailing the relationship between total rare (<1% of sample) deletion burden and grey matter volumes in the A) left and B) right putamen, C) left caudate nucleus, d) right superior temporal gyrus and e) white-matter integrity in the corpus callosum in patients with schizophrenia (N=34 for VBM & N=32 for DTI)

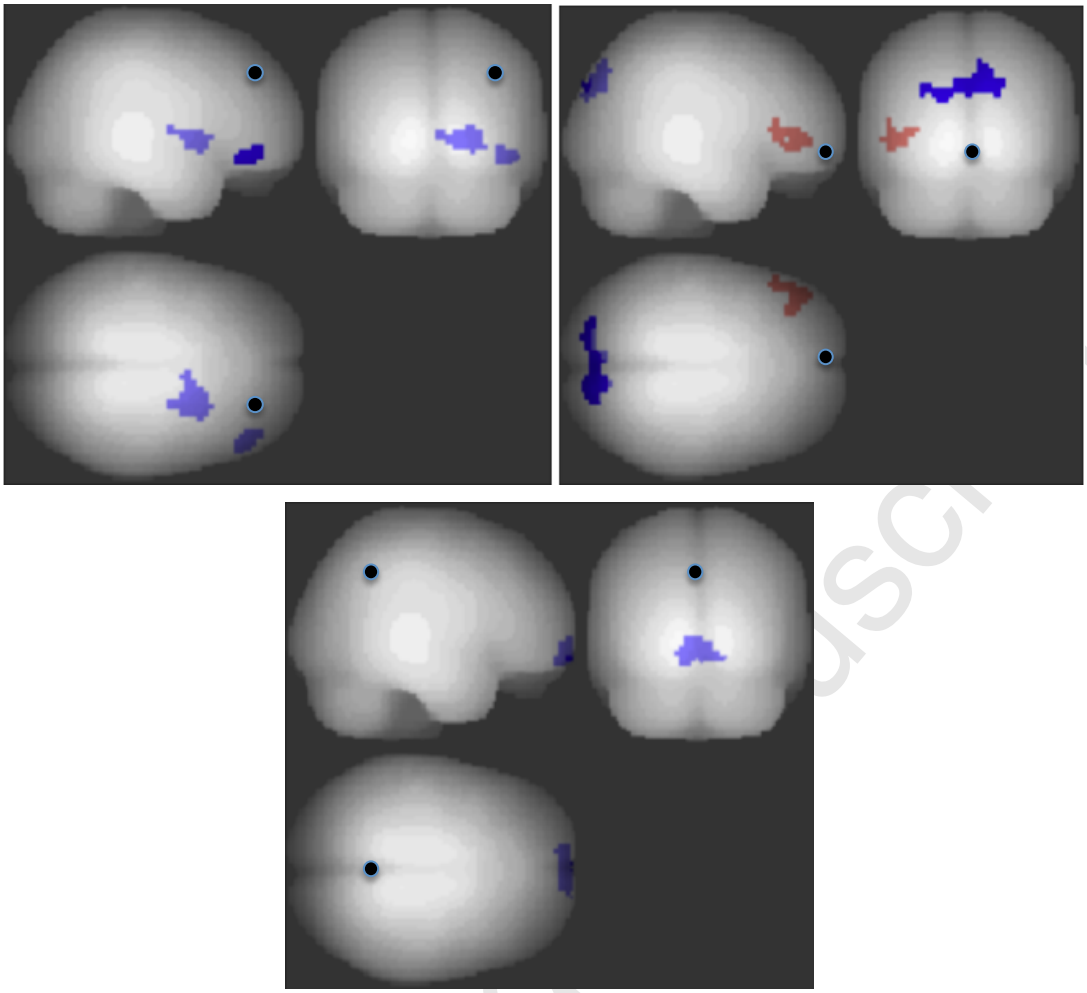

Figure 4. Regions with significant correlation between total rare (<1% of sample) deletions (base pairs) and connectivity with the A) right dorsolateral prefrontal cortex (rDLPFC), B) medial prefrontal cortex (mPFC), and C) posterior cingulate cortex (PCC). Fucntional connectivity between the rDLPFC and the right inferior prefrontal cortex (rIPFC) and right putamen; mPFC and bilateral associative visual cortex; and PCC and orbitofrontal cortex (OFC), were negatively correlated with total deletion burden; functional connectivity between the mPFC and the left inferior prefrontal cortex (lIPFC) was positively correlated with total deletion burden, in patients with schizophrenia (N=33).

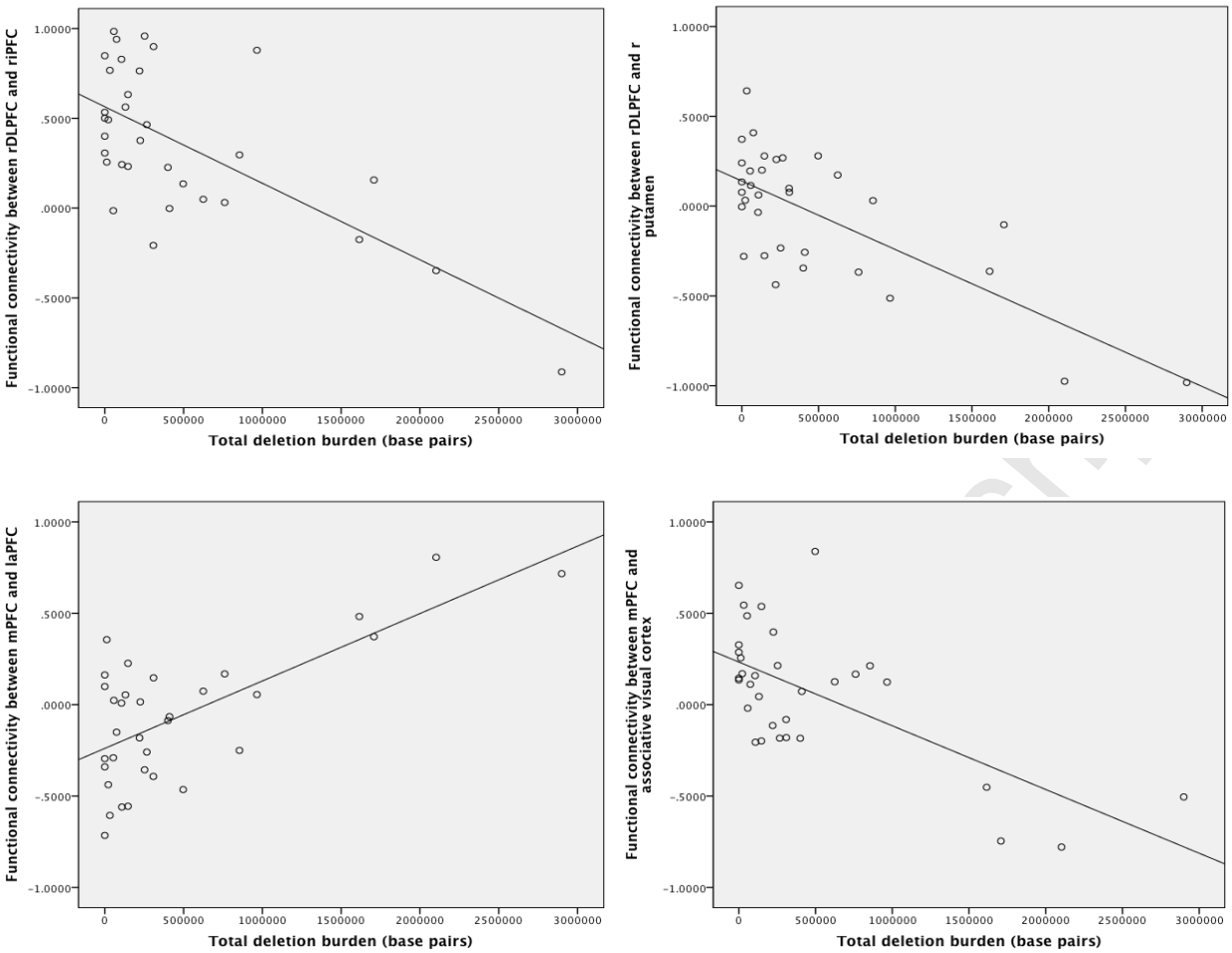

Figure 5. Scatterplots detailing the relationship between total rare (<1% of sample) deletion burden and resting-state functional connectivity between A) the right dorsolateral prefrontal cortex and the right inferior prefrontal cortex B) right dorsolateral prefrontal cortex and the right putamen C) medial prefrontal cortex and the left anterior prefrontal cortex D) and the medial prefrontal cortex and the associative visual cortex, in patients with schizophrenia (N=32).