

Online supplement

Reliability of delineation of prefrontal subregions

Four raters, masked to the group status of the participants, defined the sulcal boundaries of the superior, middle and inferior frontal gyri directly on the overall frontal white matter surface according to a set of anatomical rules (online Fig. DS1). Two of the four raters delineated the majority of the surfaces (75–80% for each region). There was no difference in the frequency distribution of raters across groups ($P > 0.4$ for all regions using a Monte Carlo estimate of Fisher's exact test). To establish inter- and intrarater reliability, all four raters delineated the superior, middle and inferior frontal gyrus regions twice on the same five participants (separated by a period of at least 2 weeks). We then quantified the overlap between two delineations (of a given region) using the Dice similarity coefficient, defined as the number of overlapping vertices divided by the average of the number of vertices in the two surfaces being compared. The overlap between raters (i.e. interrater reliability) was quantified separately for the first and second delineations, using one of the two primary raters as a 'reference' rater, thus yielding three overlap values (the three remaining raters) for each region, hemisphere and participant. For both the first and second delineations, every single interrater overlap value was greater than 83%, and the average overlap (across rater, hemisphere and participant) was 94–95% for each of the three regions. The intrarater reliability was similarly quantified by computing the overlap between the first and second delineations of each rater for each region, hemisphere and participant. Again, every single intrarater overlap

was greater than 82%, and the average was 95–96% for each region. These values indicate a high degree of consistency in the delineation of the boundaries of the three frontal gyri.

Males-only analysis

To examine whether the results for middle and inferior frontal gyrus volume might have been confounded because of gender differences across groups, we conducted a males-only analysis ($n = 67$) using a mixed model with group, hemisphere, group \times hemisphere, age, and non-prefrontal cortical grey matter volume as fixed effects. Volume of the middle frontal gyrus trended towards a main effect of group ($F(3,33) = 2.5$, $P = 0.08$), with volume in the schizophrenia group again reduced 8–12% relative to the schizophrenia-siblings group, the control-siblings group and the control group (least square means of 19.3, 21.9, 21.0 and 21.4 cm³ respectively). The effect of group on inferior frontal gyrus volume remained significant in the males-only analysis ($F(3,24) = 5.7$, $P = 0.004$), with the volume of the schizophrenia-siblings group again intermediate between the schizophrenia group and the two control groups (11.5, 12.8, 14.6 and 13.9 cm³ for the schizophrenia group, schizophrenia-siblings group, control-siblings group and control group respectively). Overall, these results for males-only are therefore consistent with the full cohort of participants. Lack of a sufficient number of females in the schizophrenia group prevented us from examining whether similar patterns would hold in a female-only cohort.

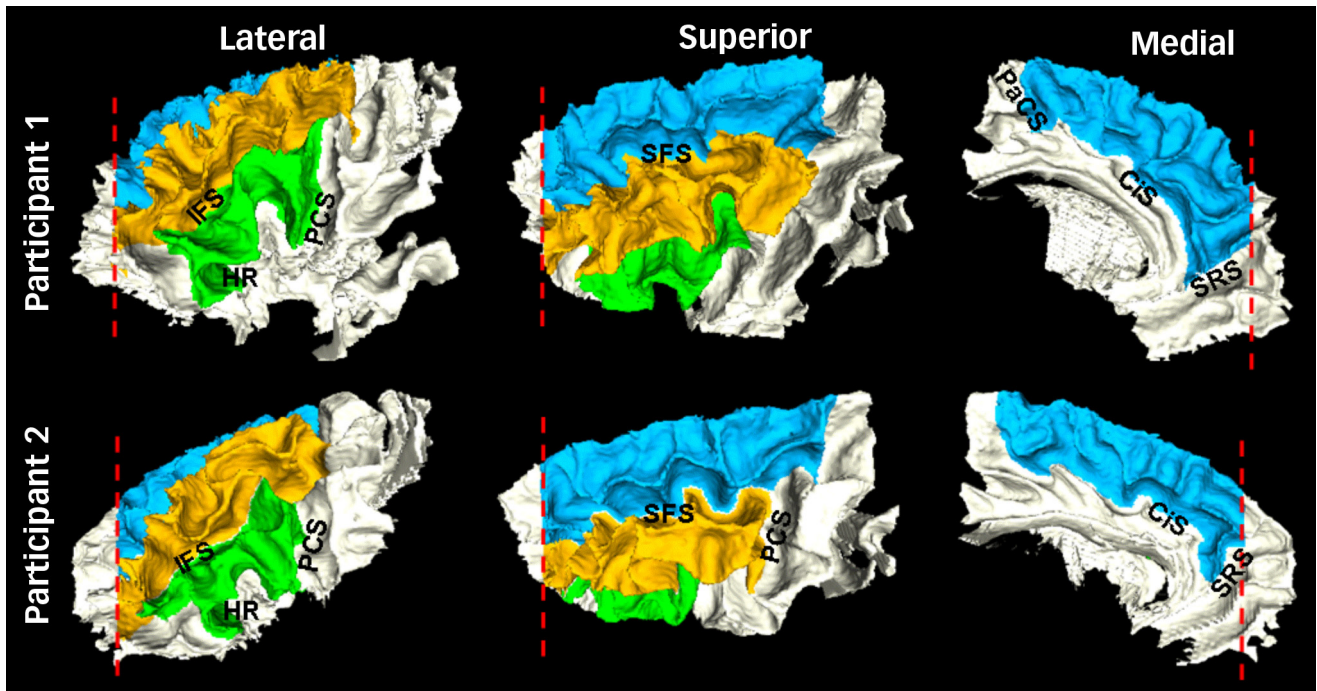


Fig. DS1 Examples of the parcellated white matter surface of the prefrontal cortex in two participants (green, inferior frontal gyrus; gold, middle frontal gyrus; blue, superior frontal gyrus; white, remainder of frontal white matter surface).

In general, the boundaries for the superior, middle and inferior frontal gyri followed the depth of prominent sulci, except when necessary to cross over the crown of a gyrus to bridge an interrupted sulcus. The posterior-lateral border for all three regions was the precentral sulcus (PCS), using the most posterior sulcus in cases of a forked termination or parallel sulci. The posterior-medial limit of the superior frontal gyrus was the paracentral sulcus (PaCS), which typically is an extension of the superior precentral sulcus and/or a branch of the cingulate sulcus. The infero-medial border of the superior frontal gyrus was the cingulate sulcus (CIS), so that the more superior paracingulate sulcus was considered part of the superior frontal gyrus if present.²² The antero-infero-medial border of the superior frontal gyrus was the superior rostral sulcus (SRS) whose posterior aspect was extended to intersect the cingulate sulcus if necessary to complete the infero-medial boundary of the superior frontal gyrus. Antero-laterally, there is no consistent sulcal boundary to delimit prefrontal cortex from the cytoarchitecturally distinct frontal pole. Therefore, a frontal pole plane (dashed red line) was defined as the coronal section (in an anterior/posterior-commissure oriented brain) passing through the anterior termination of the olfactory sulcus.²¹ This frontal pole plane defined the anterior limit of the superior and middle frontal gyri (regardless of any naturally occurring sulci that infrequently might be present). Frequently the superior rostral sulcus does not extend to the frontal pole plane and in these cases the antero-medial boundary of the superior frontal gyrus was completed by connecting the frontal pole plane to the superior rostral sulcus (along the superior edge where the surface transitions from the medial bank to the lateral convexity). Laterally, the superior frontal sulcus (SFS) and inferior frontal sulcus (IFS) defined the boundary between the superior/middle frontal gyri and middle/inferior frontal gyri respectively. The superior frontal sulcus nearly always intersects the frontal pole plane, but the inferior frontal sulcus typically had to be extended to the frontal pole plane to complete the antero-inferior border of the middle frontal gyrus. The inferior and anterior border of the inferior frontal gyrus, moving from posterior to anterior, progressed from (a) the circular sulcus in the operculum to (b) the sulcus immediately ventral to the horizontal ramus (HR) of the lateral fissure to (c) the most prominent dorsally-progressing sulcus immediately anterior to the anterior termination of the horizontal ramus to (d) the inferior frontal sulcus. Connections between these sulci were bridged when necessary. Using the nomenclature of other authors, the sulci from stages (b)–(c) of this progression would represent the lateral frontomarginal and/or radiate sulcus of Petrides & Pandya²³ or one of the variants of the fronto-orbital sulcus of Ono *et al.*²⁴ By this definition, the inferior frontal gyrus included a small portion of pars orbitalis immediately ventral to the horizontal ramus, but consisted primarily of pars opercularis and pars triangularis, similar to Buchanan *et al.*³