Title

Sulcal variability in anterior lateral prefrontal cortex contributes to variability in reasoning performance among young adults

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Abstract

Identifying structure-function correspondences is a major goal among biologists, cognitive neuroscientists, and brain mappers. Recent studies have identified relationships between performance on cognitive tasks and the presence or absence of small, shallow indentations, or sulci, of the human brain. Building on the previous finding that the presence of one such sulcus in the left anterior lateral prefrontal cortex (aLPFC) was related to reasoning task performance in children and adolescents, we tested whether this relationship extended to a different sample, age group, and reasoning task. As predicted, the presence of this aLPFC sulcus—the ventral para-intermediate frontal sulcus—was also associated with higher reasoning scores in young adults (ages 22-36). These findings have not only direct developmental, but also evolutionary relevance—as recent work shows that the pimfs-v is exceedingly rare in chimpanzees. Thus, the pimfs-v is a novel developmental, cognitive, and evolutionarily relevant feature that should be considered in future studies examining how the complex relationships among multiscale anatomical and functional features of the brain give rise to abstract thought.

Introduction

Identifying structure-function correspondences is a major goal across subdisciplines in the biological sciences. In neurobiology and cognitive neuroscience, there is broad interest in uncovering relationships between neuroanatomical features of the human brain and cognition—especially for structures in parts of the brain that are largely human-specific. Given that 60-70% of the human cerebral cortex is buried in indentations, or sulci (Zilles et al. 1988, 2013; Van Essen 2007), there is continued interest in the relationships among sulcal morphology, functional representations, and cognition. Previous work exploring this relationship has largely focused on the consistent and prominent sulci within primary sensory cortices (Yousry et al. 1997; Boling et al. 1999; Hinds et al. 2008; Cykowski et al. 2008; Li et al. 2010; Wandell and Winawer 2011; Sun et al. 2012; Benson et al. 2012). Nevertheless, recent work has begun to explore the small, shallow, and more variable sulci in association cortices that are not always present in a given hemisphere. For example, recent studies reveal relationships between the presence or absence of specific sulci in association cortices and individual differences in human cognitive abilities and clinical conditions (for review see Cachia et al. 2021), which could be mediated by differences in white matter architecture in relation to these sulcal features (Van Essen 1997, 2020; White et al. 2010; Zilles et al. 2013).

In the present study, we focus on the anterior lateral prefrontal cortex (aLPFC) given several sequential findings linking the individual variability of an aLPFC sulcus to cognitive performance. Specifically, our recent work implementing a data-driven approach on 12 LPFC sulci (Petrides 2019; Voorhies et al. 2021) showed that the morphology of an aLPFC sulcus (the para-intermediate frontal sulcus, pimfs) was the best predictor of performance on a widely used test of reasoning in a pediatric sample (ages 6-18) (Voorhies et al. 2021). However, since the pimfs is composed of two variably present components (Voorhies et al. 2021; Willbrand et al. 2022c), we then tested whether the presence of specific pimfs components was also related to

reasoning scores in a larger pediatric sample. Indeed, we found that the presence of the ventral pimfs component (pimfs-v) in the left hemisphere, specifically, was associated with better reasoning performance (Willbrand et al. 2022c). Here, we tested—and empirically support—the targeted prediction that this pattern of results across the four pimfs components (left and right pimfs-v and pimfs-d) holds across age groups and studies. Further, as in our pediatric sample, the presence or absence of left pimfs-v was linked to scores on a reasoning task but not to a control task that measures lower-level cognitive performance: processing speed. This extension of our previous result in children and adolescents to a separate sample of adults using different cognitive task variants is a notable finding, given a timely discussion among researchers regarding the reliability and generalizability of brain-behavior relationships (Marek et al. 2022; Gratton et al. 2022; Westlin et al. 2023). It is also notable because it converges with studies implicating aLPFC in various tests of reasoning, as discussed below. In addition to these tests of reasoning and processing speed, we had the opportunity in this sample to test whether performance on a test of working memory that requires transitive inference—a different form of reasoning—varies as a function of left pimfs-v presence. We discuss these findings in the context of (i) the role of aLPFC in reasoning, (ii) hypothesized relationships among the presence/absence of sulci, the morphology of sulci, and the efficiency of network communication contributing to performance on cognitive tasks, and (iii) the translational implications of aLPFC sulcal variability.

Materials and Methods

Participants

Data for the younger adult human cohort analyzed in the present study were taken from the Human Connectome Project (HCP) database (https://db.humanconnectome.org). Here we used 72 participants (50% female, 22-36 years old, 90% right-handed). These participants have also

been used in our previous work in the posterior lateral prefrontal and posteromedial cortices (Miller et al. 2021b; Willbrand et al. 2022b, 2023ba, c). HCP consortium data were previously acquired using protocols approved by the Washington University Institutional Review Board. Informed consent was obtained from all participants.

Imaging data acquisition

Anatomical T1-weighted (T1-w) MRI scans (0.7 mm voxel resolution) were obtained in native space from the HCP database as well as cortical reconstructions generated through the HCP's version of the FreeSurfer pipeline (Dale et al. 1999; Fischl et al. 1999; Glasser et al. 2013). All sulcal labeling and anatomical metric quantification was done on the cortical surface reconstructions of each participant.

Behavioral data

Overview

In addition to structural and functional neuroimaging data, the Human Connectome project also collected a wide range of behavioral metrics (motor, cognitive, sensory, and emotional processes) from the NIH toolbox (Barch et al. 2013) that illustrate a set of core functions relevant to understanding the relationships between human behavior and the brain (task details: https://wiki.humanconnectome.org/display/PublicData/HCP-YA+Data+Dictionary-+Updated+for+the+1200+Subject+Release#HCPYADataDictionaryUpdatedforthe1200SubjectRelease-Instrument). 71 of 72 participants in the present project had behavioral scores. Below we describe the three behavioral tests used.

Relational reasoning task

The ability to reason about the patterns, or relations, among disparate pieces of information—i.e., relational reasoning—has long been recognized as central to human reasoning and

learning (James 1890a, b; Cattell 1943). Tests of relational reasoning assess the ability to integrate and generalize across multiple pieces of information, and help to predict real-world performance in a variety of domains (Alexander 2016). Here, we used scores obtained for each participant on a measure of relational reasoning, the Penn Progressive Matrices Test from the NIH toolbox (Barch et al. 2013). This test is similar to the classic Raven's Progressive Matrices (Raven 1941), the WISC-IV Matrix Reasoning task (Wechsler 1949) used in our pediatric sample (Willbrand et al. 2022c), and other task variants that are ubiquitous in assessments of what is often termed "fluid intelligence." In this task, participants must consider how shapes in a 2x2, 3x3, or 1x5 stimulus array are related to one another, for example, an increase, across a row or column, in the number of lines superimposed on a circle. Specifically, participants must identify the abstract relations among items in the array (Carpenter et al. 1990) and select, among five options, the shape that completes the matrix. The task is composed of 24 different matrices, presented in order of increasing difficulty. Testing is discontinued after five incorrect choices in a row, and the total score is calculated as the number of correct responses.

Processing speed task

Participants also completed the Pattern Comparison Processing Speed Test from the NIH toolbox (Barch et al. 2013). This test was designed to measure the speed of cognitive processing based on the participant's ability to discern whether two adjacent pictures are identical as quickly as possible. Here, participants consider several possible differences (addition/removal of an element or the color or number of elements on the pictures). A yes-no button press is used to determine whether the two stimuli are identical, and the final score corresponds to the number of trials answered correctly during a 90-second period.

List sorting working memory test

Participants also completed the List Sorting Working Memory Test from the NIH toolbox (Barch et al. 2013). In this task, each participant sequences different visually and orally presented stimuli (alongside a sound clip and written text for the name of the item) in two conditions: 1-List and 2-List. In the former, participants order a series of objects (food or animals) from smallest to largest. In the latter, participants are presented with both object groups (food *and* animals) and must report the food in order of relative size in real life and then the animals in order of size. Notably, completing this task not only requires working memory manipulation and maintenance but also relational reasoning: to report the items in order of size it is necessary to compare pairs of stimuli and then engage in transitive inference across multiple items (Halford et al. 1998).

Morphological data

Defining the presence and size of the para-intermediate middle frontal sulcus

Individuals typically have anywhere from three to five tertiary sulci within the middle frontal gyrus (MFG) in LPFC (Miller et al. 2021a, b; Voorhies et al. 2021; Yao et al. 2022). The posterior MFG contains three of these sulci, which are present in all participants: the anterior (pmfs-a), intermediate (pmfs-i), and posterior (pmfs-p) components of the posterior middle frontal sulcus (pmfs). In contrast, the tertiary sulcus within the anterior MFG, the para-intermediate middle frontal sulcus (pimfs), is variably present. A given hemisphere can have zero, one, or two pimfs components (**Fig. 1**). As described in prior work (Petrides 2013, 2019; Willbrand et al. 2022c), the dorsal and ventral components of the pimfs (pimfs-d and pimfs-v) were generally defined using the following two-fold criterion: i) the sulci ventrolateral to the horizontal and ventral components of the intermediate middle frontal sulcus, respectively, and ii) superior and/or anterior to the mid-anterior portion of the inferior frontal sulcus.

We first manually defined the pimfs within each individual hemisphere with *tksurfer* (Miller et al. 2021b). Manual lines were drawn on the *inflated* cortical surface to define sulci

based on the most recent schematics of pimfs and sulcal patterning in LPFC by Petrides (2019), as well as by the *pial* and *smoothwm* surfaces of each individual (Miller et al. 2021b). Using multiple surfaces allows for the establishment of a consensus across surfaces and clearly determines sulcal boundaries. The location of the pimfs was confirmed by three trained independent raters (E.H.W., S.M., S.C.) and finalized by a neuroanatomist (K.S.W.). Although this project focused on a single sulcus, the manual identification of all LPFC sulci (2,877 sulcal definitions across all 144 hemispheres) was required to ensure the most accurate definitions of the pimfs components. For in-depth descriptions of all LPFC sulci, see (Petrides 2019; Miller et al. 2021a, b; Voorhies et al. 2021; Yao et al. 2022; Willbrand et al. 2022a).

The size of the pimfs was quantified as surface area (in mm^2), as a quantitative comparison to the qualitative metric of sulcal incidence. The surface area of each pimfs label was extracted with the mris_anatomical_stats FreeSurfer function (Fischl and Dale 2000). For participants with two pimfs components, the surface area was quantified as a sum of both components. For participants with one pimfs component, the surface area was quantified as that single component. As in previous work (Clark et al. 2010; Rollins et al. 2020), the surface area was set to zero for participants with no pimfs component. To control for individual differences in brain size, as in prior work (Willbrand et al. 2022c, 2023c; Hathaway et al. 2023), we normalized the surface area as a percent of the hemispheric surface area.

Probability map generation

As in prior work (Miller et al. 2020, 2021b; Voorhies et al. 2021; Willbrand et al. 2022b; Hathaway et al. 2022), sulcal probability maps were calculated to display the vertices with the highest alignment across participants for a given sulcus. The label file for each pimfs component was first transformed from the individual to the fsaverage surface. Once transformed to this common template space, the proportion of participants for whom a given vertex is labeled as the given pimfs component was then calculated. For vertices where the pimfs components

overlapped, we employed a “winner-take-all” approach. Here, the component with the highest overlap across participants was assigned to that overlapping vertex. With the publication of this article we provide un-thresholded maps and constrained versions of these maps (i.e., maximum probability maps, MPMs) to improve map interpretability. We show the 10% overlap MPMs in **Figure 1C**.

Analysis I: Comparing the incidence rates of the pimfs components

We first compared the incidence rates of the pimfs components—both as number of components (2 vs < 2) and as the presence of the specific pimfs component (dorsal vs ventral)—in each hemisphere with Chi-squared (χ^2) tests. Note that all statistical tests in the present project were implemented in R (v4.1.2; https://www.r-project.org/) and each set of analyses was corrected for multiple comparisons (with the false-discovery rate; FDR). Chi-squared tests were carried out with the chisq.test function from the stats R package.

Analysis II: Relating the presence and size of the pimfs to hemisphere, age, and gender

Prior work has indicated that the presence of variable sulci may differ between hemispheres and by participant gender (Paus et al. 1996; Clark et al. 2010; Wei et al. 2017; Amiez et al. 2019, 2021). Further, although sulcal patterning emerges before birth and is stable across the lifespan (Cachia et al. 2021), there could have been an age imbalance in pimfs incidence in our sample, purely by chance. So, too, could there have been an imbalance in pimfs incidence between genders in our sample. Thus, we sought to test for differences in incidence rates as a function of hemisphere, gender, and age. To this end, we implemented three binomial logistic regression GLMs with hemisphere (left, right), age, and gender (male, female), as well as their interactions, as factors for i) number of components [0 (fewer than 2 components), 1 (2 components)], ii) pimfs-d presence [0 (absent), 1 (present)], and iii) pimfs-v presence [0 (absent), 1 (present)]. Finally, in addition to these categorical analyses, we examined a continuous variable,

conducting a multiple linear regression for normalized total surface area of the pimfs component(s). GLMs were implemented with the glm function from the stats package. ANOVA χ^2 tests were applied to each GLM with the Anova function from the car package. Linear regressions were performed with the lm function from the stats package.

Analysis III: Relating the presence of the pimfs to reasoning performance

These analyses were performed on the 71 participants with behavioral scores. Participant age and gender were not considered in these analyses, as Analysis II showed that they did not differ in terms of pimfs presence (**Results**) or reasoning performance (*age*: ß = -0.01, p = 0.98; *gender*: χ^2 = 0.04, p = 0.84). We first ran two-sample t-tests to assess whether the number of components in each hemisphere (*two* vs *less than two*) related to reasoning performance (Penn Progressive Matrices Test). In the main text, we report differences between groups as the percentage increase in average scores (μ) from the "less than two" group to the "two" group with the following equation:

$$\frac{\mu(two) - \mu(less\ than\ two)}{|\mu(less\ than\ two)|} \times 100$$

Next, to determine if the presence of a specific pimfs component was related to reasoning performance, we ran additional two-sample t-tests to test for an effect of the presence of the pimfs-v and pimfs-d (*present* vs *absent*) in each hemisphere. As in the prior analysis, we report differences between groups as the percentage increase in μ from the "absent" group to the "present" group.

To determine whether the observed relationship between the left pimfs-v presence and reasoning (**Fig. 2B**) was impacted by differences in sample size between participants with and without this sulcus, we iteratively sampled a subset of participants from the left pimfs-v present group (N = 57) to match that of the left pimfs-v absent group (N = 14) 1,000 times and conducted a Welch's t-test for each sampling (to account for potential unequal distributions

when resampling). To evaluate the bootstrapped effect size, we report the median and 95% confidence interval for the effect size.

Next, given the wide age range (22-36 years old) and prior work indicating that reasoning performance peaks in the early 20s (McArdle et al. 2002), we implemented a 3-step procedure to ensure that age did not confound the results and to further evaluate the model fit. First, we ran a linear regression with left pimfs-v presence and age as predictors for reasoning in the full sample (N = 71 with reasoning scores). We then ran a Chi-squared test to compare the previously described regression model to one including age only. Second, to further confirm that age did not drive the effect of left pimfs-v presence on reasoning scores, we conducted variable-ratio matching on age (ratio = 3:1, min = 1, max = 5; optimal ratio parameters were based on the calculation in (Ming and Rosenbaum 2000) with the MatchIt package. Here, the distance between each member of each group (left pimfs-v presence, left pimfs-v absence) was calculated with a logit function:

$$Estimate\ \pi_i = Pr(noPimfsv_i = 1|X) = \frac{1}{1 + e^{-X_i\beta}}$$

$$Distance(X_i, X_j) = \pi_i - \pi_j$$

where X is participant age in groups without (i) and with (j) a left pimfs-v. Matches were based on a greedy nearest-neighbor interpolation where each participant in the smaller group (left pimfs-v absent) received 1-5 unique matches from the larger group (left pimfs-v present). Afterwards, a weighted linear regression was run in the matched sample, with left pimfs-v presence and age as predictors of reasoning, to confirm the robustness of our initial finding with the whole sample. Third, we employed a two-pronged analysis to assess and verify the unique variance explained by left pimfs-v presence, while accounting for age-related effects on reasoning. First, we ran a Chi-squared test to compare the previously described weighted-regression model to one with age only. Second, as described and implemented in prior work (Voorhies et al. 2021; Yao et al. 2022; Willbrand et al. 2022c), we fit these weighted-regression

models with repeated K-fold cross-validation (CV; five-fold, 10 repeats). Since these are nested models, the best fit was determined as the model with the lowest cross-validated $RMSE_{cv}$ and the highest R^2_{cv} value. We did not conduct this second procedure with gender given the lack of relation between gender and either 1) pimfs incidence (in this sample; **Results**) or 2) reasoning, both in this sample (**Materials and Methods**) and in a larger sample (N = 523) (Wendelken et al. 2017)**.**

T-tests were implemented with the t.test function from the R stats package. T-test effect sizes are reported with Cohen's d (d) metric. The median and 95% confidence intervals were calculated with the MedianCI function from the DescTools R package. Linear regressions were run with the lm function from the stats package. Variable-ratio matching was implemented with the matchit function from the MatchIt package.

<u>Analysis IV: Control behavioral analyses</u>

To ascertain whether the observed relationship between sulcal morphology and cognition is specific to reasoning performance, or generalizable to other measures of cognitive processing, we tested this sulcal-behavior relationship with measures of processing speed (Pattern Comparison Processing Speed Test) and list-sorting working memory (List Sorting Working Memory Test). Participant age and gender were not considered in these analyses, as they were not reliably associated with these tests of processing speed (*age*: ß = -0.05, $p = 0.18$; *gender*: $\chi^2 = 0.05$, $p = 0.84$) or working memory (*age*: ß = -0.001, $p = 0.98$; *gender*: $\chi^2 = 1.58$, $p = 0.62$). Two-sample t-tests were run to test for differences in performance on each measure as a function of left pimfs-v presence (*present* vs *absent*). We then used the Akaike Information Criterion (AIC) to compare the model predictions to reasoning predictions. Briefly, the AIC provides an estimate of in-sample prediction error and is suitable for non-nested model

comparison. By comparing AIC scores, we are able to assess the relative performance of the two models. If the ΔAIC is >2, it suggests an interpretable difference between models. If the ΔAIC is >10, it suggests a strong difference between models, with the lower AIC value indicating the preferred model (Wagenmakers and Farrell 2004; Burnham and Anderson 2004).

Given that there was also a significant correlation between the Penn Matrices and List Sorting test scores (correlation matrix between all three behavioral variables in **Supplementary Fig. 4A**), and that List Sorting performance varied as a function of left pimfs-v sulcal presence/absence (**Supplementary Fig. 3A**), we tested whether this relationship was mediated by reasoning performance, consistent with the hypothesis that the behavioral-sulcal association for List Sorting is explained by relational reasoning demands of this specific working memory task. To this end, we implemented a bootstrapped causal mediation analysis (1,000 simulations) to quantify the average causal mediation effect (ACME) of reasoning on the left pimfs-v presence and WM relationship (mediation diagram in **Supplementary Fig. 4B**).

T-tests were implemented with the t.test function from the R stats package. T-test effect sizes are reported with Cohen's d (d) metric. AIC values were quantified with the AIC function from the stats R package. The causal mediation analysis was implemented with the mediate function from the mediation package.

<u>Analysis V: Relating the size of the pimfs to reasoning performance</u>

As in prior work (Clark et al. 2010; Garrison et al. 2015; Cachia et al. 2018; Rollins et al. 2020; Willbrand et al. 2022c), to determine whether it was truly a discrete sulcal metric that mattered, we followed up by testing whether a related continuous metric—the size , i.e., normalized surface area, of the pimfs—was also related to reasoning performance. To do so, we implemented a multiple linear regression with normalized total surface area of the pimfs

component(s) in left and right hemispheres as predictors. Age and gender were not included, as they were not related to pimfs surface area (**Results**) or to reasoning performance. Linear regressions were implemented with the lm function from the stats package.

Results

The pimfs was variably present within the 144 younger adult hemispheres examined (four example hemispheres depicting different types of pimfs patterning are presented in **Fig. 1A**). It was more common for participants to have two components in a given hemisphere (*left*: 72.22% of participants; *right*: 77.78%) than either one (*left*: 25%; *right*: 20.83%) or none (*left*: 2.78%; *right*: 1.39%; χ^2s > 54, *p*s < 1.59e-12 in both hemispheres). When only one pimfs component was present, it was equally likely to be a dorsal or ventral component (χ^2s < 2, *p*s > .31 in both hemispheres; **Fig. 1B**). The number of pimfs components and the presence of the pimfs-d and pimfs-v did not differ between hemispheres (*p*s > .23; **Fig. 1B**) or by participant age and gender (*p*s > .23); nor did the surface area of the pimfs differ by these features (*p*s > .60). There were no significant interactions between these variables in any analysis (*p*s > .23). These incidence rates were similar to those observed in our previous sample of children and adolescents (Willbrand et al. 2022c). To aid future identification in other samples, we share probabilistic maps of the pimfs components (**Fig. 1C**).

Since the pimfs was variably present among younger adults, we statistically tested whether this variability was related to reasoning performance, as previously found for children and adolescents using a similar matrix reasoning task (Willbrand et al. 2022c). The presence of two pimfs components in the left hemisphere was associated with 21% better reasoning performance on average (mean ± std = 18.1 ± 4.21) relative to either one or none (mean ± std = 15.0 ± 5.59; t(69) = 2.54, p = 0.026, d = 0.67). This effect was not driven by the fact that individuals with two components tended to have a larger overall pimfs surface area, since pimfs surface area (normalized by hemisphere surface area) was not related to reasoning

(*p*s > 0.90; **Supplementary Fig. 1**). As previously found in children and adolescents (Willbrand et al. 2022c), this effect was driven by the presence or absence of the left pimfs-v: participants with a left pimfs-v (mean ± std = 18.1 ± 4.18) had on average 34% higher reasoning scores relative to those without it (mean ± std = 13.5 ± 5.57; t(69) = 3.44, *p* = 0.004, *d* = 1.03; **Fig. 2A**). Neither the right pimfs-v nor pimfs-d showed this effect (ts < 1.32, *p*s > 0.38, *d*s < 0.47). To account for the difference in sample sizes between adults with and without the left pimfs-v, we iteratively sampled a size-matched subset of the left pimfs-v present group 1,000 times. This procedure confirmed the behavioral difference (median [95% CI] *d* = 0.92 [0.90-0.94]; **Fig. 2B**). Finally, although reasoning performance was unrelated to age in this younger adult sample (ß = -0.01, *p* = 0.98), we conducted additional analyses confirming that age did not confound the results (**Supplementary Results**; **Supplementary Fig. 2**).

Finally, to assess the generalizability and/or specificity of this brain-behavior relationship, we tested whether left pimfs-v presence was associated with performance on the Pattern Comparison Processing Speed Test or the List Sorting Working Memory Test, as processing speed and working memory are foundational cognitive skills that support reasoning (Kail and Salthouse 1994; Fry and Hale 2000; Ferrer et al. 2013; Kail et al. 2016; Holyoak and Monti 2021). The List Sorting test requires reordering items according to their relative size, thus requiring relational reasoning, in the form of transitive inference, in addition to working memory (**Materials and Methods**). Participants with a left pimfs-v (mean ± std = 114 ± 12.3) had on average 9% better performance on the List Sorting test on average relative to those without it (mean ± std = 105 ± 11.5; t(69) = 2.42, *p* = 0.035, *d* = 0.72; **Supplementary Fig. 3A**). While significant, this effect was not as large as for the Penn Matrices task task ($\Delta AIC_{(\text{working memory - reasoning})}$ = 142.23). Additionally, the relationship between left pimfs-v presence and List Sorting scores was significantly mediated by Penn Matrices scores (via an indirect effect computed for 1,000 bootstrapped samples; average causal mediation effect [95% CI] = 6.13 [1.88, 10.88], *p* = 0.006; **Supplementary Fig. 4B**), further indicating that the relationship between left pimfs-v and

relational reasoning is the stronger one. By contrast, left pimfs-v presence was not related to processing speed test performance (t(69) = -0.24, *p* = 0.81, *d* = -0.07; **Supplementary Fig. 3B**).

Discussion

The pimfs exhibits prominent variability in humans that is robustly linked to variability in relational reasoning performance across age groups: in young adulthood, as reported here, and in childhood and adolescence (ages 6-18), as reported previously (Willbrand et al. 2022c). The pattern of results across the two studies was strikingly similar, with left pimfs-v–but not right pimfs-v or left or right pimfs-d—implicated in a test of matrix reasoning. We found that children and adults with left pimfs-v had on average 28% and 34% higher reasoning scores, respectively, than those without it. In the same sample of younger adults, we recently showed that pimfs-v and pimfs-d exhibited different patterns of large-scale resting-state functional connectivity, whereby the pimfs-v was associated with control-related networks and the pimfs-d was associated with attention-related networks (Willbrand et al. 2023a). Thus, the present behavioral dissociation between these sulcal components likely stems from participation in different brain networks and cognitive functions. In addition to showing that the sulcal-behavioral relationship did not generalize to all sulci, we showed that it did not generalize to all cognitive tasks. In both the adult and pediatric samples, the incidence of left pimfs-v was related to a test of relational reasoning but not processing speed—a finding suggesting some degree of specificity in this anatomical-behavior relationship. Notably, the studies covered different age ranges—ages 22-36 vs. 6-18—and also used different cognitive measures [our previous study used WISC-IV Matrix Reasoning task (Wechsler 1949) and the Woodcock-Johnson Psychoeducational Battery Cross Out task (Brown et al. 2012)]. Thus, taken together, these findings establish a robust anatomical-behavioral association that does not generalize to all

forms of cognition or to all sulci, which converges with the observed functional dissociation between neighboring sulcal components (Willbrand et al. 2023a).

In addition to the abovementioned cognitive measures, both studies also included tests of working memory. Children and adolescents completed a standard task involving repeating a series of numbers in order or in reverse order [WISC-IV Digit Span WM task (Wechsler 1949)]. By contrast, adults completed a novel List Sorting task that requires participants to reorder a series of WM representations according to their size in real life. Size ordering, an example of transitive inference, is recognized as a form of relational reasoning (Halford et al. 1998). We found an effect of left pimfs-v presence on List Sorting in adults, but not on Digit Span in children. We posit, based in part on prior fMRI findings (Wendelken et al. 2008a), that the apparent discrepancy between these findings relates to substantive differences in task demands: namely, that List Sorting requires relational reasoning. This hypothesis remains to be tested.

The anatomical-behavioral link reported here and in our previous study (Willbrand et al. 2022c) appears to provide converging evidence with fMRI research on relational reasoning. Neurosynth, a meta-analytic tool drawing on over 14,000 fMRI studies (Yarkoni et al. 2011), shows that the most probable location of the pimfs-v includes, and forms the dorsal border of, a functionally defined area in aLPFC often referred to as rostrolateral prefrontal cortex that has been implicated in higher relational reasoning (Christoff et al. 2001; Kroger et al. 2002; Bunge et al. 2005; Wendelken et al. 2008a, b; Crone et al. 2009; Wendelken and Bunge 2010; Dumontheil et al. 2010; Krawczyk 2012; Vendetti and Bunge 2014; Hobeika et al. 2016; Hartogsveld et al. 2018; Assem et al. 2020; Holyoak and Monti 2021) (**Supplementary Fig. 5**). Future research should investigate this intriguing overlap, directly testing the spatial correspondence between the pimfs-v and reasoning-related task activations in individual participants. Future research should also address why, given these converging lines of evidence, some neuropsychological studies show that damage to aLPFC affects reasoning task

accuracy (Urbanski et al. 2016; Bendetowicz et al. 2018) while others have not (Burgess 2000; Tranel et al. 2008; Waechter et al. 2013).

While we focus on the pimfs in the present study, and do show a sizeable relationship to high-level cognitive performance, we hypothesize that variable morphology of this sulcus reflects and/or drives neural differences more broadly. Indeed, the presence/absence and morphology of sulci are theorized to be anatomically linked to cortical white matter development (Sanides 1962, 1964; Van Essen et al. 2014; Reveley et al. 2015; Van Essen 2020; Cottaar et al. 2021; Miller et al. 2021b; Cachia et al. 2021), and the presence of sulci relates to changes in the local cytoarchitectonic organization of gray matter (Amiez et al. 2021). Neural efficiency is the foundation of our hypothesis regarding relationships between sulcal anatomy and reasoning observed in these and other studies (Voorhies et al. 2021; Willbrand et al. 2023b). Specifically, we (and others; Garrison et al., 2015) hypothesize that these sulcal-behavioral relationships stem from individual differences in white matter projections and, in turn, the distributed functional brain networks that underlie higher-level cognition. Future research should investigate this multiscale, mechanistic relationship describing the neural correlates of reasoning, integrating structural, functional, and behavioral data.

Given that the pimfs is rare in non-human hominoids (Hathaway et al. 2022; Amiez et al. 2023), the presence of left pimfs-v could reflect evolutionarily expanded white and gray matter properties that enhance neural communication in this higher cognitive area (Van Essen 1997, 2020; White et al. 2010; Zilles et al. 2013). Additionally, given (i) evidence implicating sulcal incidence to cognition in chimpanzees (Hopkins et al. 2021) and (ii) hypotheses that the disproportionate expansion of aLPFC in humans compared to non-human primates contributes to species differences in reasoning capacity (Semendeferi et al. 2001; Vendetti and Bunge 2014), another testable hypothesis is whether the incidence of the pimfs is also cognitively relevant in chimpanzees.

While the cognitive relevance of the pimfs has only been examined in neurotypical populations (Voorhies et al. 2021; Yao et al. 2022; Willbrand et al. 2022c), numerous studies have shown that variations in sulcal incidence are clinically relevant (Yücel et al. 2002, 2003; Le Provost et al. 2003; Fornito et al. 2006, 2008; Shim et al. 2009; Meredith et al. 2012; Gay et al. 2017; Nakamura et al. 2020; Harper et al. 2022). Thus, the present results raise the question: Does the incidence and/or morphology of the pimfs differ in clinical populations exhibiting impaired reasoning? Schizophrenia is a prime candidate for future investigations, given that it is marked by impaired reasoning (Weickert et al. 2000; Bowie and Harvey 2006; Keefe and Harvey 2012; Zhang et al. 2017; Alkan et al. 2021; McCutcheon et al. 2023) and has repeatedly been associated with altered aLPFC structure and function (Barnes et al. 2011; Tu et al. 2012; Kaplan et al. 2016; Kang et al. 2018; Pillinger et al. 2019; Nazli et al. 2020; Shinba et al. 2022). To help guide future studies examining the cognitive, evolutionary, developmental, clinical, and functional relevance of the pimfs, we share probabilistic predictions of the pimfs from our data (**Fig. 1C**).

In conclusion, we have shown that left pimfs-v presence is cognitively relevant in young adulthood, which extends previous work showing that left pimfs-v presence is cognitively relevant in childhood and adolescence. The combination of findings across studies establishes pimfs-v presence/absence as a novel developmental, cognitive, and evolutionarily relevant feature that should be considered in future studies in neurotypical and clinical populations examining how the complex relationships among multiscale anatomical and functional features of the brain give rise to abstract thought.

Figures

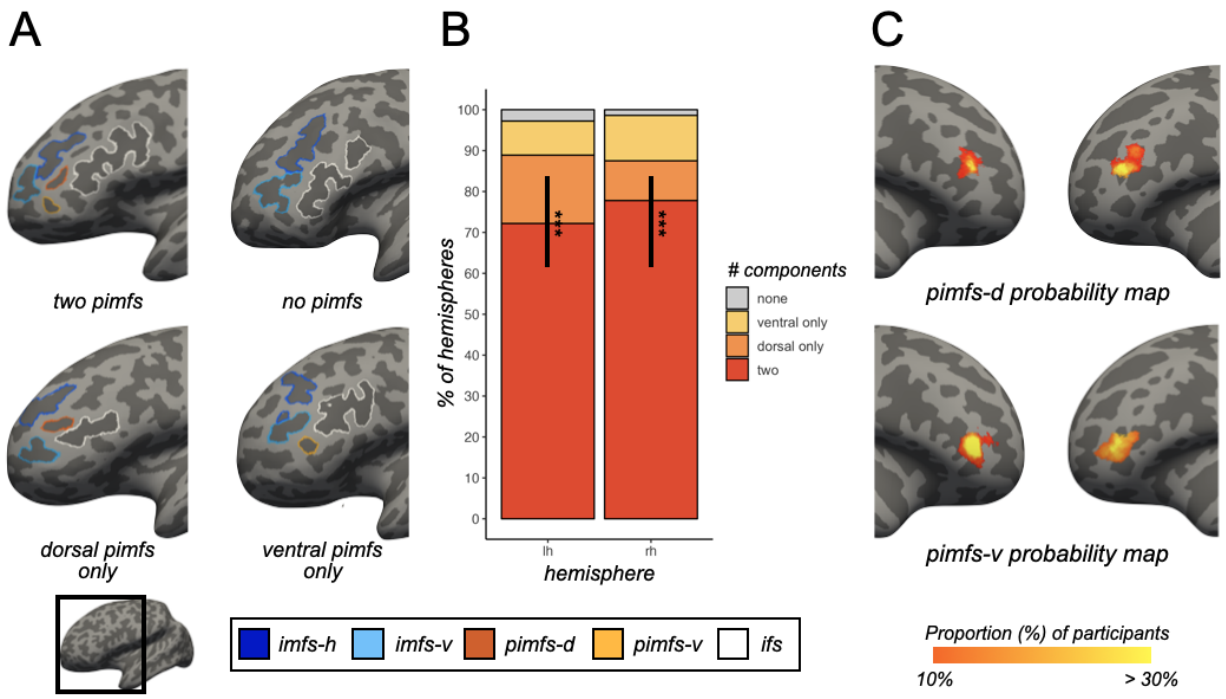

Figure 1. The para-intermediate frontal sulcus (pimfs) is variable across individuals and hemispheres. A. Inflated left hemispheres (sulci: dark gray; gyri: light gray; cortical surfaces are not to scale) depicting four types of the pimfs: (i) both pimfs-v/d present, (ii) neither present, (iii) pimfs-d present, (iv) pimfs-v present. Prominent sulci surrounding the pimfs are shown: horizontal (imfs-h) and ventral (imfs-v) intermediate frontal sulci and inferior frontal sulcus (ifs; see legend). **B.** Stacked bar plot depicting pimfs incidence in left (lh) and right (rh) hemispheres (N = 72; see rightward legend). **C.** Maximum probability maps (MPMs) for pimfs-d (top) and pimfs-v (bottom) on the inflated *fsaverage* cortical surface (left surfaces: rh; right surfaces: lh). For visual clarity, the MPMs were thresholded at 10% overlap across participants (the warmer the color, the higher the overlap). (*** $p < 0.001$).

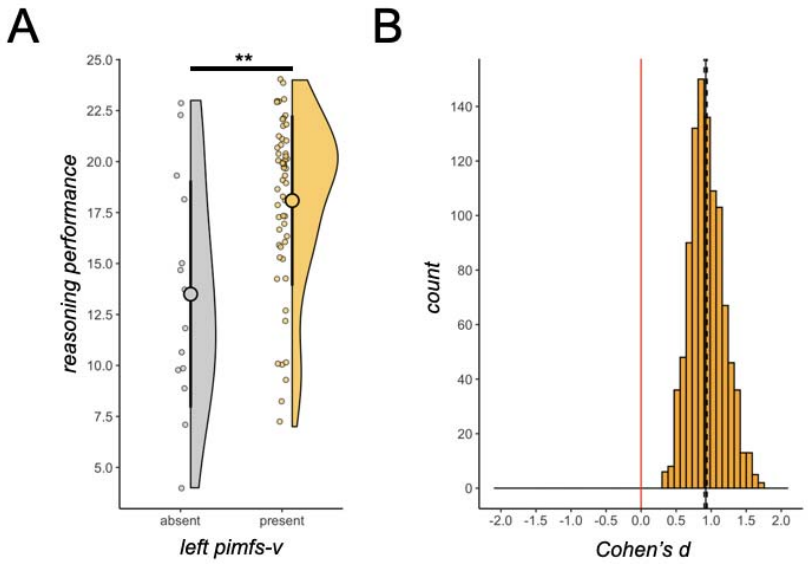

Figure 2. Relational reasoning is related to left pimfs-v presence. A. Raincloud plots (Allen et al. 2021) depicting Penn Progressive Matrices task score as a function of left pimfs-v presence in younger adults (present, N = 57; absent, N = 14). Large dots and error bars represent mean ± std reasoning score; violin plots represent kernel density estimate. Small dots indicate individual participants. **B.** Histogram visualizing results of the iterative resampling of left pimfs-v presence in A 1,000 times. Distribution of the effect size (Cohen's d) is shown, along with the median (black line) and 95% CI (dotted lines). Red line corresponds to zero, highlighting that left pimfs-v absence was never associated with higher reasoning scores than left pimfs-v presence. (** $p < .01$).

Competing interests statement

The authors declare no competing financial interests.

Data accessibility statement

Data, code, analysis pipelines, and sulcal probability maps, are on GitHub (https://github.com/cnl-berkeley/stable_projects/tree/main/CognitiveRelevance_PrefrontalStructure).

Author contributions statement

EHW, SAB, and KSW designed research; EHW, SJ, SC, CBH, WIV, and KSW performed manual sulcal labeling; EHW, SAB, and KSW analyzed data; EHW, SAB, and KSW wrote the paper; all authors gave final approval to the paper before submission.

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