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## A biologically informed polygenic score of neuronal plasticity moderates the association between cognitive aptitudes and cortical thickness in adolescents

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## ABSTRACT

Although many studies of the adolescent brain identified positive associations between cognitive abilities and cortical thickness, little is known about mechanisms underlying such brain-behavior relationships. With experience-induced plasticity playing an important role in shaping the cerebral cortex throughout life, it is likely that some of the inter-individual variations in cortical thickness could be explained by genetic variations in relevant molecular processes, as indexed by a polygenic score of neuronal plasticity (PGS-NP). Here, we studied associations between PGS-NP, cognitive abilities, and thickness of the cerebral cortex, estimated from magnetic resonance images, in the Saguenay Youth Study (SYS, 533 females, 496 males: age=15.0 ± 1.8 years of age; cross-sectional), and the IMAGEN Study (566 females, 556 males; between 14 and 19 years; longitudinal). Using Gene Ontology, we first identified 199 genes implicated in neuronal plasticity, which mapped to 155,600 single nucleotide polymorphisms (SNPs). Second, we estimated their effect sizes from an educational attainment meta-GWAS to build a PGS-NP. Third, we examined a possible moderating role of PGS-NP in the relationship between performance intelligence quotient (PIQ), and its subtests, and the thickness of 34 cortical regions.

In SYS, we observed a significant interaction between PGS-NP and object assembly vis-à-vis thickness in male adolescents ( $p = 0.026$ ). A median-split analysis showed that, in males with a 'high' PGS-NP, stronger associations between object assembly and thickness were found in regions with larger age-related changes in thickness ( $r = 0.55$ ,  $p = 0.00075$ ). Although the interaction between PIQ and PGS-NP was non-significant ( $p = 0.064$ ), we performed a similar median-split analysis. Again, in the high PGS-NP males, positive associations between PIQ and thickness were observed in regions with larger age-related changes in thickness ( $r = 0.40$ ,  $p = 0.018$ ). In the IMAGEN cohort, we did not replicate the first set of results (interaction between PGS-NP and cognitive abilities vis-à-vis cortical thickness) while we did observe the same relationship between the brain-behaviour relationship and (longitudinal) changes in cortical thickness (Matrix reasoning:  $r = 0.63$ ,  $p = 6.5e-05$ ). No statistically significant results were observed in female adolescents in either cohort. Overall, these cross-sectional and longitudinal results suggest that molecular mechanisms involved in neuronal plasticity may contribute to inter-individual variations of cortical thickness related to cognitive abilities during adolescence in a sex-specific manner.

## 1. Introduction

### 1.1. Cognitive aptitudes

Several studies have deepened our understanding of the neural correlates of various cognitive domains, and the extent to which cognitive aptitudes are influenced by genes and the environment, and their interplay (Cabeza et al., 2018; Park and Reuter-Lorenz, 2009; Reuter-Lorenz et al., 2021). A reliable way to assess an individual's cognitive aptitudes is through the assessment of intelligence quotient (IQ) using psychometric tests such as the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 2003). These tests attempt to capture both "crystallized" and "fluid" intelligence. Crystallized intelligence refers to the acquisition and accumulation of knowledge. Fluid intelligence refers to decision-making and perceptual abilities (a combination of visual-spatial organization and visual-motor skills) (Kent, 2017), which underlie – in part – inter-individual differences in our aptitudes (Gignac, 2014).

In an effort to understand the mechanisms underlying inter-individual variation in cognitive abilities, genetic studies have attempted to quantify their heritability in two main ways. Twin studies model phenotypic similarities and differences as a function of the amount of genetic and environmental influences shared between the members of a twin pair (Bouchard and McGue, 2003). Using twin studies, the heritability estimate of cognitive abilities varies between 50% and 80%. It has been reported that heritability increases in childhood into adulthood (with a peak around 18–20 years) (Bouchard and McGue, 2003), and decreases after age 60 (Reynolds and Finkel, 2015). Another approach to estimating heritability of cognitive abilities is based on genome-wide (cumulative) assessment of (common) single nucleotide polymorphisms (SNP), so-called SNP-based heritability (Yang et al., 2017). In 2014, a GWAS assessed heritability from SNPs in 6815 individuals for educational attainment and the g-factor, and quantified a heritability of 21% and 29%, respectively (Marioni et al., 2014). In 2017, a meta-GWAS on general cognitive function in 35,298 individuals from 24 cohorts observed a contribution of SNP heritability of 21.5%, as well as a robust polygenic relationship between educational attainment and cognitive performance (Trampush et al., 2017).

### 1.2. Cortical thickness

The thickness of the human cerebral cortex increases rapidly after birth, peaking between the first and second year of life, then gradually decreasing during childhood and adolescence (Gilmore et al., 2018). Different genetic (Grasby et al., 2020) and environmental (Draganski et al., 2004a, 2006) processes are involved in cortical maturation. Structural and functional changes at the micro-structural level include variations in dendritic and axonal arborization (Boivin et al., 2018), axon diameter (Pesaes et al., 2015) and myelination (Tamnes et al., 2010). Previous neuroimaging research has shown that maturation of cortical thickness decreases in a monotonic linear fashion between 5 and 20 years of age (Ducharme et al., 2016), while overall white-matter volume increases throughout adolescence (Lebel and Deoni, 2018). These developmental phenomena also appear to manifest with certain specificity with regards to sex. Sex differences are present in the maturing cerebral cortex, with somewhat greater regional variability in cortical thickness and thinning during male (vs. female) adolescence (Wierenga et al., 2022; Frangou et al., 2022).

Considering the genetic overlap observed between brain structure, educational attainment and cognitive abilities (Jansen et al., 2020), a better understanding of possible mechanisms underlying such brain-behavior relationships (and their directionality) is needed. Several studies suggest that function (e.g., learning experience) can change structure (e.g., cortical thickness) over a relatively short period of time (i.e., a "function-to-structure" change). For example, by measuring cortical thickness in medical students three months before and a few days after an exam, an increase in thickness was observed in the posterior parietal cortex following such an extensive learning period (Draganski et al., 2006); it persisted at three months after the end of the exam period (Draganski et al., 2006). Together, the results of such studies support the idea that an individual's capacity for neuronal plasticity may be one of the factors contributing to the developmental trajectory of the cerebral cortex during adolescence. We address this question by examining an interaction between polygenic scores for neuronal plasticity and cognitive aptitudes vis-à-vis cortical thickness during adolescence.

### 1.3. Goal of the study and hypotheses

Although neuronal plasticity may play a role in the association between cognitive abilities and cortical thickness, measuring empirically the contribution of this molecular process is challenging in humans. To overcome this limitation, we have developed a polygenic score to index the contribution of this molecular mechanism. This approach is similar, for example, to a design and development of a polygenic score of mesocorticolimbic and hippocampal insulin receptor-related gene networks, and its relationship with phenotypes of interest (Hari Dass et al., 2019). It identifies relevant genes through gene ontology, and assigns effect alleles and effects sizes using existing GWAS-based results obtained for a relevant phenotype. The aim of the present study is to assess the moderating role of a polygenic neuronal plasticity score with regards to the relationship between cognitive abilities and cortical thickness in adolescents. Considering sex differences in cognitive aptitudes and brain maturation during adolescence (Blakemore, 2012), the assessment of these objectives in a sex-specific way could inform us about the underpinning biology. Since learning and memory rely – in part – on molecular processes of neuronal plasticity (Draganski et al., 2006) and since similar molecular processes play a role in translating experience to structural modifications of the cerebral cortex (Draganski et al., 2004a, 2004b), we hypothesize that a) cognitive measures will be associated with cortical thickness (to a various degree) across a set of cortical regions; and that b) PGS-NP score will modify such brain-behaviour relationships.

## 2. Materials and Methods

### 2.1. Participants

We included participants from two community-based cohorts in which the protocol included cognitive assessments, T1-weighted MR imaging and genotyping. Cross-sectional data from the Saguenay Youth Study (SYS) cohort of 1029 healthy adolescents (mean age =  $15.0 \pm 1.8$ , 533 females, 496 males) were recruited from a unique population (European ancestry) with a founder effect in the Saguenay-Lac-Saint-Jean region in Quebec, Canada between 2003 and 2012 (Pausova et al., 2017). Longitudinal data were obtained in IMAGEN participants of mostly European descent ( $n = 1122$ ; mean ages at baseline (follow-up 2) =  $14.4 \pm 0.4$  years ( $19.07 \pm 0.75$  years), 566 females, 556 males) recruited in local schools at eight sites located in England (2 sites), France (1 site), Ireland (1 site), and Germany (4 sites); these participants had MRI data available for both baseline and the second follow-up. The number of IMAGEN participants for each site (and their age and sex) is presented in Supplementary Table 1A. Additional details on recruitment and assessments for SYS (<http://saguenay-youth-study.org/>) (Pausova et al., 2017) and IMAGEN (<https://imagen-europe.com/standard-operating-procedures>) (Schumann et al., 2010) cohorts are available. Demographics of the two samples are further described in Supplementary Tables 1B (SYS) and 1C (IMAGEN). Ethics research boards approvals, as well as consent from all participants and their parents, were obtained for these studies.

### 2.2. Cognitive assessment

SYS adolescents underwent two three-hour cognitive assessment separated by a lunch break. The WISC-III (except Mazes) was the standardized psychological instrument used to assess cognitive abilities. Two composite scores were of calculated, namely performance IQ (PIQ) and verbal IQ (VIQ). The performance IQ composite score was calculated from the following five test scores: Picture completion, Coding, Picture arrangement, Block design and Object assembly. Since our hypothesis stated that neuronal plasticity would be related to variations in cognitive performance that were more related to fluid intelligence (assessed by performance IQ) rather than to crystallized intelligence

(assessed by verbal IQ), we assessed performance IQ-related scores as the main outcomes to limit multiple comparisons. For completeness, verbal IQ-related results are presented in [supplementary material](#).

IMAGEN adolescents completed four WISC-IV subtests at baseline: two subtests related to verbal comprehension (Vocabulary and Similarities), and two tests related to perceptual reasoning (Block design and Matrix reasoning). For the reasons mentioned above, only the latter two tests were considered here.

Because participants in both cohorts completed different tests from different versions of psychological instruments, namely WISC-III (SYS) and four subtests of WISC-IV (IMAGEN), we focused on the subtests that involved perceptual reasoning in our analysis. We therefore evaluated the five performance IQ subtests completed by SYS participants and the two subtests completed by IMAGEN adolescents. All scores were age-standardized in both cohorts prior to statistical analyses.

### 2.3. Genotyping

SYS adolescents were genotyped either with the Illumina Human610-Quad BeadChip or the HumanOmniExpress BeadChip. Quality control was performed using PLINK (Purcell et al., 2007). Variants were excluded if the call rate was  $< 95\%$ , the minor allele frequency was  $< 0.01$  and were not in Hardy–Weinberg equilibrium ( $P < 1 \times 10^{-6}$ ). Haplotype phasing was performed with Shape-IT (Delaneau et al., 2008) using SNPs that underwent quality control, and were present on both genotyping platforms and the 1000 Genomes SNPs in European reference panel (Phase 1, Release 3) (Genomes Project, 2015). The phased genotype data underwent imputation with IMPUTE2 (Van Leeuwen et al., 2015), and variants with either a low imputation quality (information score  $< 0.5$ ) or low minor allele frequency ( $< 0.01$ ) were excluded. An extensive description of the SYS genotyping process is available elsewhere (Shin et al., 2015).

IMAGEN adolescents were genotyped either using Illumina Human610-Quad Beadchip or Illumina Human660-Quad Beadchip. Variants with completeness  $< 95\%$  and participants with a genotyping rate  $< 95\%$  were excluded. Variants that failed to be in Hardy–Weinberg equilibrium ( $p < = 1e-10$ ) or had low minor allele frequency ( $MAF < 0.01$ ) were removed. Quality control was performed using PLINK (Purcell et al., 2007). A thorough description of the IMAGEN genotyping procedures are described under the Baseline Standard Operating Procedures section (<https://imagen-project.org/>).

### 2.4. PGS-NP Calculation

To index a PGS-NP, we started by selecting Gene ontology (GO) terms associated with neuronal plasticity, as well as those associated with long-term depression and long-term potentiation; the latter two processes are common experimental models of synaptic plasticity across the mammalian brain (Malenka and Bear, 2004). This was achieved by using Gene Ontology Browser on the Mouse Genome Informatics (<http://www.informatics.jax.org/>). Using this browser and the three relevant terms (i.e., “neuronal plasticity”, “long term potentiation”, “long term depression”), we identified a total of 26 GO terms categorized in molecular function (18 of neuronal plasticity, 4 of long-term depression and 4 long-term potentiation, Supplementary Table 2). To extract genes associated with these 26 GO terms, we used the curated databases of the web-based tool QuickGO (Binns et al., 2009) on March 5, 2021. A total of 223 symbols (RNA, complexes, and proteins) were annotated in *Homo sapiens*. We then converted the gene symbols to gene entrez IDs to remove symbols without a homologous gene. To extract all SNPs associated with the 199 genes of neuronal plasticity, we used the 1000 Genomes Project (Phase 1, Release 3, mapped to build GRCh37) (Genomes Project, 2015) reference panel. From 84.7 million SNPs of the reference panel, 155,600 SNPs were linked to the 199 genes.

To assign an effect size to each of these SNPs, the following criteria were used to select a GWAS from which the summary statistics would be

used: a) sample size, b) community-based (i.e., not case-control), and c) relevance of the phenotype with regards to cognitive abilities. After careful considerations, the summary statistics of a GWAS on educational attainment in 766,345 individuals (after excluding 23andMe) were selected (Lee et al., 2018) to assign an effect size to each of the “neuronal plasticity” SNPs. Although two GWASs assessed cognitive performance and intelligence, these studies had substantially smaller samples (257,841 (Lee et al., 2018) and 269,867 (Savage et al., 2018), respectively) than the GWAS on educational attainment. In addition, a review of the literature notes the strong genetic correlation that exists between educational attainment and cognitive abilities (Malanchini et al., 2020). The intersection of the 10.1 million SNPs from the educational attainment GWAS with the 155,600 SNPs associated with the “neuronal plasticity” genes yielded a total of 40,804 SNPs to which effect sizes were assigned based on the summary statistics from the educational attainment GWAS (Lee et al., 2018). The list of these SNPs with the corresponding summary statistics is available in the following public repository (<https://github.com/XNavarri/PGS-Neuronal-Plasticity>).

These SNPs enter the following steps for calculating PGS-NP. PRSice-2 was used to compute PGS-NP for each participant, with p-value thresholds of  $5e-8$ ,  $1e-5$ ,  $0.05$ , and  $1$ , with the default clumping parameters used ( $r^2 = 0.1$ ,  $kb = 250$  kb,  $p = 1$ ) (Choi and O’Reilly, 2019). The PGS-NP was adjusted for the first 10 principal components capturing genetic variations related to population structure. The following analytical design used the PGS-NP without thresholding the SNPs since the educational attainment GWAS noted that the predictive power was greater for polygenic scores constructed with less stringent thresholds (Lee et al., 2018). For unthresholded SNPs, a total of 2658 and 2615 post-clumping SNPs were used, respectively, for PGS-NP calculations in SYS and IMAGEN.

## 2.5. MRI data acquisition and processing

In SYS, a Phillips 1.0-Tesla MRI system was used to acquire T1-weighted anatomical images using 3D RF-spoiled gradient echo scan with 140–160 slices, 1-mm isotropic resolution,  $TR = 25$  ms,  $TE = 5$  ms, flip angle =  $30^\circ$ ). Additional information on the MRI acquisition and processing were previously described elsewhere (Pausova et al., 2007).

In IMAGEN, 3.0-Tesla MRI systems by different manufacturers were used to obtain high-resolution T1-weighted anatomical images (Siemens: five sites, Philips: two sites, General Electric: one site). The magnetic resonance protocol and harmonization across sites are described elsewhere (Schumann et al., 2010). FreeSurfer (Version 5.3.), a fully automated and validated segmentation software, was used to parcellate the cerebral cortex in 68 unilateral cortical regions with the Desikan-Killiany atlas as reference in both cohorts (Desikan et al., 2006; Fischl et al., 2002). The detection of poorly segmented and/or mislabelled structures and outliers was accomplished by a series of visual inspection in standard planes.

## 2.6. Statistical analysis

The threshold of significance for an interaction between PGS-NP and cognitive abilities vis-à-vis cortical thickness was set at a nominal  $p = 0.05$ . As such, we present our findings as a proof of principle, and rely on replication to evaluate their robustness. Analysis on inter-regional profiles were not corrected for multiple testing due to the conservative nature of the non-parametric permutation analysis used here (see below); additional corrections for multiple comparisons would likely increase the chance of type II errors. All virtual histology results underwent a false-discovery rate (FDR) procedure correcting for nine cell types.

### 2.6.1. Inter-regional profiles of cortical thickness

We started by evaluating the moderating role of standardized (z scored in each cohort) PGS-NP in the relationship between thickness and

cognition in a sex-specific manner. Thus, we tested for a moderating effect of PGS-NP on the relationship (beta regression estimates) between IQ composite scores (predictors) and cortical thickness (unadjusted for age) in each of the 34 (left) cortical regions (dependent variables). We evaluated only regions of the left hemisphere due to the availability of gene-expression data in the Allen Human Brain Atlas (see section on virtual histology for details). We used a non-parametric permutation approach to determine if cognitive performance was interacting with PGS-NP vis-a-vis cortical thickness for each profile of cortical regions. To generate a distribution of the null profile to which we compared the IQ-by-PGS NP beta coefficients profiles, we started by fitting a linear model with the interaction ( $\text{thickness} \sim \text{IQ} + \text{PGS-NP} + \text{IQ} \times \text{PGS-NP}$ ). By defining the original statistic as the sum of the coefficients, we extracted the 34 beta coefficients and calculated the sum for the observed profile. Under the null hypothesis of no IQ-by-PGS-NP interaction without the interaction term, we then fitted a linear model with the main effects only ( $\text{thickness} \sim \text{IQ} + \text{PGS-NP}$ ), and extracted the residuals for each region. With the residuals obtained under the null hypothesis, we fitted the interaction models ( $\text{residuals} \sim \text{IQ} + \text{PGS-NP} + \text{IQ} \times \text{PGS-NP}$ ). We then shuffled (jointly) the IQ and PGS-NP columns to obtain a resample from which we were able to obtain the beta coefficients of the interaction and calculate the test statistic (i.e., sum of the 34 beta estimates). After repeating the shuffle and the calculation of the test statistic 5000 times, we calculated the two-tailed p-value of the null hypothesis (i.e., absence of an interaction) as the proportion of datasets with absolute value of the test statistic  $\geq$  absolute value of the original test statistic. Because the main hypothesis focused on the influence of plasticity on performance IQ, we ran a similar inter-regional profile analysis for the five performance IQ subtests.

To complement IQ-by-PGS-NP interaction analyses, we used a median split of the PGS-NP to divide participants into “High” and “Low” PGS-NP group, sex stratified. The interaction statistics will be reported first in accordance with our hypothesis on the moderating role of the PGS-NP. For each group (e.g., “Low PGS-NP” males), we evaluated the relationship (Pearson correlation coefficient  $r$ ) between performance IQ composite scores (predictors) and cortical thickness in each of the 34 left cortical regions (dependent variables). Pearson correlation coefficients were transformed into z-scores with the Fisher Z-transformation before proceeding with additional analyses.

In IMAGEN, we used the same approach to evaluate the potential moderating role of PGS-NP on the relationship between thickness and cognitive performance. A median split was also used to divide participants into “High” and “Low” PGS-NP groups, sex stratified. In each group, we computed inter-regional profiles by extracting the beta coefficients of the interaction term between cognitive performance and PGS-NP for the two performance IQ-related subtests with left cortical thickness at baseline (14 years of age, similar to the mean age of the SYS cohort).

### 2.6.2. Profiles of cortical thinning

The second part of the analytic plan focused on the relationship between the brain-behavior relationship and age-related changes in cortical thickness (“thinning”).

In SYS (cross-sectional data), we studied this relationship by correlating age with cortical thickness and then multiplying  $r$  coefficients by  $-1$  (magnitude of age-thickness relationship). This “thinning” profile was then plotted against the profile of cognition-thickness relationship. The similarity between the inter-regional correlation profiles allowed us to determine whether regions that undergo more thinning are the ones showing stronger relationships between cognition and thickness.

In IMAGEN (longitudinal data), we studied this relationship by determining whether regions undergoing more thinning, between baseline and the follow up visit in IMAGEN, are the ones showing stronger relationships between cognitive performance and thinning. To achieve this aim, we plotted the correlation-coefficient profile of cognition-thinning against the population mean of cortical thinning

between the two time points (greater value, more thinning) for each cortical region. The degree of thinning was estimated as a difference between the value of thickness at baseline (Base; mean age  $14.0 \pm 0.40$ ) and follow up (FU; mean age:  $19.1 \pm 0.75$ ):  $\text{thinning} = [\text{thickness}(\text{FU}) - \text{thickness}(\text{Base})] \text{ multiplied by } -1$ .

Finally, in IMAGEN, we were also able to examine the relationship between cognitive abilities at baseline and longitudinal cortical thinning. We calculated the cortical thinning (obtained in the analysis explained in the previous paragraph). We correlated the thinning magnitude (larger value; more thinning) obtained in each participant with their cognitive performance at baseline, controlling for age and site. These cognition-thinning profiles were plotted as a function of PGS-NP (i.e., cognition-by-PGS NP interaction beta estimates) in a sex-specific manner.

2.6.3. Virtual histology

A virtual histology analysis was performed as an exploratory analysis on inter-regional profiles capturing the relationship between performance IQ-related scores and thickness. This analysis was performed using the median-split profiles to simplify the interpretation of the results. Briefly, the virtual histology approach used publicly available datasets of gene expression (Allen Human Brain Atlas and BrainSpan Atlas) to extract a list of 2511 genes with consistent gene-expression profiles across individuals in the 34 cortical regions (left hemisphere) of the Desikan-Killiany anatomical atlas (French and Paus, 2015). Virtual histology was used to test spatial correlations between the strength of the performance IQ-thickness relationship and inter-regional variations of gene expression for nine cell-specific gene panels (i.e., astrocyte, CA1 pyramidal, endothelial, ependymal, interneuron, microglia, mural,

oligodendrocyte and S1 pyramidal) (Shin et al., 2018), and four anatomical components of neurons (dendrite, spine, myelin and axon) (Liao et al., 2021; Parker et al., 2020). All analyses were performed in R (4.1.0) Project for Statistical Computing. A scheme of the steps of this analysis is provided in Supplementary Figure 1.

3. Results

3.1. SYS

3.1.1. Cognitive aptitudes against thickness

For performance IQ, male adolescents did not show a significant interaction between performance IQ and PGS-NP vis-à-vis thickness (Fig. 1A,  $p = 0.065$ ). In female adolescents (Fig. 1B), no significant interaction between performance IQ and PGS-NP was observed ( $p = 0.443$ ), and no distinguishable relationships were observed across the cortical regions based on a median split (Fig. 1D). No significant interactions were observed between verbal IQ and PGS-NP in both males and females ( $p$ -values between 0.495 and 0.830; Supplementary Figure 2).

Regarding performance IQ subtests, a significant positive interaction between object assembly and PGS-NP vis-à-vis thickness was observed in males (Supplementary Figure 3I,  $p = 0.026$ ) but not in females (Supplementary Figure 3J,  $p = 0.640$ ).

3.1.2. Cognitive aptitudes against thinning

Supported by the relationship between performance IQ and thickness as a function of PGS-NP shown in Fig. 1C, we extended our cross-sectional investigation on performance IQ by evaluating the

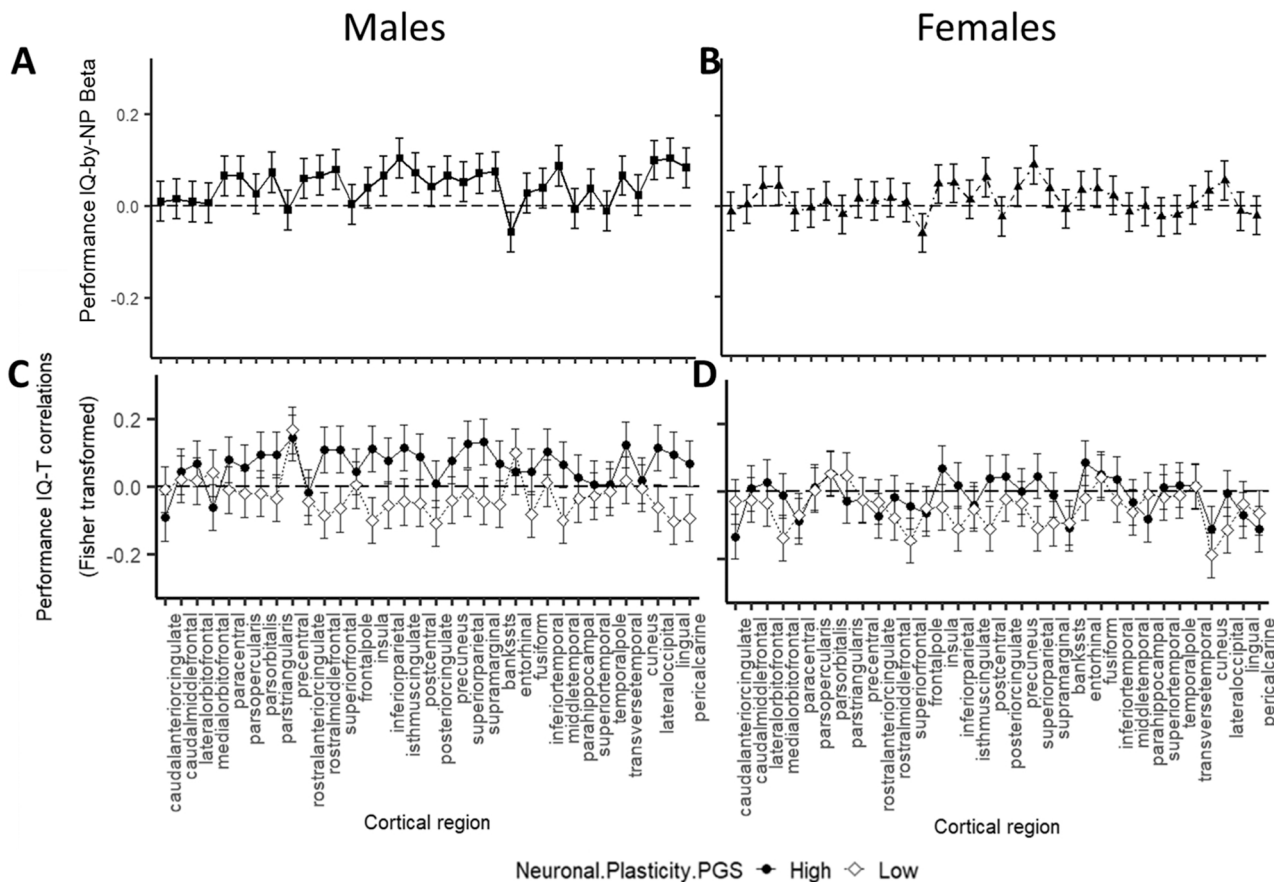


Fig. 1. Inter-regional profiles for the interaction beta between performance IQ and PGS-NP (top row) and stratified based on a median split of PGS-NP (bottom row) in the Saguenay Youth Study cohort. High PGS-NP (black dots) and low PGS-NP (white diamonds) groups' Fisher-transformed correlation coefficients between performance IQ abilities and cortical thickness are plotted for each cortical region. Error bars represent one standard error around the beta estimates.

relationship between the cognition-thickness relationship and age-thickness (“thinning”) relationship.

As shown in Fig. 2A, no similarities are observed between the magnitude of age-thickness (higher value, more thinning) and the performance IQ-thickness inter-regional correlation coefficients profiles in all males ( $r = 0.061$ ,  $p = 0.73$ ). But in high PGS-NP males (Fig. 2B), we clearly see that regions undergoing more thinning show stronger performance IQ-thickness relationships ( $r = 0.4$ ,  $p = 0.018$ ) and Object assembly-thickness relationships (Fig. 2E,  $r = 0.55$ ,  $p = 0.00075$ ). No such relationships were found in low PGS-NP males (performance IQ:  $r = -0.22$ ,  $p = 0.21$ , Fig. 2C: Object assembly:  $r = 0.046$ ,  $p = 0.80$ ), and in females (performance IQ: high PGS-NP:  $r = 0.15$ ,  $p = 0.40$ ; low PGS-NP:  $r = 0.25$ ,  $p = 0.15$ ; Object assembly: high PGS-NP:  $r = 0.11$ ,  $p = 0.53$ ; low PGS-NP:  $r = -0.23$ ,  $p = 0.18$ ).

### 3.1.3. Virtual histology

As shown in supplementary Figure 4, higher performance IQ performance was associated with thicker cortices in high PGS-NP males. This performance IQ-thickness profile correlates positively – across the 34 cortical regions - with oligodendrocytes and S1 pyramidal panels, and negatively with CA1 pyramidal, astrocyte and ependymal panels (Supplementary Table 5). That is, regions with low expression of CA1 pyramidal, astrocytes and ependymal panels show stronger relationships between cognition and thickness in males with high PGS-NP. We see (mostly) the opposite pattern in males with low PGS-NP: the performance IQ-thickness profile correlates positively with CA1 pyramidal,

astrocyte and microglia panels. Furthermore, the performance IQ-thickness profile in males with high PGS-NP correlates negatively with the dendrite and spine panels (Supplementary Table 6).

Similarly, higher object assembly performance was associated with thicker cortices in males with a high PGS-NP. This profile correlates positively across the 34 regions with oligodendrocytes and S1 pyramidal panels, and negatively with CA1 pyramidal, astrocyte and ependymal panels (Supplementary Table 7). The profile of low PGS-NP males, on the other hand, only correlates positively with the microglia panel. Additionally, the Object Assembly-Thickness profile in high PGS-NP males correlates negatively with the spine panel (Supplementary Table 8).

## 3.2. IMAGEN

### 3.2.1. Cognitive aptitudes against thickness at baseline

As shown in Fig. 3A-D, at baseline, no interactions between cognitive performance and PGS-NP vis-à-vis cortical thickness were observed in both males and females (statistics in Supplementary Table 4).

### 3.2.2. Cognitive aptitudes against thinning

Turning to thinning (i.e., thickness (FU)-thickness (Base); Fig. 3E-H), no interaction between cognitive performance (at baseline) and PGS-NP via-a-vis thinning was observed in either males or females (Supplementary Table 4).

Similarities between the cognition-thinning profiles and the mean

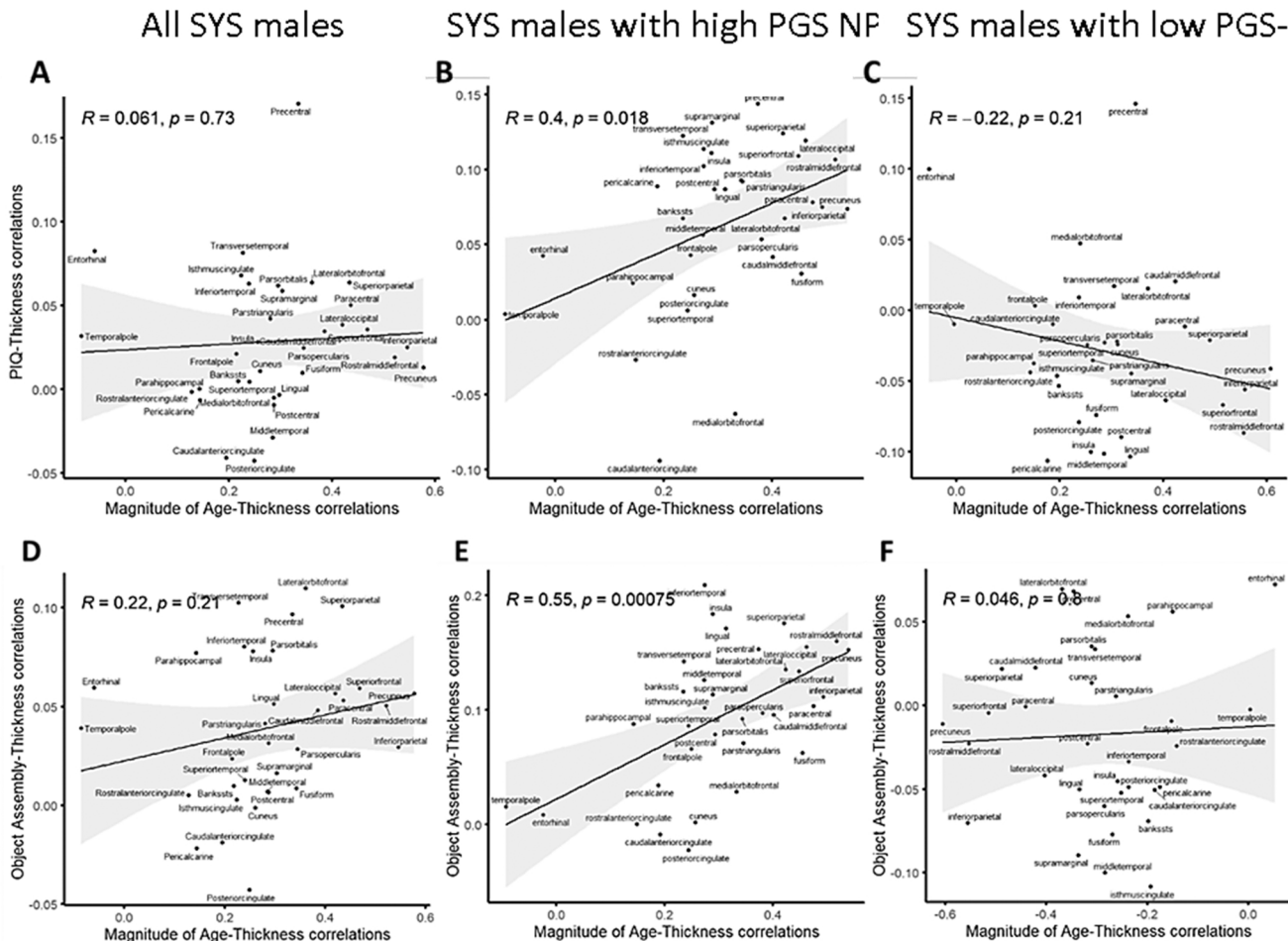
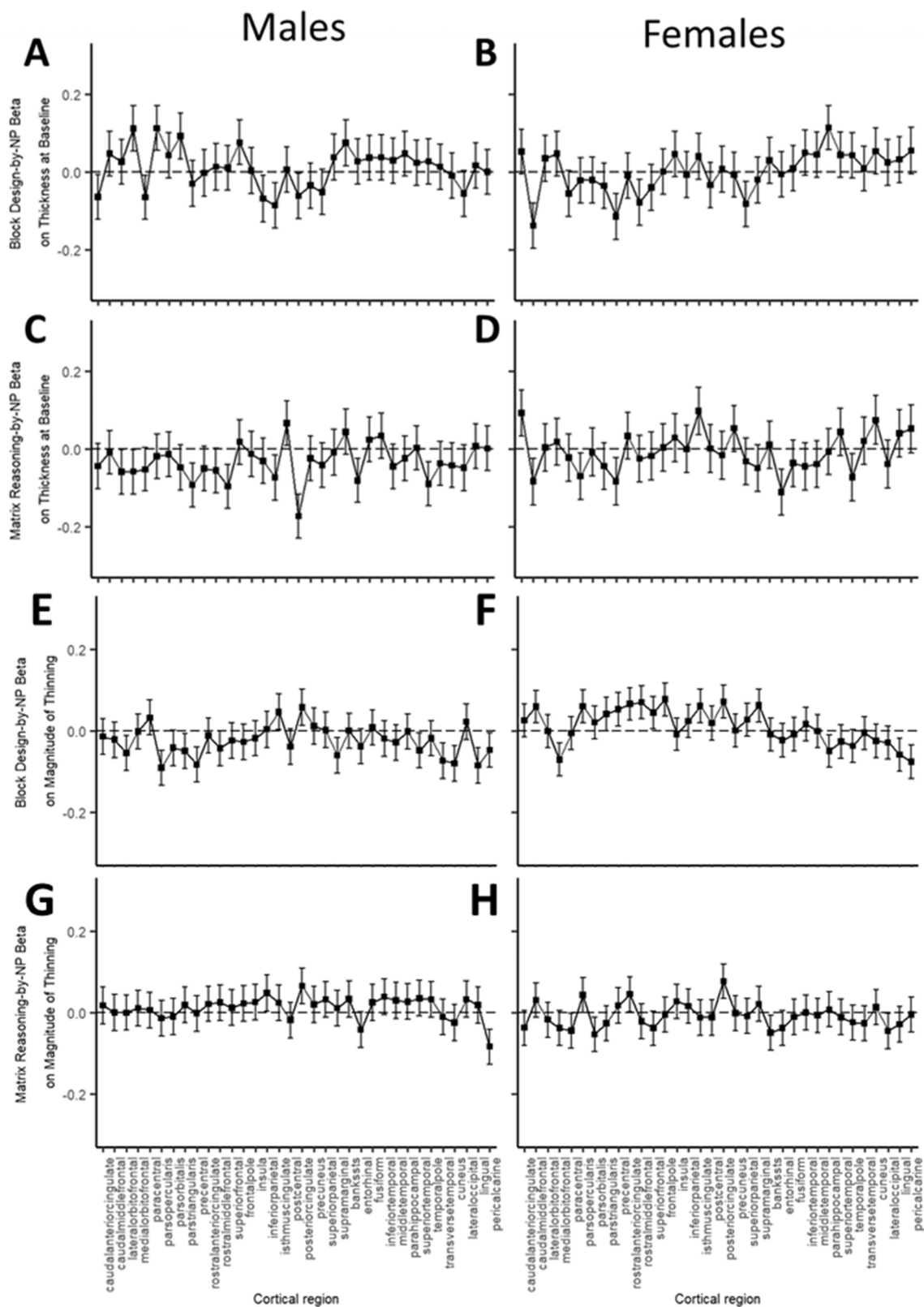


Fig. 2. Similarities between inter-regional correlation-coefficient profiles of the association between cortical thickness and performance IQ (top row) and object assembly (bottom row) and the association between age and thickness in all males (A,D), SYS males with high (B,E) and low (C,F) PGS-NP in the Saguenay Youth Study cohort.



**Fig. 3.** Inter-regional profiles for the interaction beta between subtests related to performance IQ and PGS-NP IMAGEN. Associations between cortical thickness and the interaction between PGS-NP and block design (A,B) and matrix reasoning (C,D) are plotted in a sex-specific manner. Associations between the magnitude of cortical thinning (higher value, more thinning) and the interaction between PGS-NP and block design (E,F) and matrix reasoning (G,H) are similarly plotted in a sex-specific manner. Black and white dots represent the beta of the interaction term between baseline cognitive performance and PGS-NP. Error bars represent one standard error around the beta estimates.



thinning (higher value, more thinning) profiles across IMAGEN males for the 34 cortical regions are shown in Fig. 4. For block design, the profiles did not show similarities in all male groups (all males:  $r = 0.31$ ,  $p = 0.71$ ; high PGS-NP males:  $r = 0.28$ ,  $p = 0.11$ ; low PGS-NP:  $r = 0.33$ ,  $p = 0.055$  Fig. 4A-C). For matrix reasoning, the matrix reasoning-thinning profile correlated positively with the thinning profile in all groups. In all males, regions with more thinning showed stronger reasoning-thinning associations (Fig. 4D,  $r = 0.63$ ,  $p = 6.5e-05$ ). Such similarities were also observed in high PGS-NP males (Fig. 4E,  $r = 0.53$ ,  $p = 0.0012$ ) as well as in low PGS-NP males (Fig. 4F,  $r = 0.42$ ,  $p = 0.014$ ). No relationships were observed in IMAGEN females (statistics in Supplementary Figure 5).

4. Discussion

To determine whether neuronal plasticity genes moderate the structure-function relationship between cortical thickness and cognitive aptitudes in the context of experience, we developed a polygenic neuronal plasticity score consisting of genes implicated in neuronal plasticity, as indicated by a curated database.

The first objective of this study was to determine whether the capacity for neuronal plasticity, indexed by a polygenic score, moderates the relationship between cortical thickness and cognitive abilities during adolescence. The complementary cross-sectional results from SYS and longitudinal results from IMAGEN support – to some extent – this hypothesis for adolescent males. Although the interaction between performance IQ and PGS-NP was not significant (at  $p = 0.06$ ), the overall difference in the correlation coefficients between the two male

groups across the 34 cortical regions was consistent with our prediction (i.e., the cognition-thickness relationship appears stronger in high PGS males). Furthermore, the interaction was significant for one of the performance IQ subtests (Object assembly  $p = 0.03$ ). The suggestive differences in the thickness-cognition relationship between individuals with high and low PGS-NP are all the more striking when viewed in the context of adolescence, a period of life during which brain plasticity is “deprivileged” in favor of stability (unlike the first years after birth when it is strongly favoured), and ultimately the achievement of a balance between plasticity and stability that is maintained with age (Lindenberger and Lövdén, 2019). We speculate that neuronal plasticity capacities remain enabled longer in high PGS-NP males and contribute to their cognitive and brain trajectories during later life (Tucker-Drob, 2019). We note, however, that this tentative cognition-structure-PGS relationship was not replicated in IMAGEN. Future studies are required to test this hypothesis in other context, both developmental (childhood, adulthood) and experiential (e.g., enriched educational or occupational environment).

The second objective of the current study was to assess whether the regions with a positive association between cortical thickness and cognitive performance were those that thinned the most during adolescence. This was the case in both cohorts. In SYS males with high PGS-NP, higher performance IQ and object assembly scores were associated with higher cortical thickness, and those regions would thin more with age ( $r = 0.4$ ,  $p = 0.018$  for performance IQ;  $r = 0.55$ ,  $p = 0.00075$  for object assembly, see Fig. 2B and E). In IMAGEN males, regions with stronger reasoning-thinning relationships are also the ones thinning more between the two timepoints independently of the PGS-NP

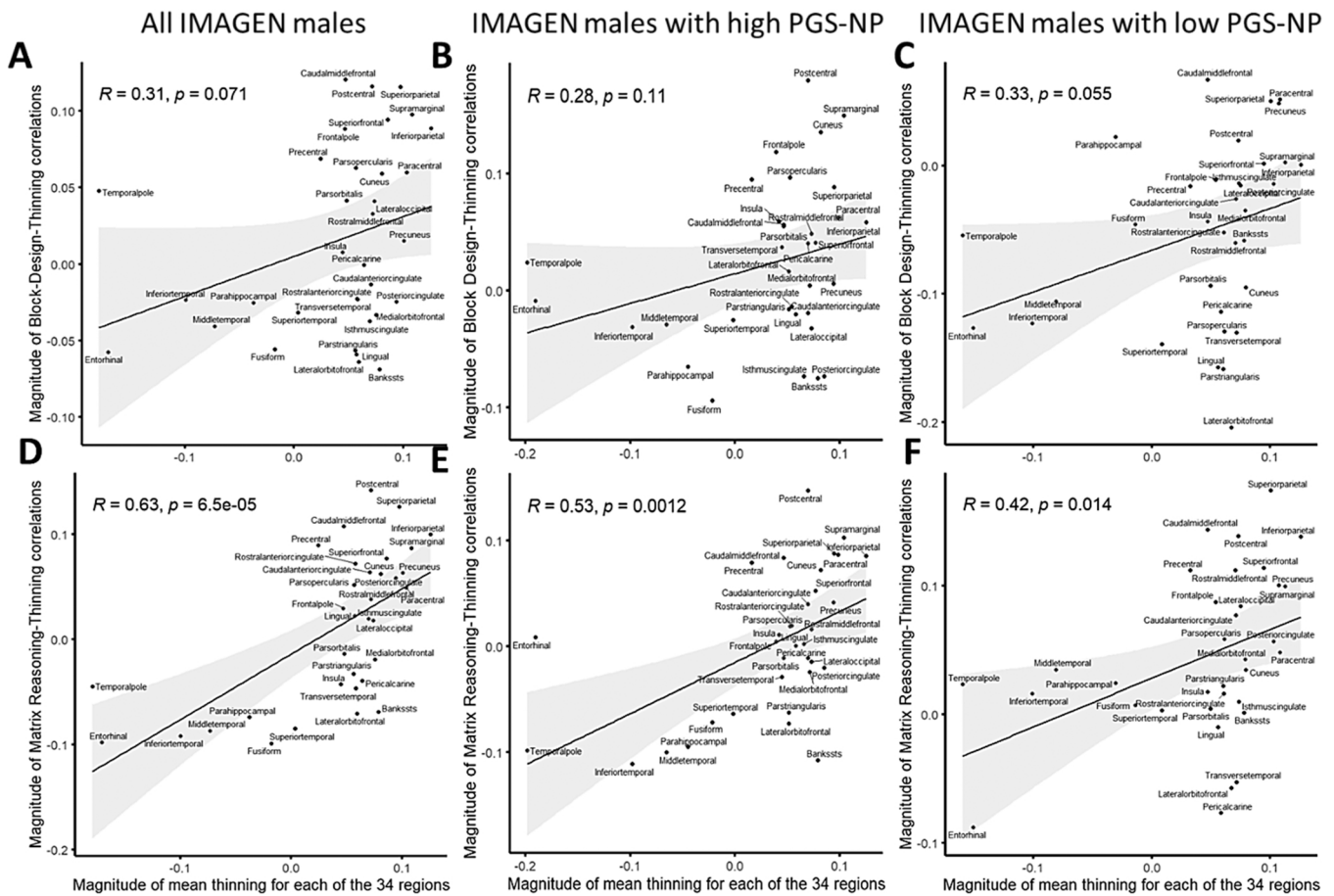


Fig. 4. Similarities between inter-regional correlation-coefficient profiles of the association between two performance IQ-related subtests (top row: block design, bottom row: matrix reasoning) and the magnitude of thinning and the magnitude of mean thinning score across participants for each of the 34 cortical regions in IMAGEN.

( $r = 0.63$ ,  $p = 6.5 \times 10^{-5}$  for all IMAGEN males, see Fig. 4).

In SYS males with high PGS-NP, regions with stronger thickness-cognition relationships are the ones showing lower expression of CA1 pyramidal ( $p_{FDR}=0.0005$ ), astrocytes ( $p_{FDR}=0.0005$ ) and ependymal ( $p_{FDR}=0.0150$ ) cell panels as well as the dendrite ( $p_{FDR}=0.04$ ) and spine ( $p_{FDR}=0.01$ ) component panels. These regions also showed higher expression of oligodendrocytes and S1 pyramidal panels. Interestingly, these regions are also the ones showing more age-related thinning (Fig. 2B and E). These virtual histology results are consistent with previous findings (Shin et al., 2018; Patel et al., 2019; Vidal-Pineiro et al., 2020) suggesting that cortical thinning reflects, to some extent, intracortical myelination. Cortical thickness, on the other hand, seems to be carried by dendritic and axonal arborization. Behaviour-related variations in cortical thickness and their association with dendrites and spines (weaker relationship in regions with more gene expression related to these cellular compartments) support a learning-induced function of cortical arborization whereby experience leads to a phase of growth that is followed by a phase of stabilization and elimination of terminals that existed before exposure (Lindenberger and Lövdén, 2019). We speculate that the cortical microcircuitry that determines the exploration-selection-refinement learning model is enhanced in high PGS-NP males whose cortical neural circuits is organized in a more sparse manner (i.e., increased thickness), and might process information somewhat differently due to a lower neurite density (Genç et al., 2018) and larger dendrites as suggested previously for high IQ individuals (Goriounova et al., 2018; Goriounova and Mansvelter, 2019). It remains difficult, however, to quantify the respective contribution of genetics and exposure on this reinforcement.

The sex-specificity of the results raises a question of sex hormones, such as dehydroepiandrosterone (DHEA) and testosterone, in the maturing brain. Indeed, others observed positive relationship between cortical thickness and DHEA levels in early pubertal adolescents, possibly mitigating the negative testosterone-related association with cortical thickness (Nguyen et al., 2013a). Longitudinal sex-specific relationships were also observed during adolescence in certain cortical regions, with testosterone-related thinning observed in males while thickening was observed in females (Nguyen et al., 2013b). Sex differences were observed in temporal and occipital regions with high androgen receptor density, where higher testosterone levels were associated with thicker cortices in males and thinner cortices in females (Bramen et al., 2012). Another study, however, reported a relationship between age-related cortical thinning and inter-regional variations of androgen receptors mRNA expression levels in males only (Wong et al., 2018). Further studies are required to determine which biological mechanisms related to sex hormones are involved in cortical maturation.

Performance IQ and object assembly results are similar in terms of the inter-regional profiles of the two male groups in SYS (Fig. 1), their relationships with thinning (Fig. 2) and virtual histology (Supplementary Figure 4). The consistency of the results observed between the composite score and one of the subtests is an additional factor supporting the directionality of the relationships between performance IQ, thickness, and PGS-NP despite the absence of a significant interaction in SYS males. Taken together, these results might challenge the non-rejection of the null hypothesis (i.e., no significant interaction). Sufficiently powered studies are required to determine the role of PGS-NP on the cognition-thickness relationship.

There are several limitations to our study. First, the polygenic score of neuroplasticity was calculated using weights based on a proxy phenotype, namely educational attainment. This strategy reflects the absence of a sufficiently powered GWAS with a phenotype more directly related to neuronal plasticity, be it behavioral (e.g., learning rate) or physiological (e.g., change in the cortical excitability following repetitive transcranial magnetic stimulation). The educational attainment GWAS is well powered ( $n \sim 700,000$ ) and fitting; it correlates strongly with cognitive performance phenotypically ( $r \sim 0.40$ ) (Deary et al.,

2007) and genetically ( $r \sim 0.70$ ) (Rietveld et al., 2014). Note also that, by design, polygenic scores do not allow one to make any inferences about the directionality and causality of the relationship between the functioning of a gene (high/low) and the phenotype of interest. Second, the lack of replication in the association between performance IQ-related subtests and cortical thickness in IMAGEN males at baseline limits the generalization of the results initially observed in SYS males. Due to the nature of the cohorts, it is not possible to compare directly the results of IMAGEN with the results of the Saguenay Youth Study regarding cortical thinning. The availability of a second longitudinal cohort to serve as a reference would allow us to assess the validity of the longitudinal observations. Nevertheless, our results converge with other previously published results on cortical thinning and cognitive performance in adolescents (Schnack et al., 2015). In males with high PGS-NP in both cohorts, we observed that higher performance IQ-related scores were associated with more thinning. Third, the virtual histology approach compares inter-regional correlations profiles from different participants (i.e., *in vivo* thickness measures in SYS and IMAGEN and *ex vivo* cell-specific gene expression). Additionally, sex differences in cortical laterality may contribute to the results obtained in the sex-specific analyses since our analysis was performed on the left hemisphere due to methodological limitations in the virtual histology approach (Sowell et al., 2007). Although the use of a median-split analysis used in the follow-up of the initial findings obtained with continuous PGS values is statistically suboptimal (given the loss of statistical power (Maxwell and Delaney, 1993)), it is useful for interpreting the role of PGS-NP in the brain-behavior relationship and virtual histology results. Moreover, differences in the distribution of the post-clumping SNPs used in the calculation of the PGS-NP across the cohorts was moderate, which might have contributed to the lack of replicability of the findings. Finally, the structure-function directionality was not assessed in the current study due to the experimental design. A better understanding of time-varying relationships between cortical thickness and cognitive performance *across* and *within* participants could inform us on the directionality and temporal precedence.

#### 4.1. Conclusion

In light of the results and in the context of experience-induced plasticity, it is conceivable that an individual with a higher genomic propensity for neuronal plasticity also has a stronger thickness-fluid intelligence relationship. A better understanding of possible mechanisms influencing the structure-function relationship between cortical thickness and cognitive abilities is central to our understanding of brain maturation during adolescence. In Saguenay Youth Study males, we observed a moderating effect of PGS-NP on the thickness-object assembly relationship and a trend for thickness-performance IQ relationship. These observations were not replicated, however, in IMAGEN. Regions that showed stronger thickness-cognition associations showed more age-related thinning, and this profile was associated with the expression of genes specific to CA1 pyramidal, astrocytes and ependymal in males with high PGS-NP. Still in high PGS-NP males, regions that showed stronger thinning-cognition associations were thinning more between 14 and 19 years of age. These results inform us about the influence of a molecular mechanism explaining in part the inter-individual variations observed in the structure-function relationship in the context of experience during adolescence in a sex-specific manner. We speculate that individuals with high PGS-NP show greater rate of change in cortical thickness across adolescence in part due to a differential impact of experience during this period of development.

#### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Banaschewski served in an advisory or consultancy role for eye level,

Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Janssen, Medice and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships. Dr Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses. Dr Poustka served in an advisory or consultancy role for Roche and Viforpharm and received speaker's fee by Shire. She received royalties from Hogrefe, Kohlhammer and Schattauer. The present work is unrelated to the above grants and relationships. The other authors report no biomedical financial interests or potential conflicts of interest.

### Data Availability

Data will be made available on request. Saguenay Youth Study data is available upon request. IMAGEN data is available upon request to the corresponding committee in accordance with the data access policy.

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### Disclosure

Dr Banaschewski served in an advisory or consultancy role for eye

level, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Janssen, Medice and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships. Dr Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses. Dr Poustka served in an advisory or consultancy role for Roche and Viforpharm and received speaker's fee by Shire. She received royalties from Hogrefe, Kohlhammer and Schattauer. The present work is unrelated to the above grants and relationships. The other authors report no biomedical financial interests or potential conflicts of interest.

### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.dcn.2023.101232](https://doi.org/10.1016/j.dcn.2023.101232).

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