Polygenic Risk Scores for Autism spectrum disorder and Alzheimer's disease enable the identification of new white matter tract biomarkers

Thomas RIQUELME[1], Antoine GRIGIS[1], Cathy PHILIPPE[1] and Vincent FROUIN[1]

[1] Neurospin, Institut Joliot, CEA, 91191, Gif-sur-Yvette, France

Corresponding Author: vincent.frouin@cea.fr

Abstract *Background : In the era of Genome-Wide Association Studies (GWAS) of various phenotypes, including complex trait diseases, Polygenic Risk Scores (PRS) offer the possibility to assess the shared aetiology between heritable traits. Moreover, used as proxies, they also provide the opportunity to study the link between genetic variants, newly available endophenotypes such as phenotypes derived from brain imaging data, and classical phenotypes. Method : Here, from GWAS summary statistics established on very large cohorts and using PRSice, we computed PRS_ASD for Autism Spectrum Disorder (ASD) and PRS_AD for Alzheimer's disease (AD) for healthy subjects in two large imaging-genetic cohorts, UK Biobank (UKB, about 15K subjects) and Human Connectome Project (HCP, 820 subjects). We tested PRS_ASD and PRS_AD for association with diffusion-MRI derived phenotypes obtained in 48 white matter tracts and corrected the p-values for multiple testing. Results : For both ASD and AD, we found about ten white matter tracts significantly associated with PRS_ASD and PRS_AD risk scores, recovering already known associations between these brain imaging features and these two complex traits diseases. Conclusion : This work illustrates how polygenic risk score analysis may help in detecting the brain structures in which the genetic predisposition for a syndrome manifests itself in the general population.*

Keywords Imaging-genetics, *Polygenic risk scores, Autism spectrum disorder, Alzheimer's disease, UK Biobank*

1 Introduction

A Polygenic Risk Score (PRS) is a cumulative genetic risk computed with one subject's genome variants. The variants and associated weights used for the score are obtained from summary statistics of reference GWAS carried out to study a trait of interest. In recent years, summary statistics of powerful reference GWAS were made publicly available for Alzheimer's disease or psychiatric syndromes, for instance. PRS based studies have gained interest as this score can be tentatively correlated to a newly available phenotype in an independent cohort, and offer a mean to detect shared aetiology between traits [1].

In this study, we computed PRS for Autism Spectrum Disorder (ASD) and Alzheimer's disease (AD) for each subject in two large healthy population cohorts, UK Biobank (UKB) and Human Connectome Project (HCP). Then, we assessed the correlations between these PRSs and diffusion MRI white matter tract measurements. We aimed to identify potential association between white matter tract biomarkers and PRS for ASD or AD.

2 Material and methods

In this work, we used the two largest imaging-genetic cohorts available as open data to date: Human Connectome Project/Young adult and UK Biobank. The HCP cohort consists in 820 Caucasian subjects with detailed pedigree (extended family pedigree with twins and siblings) as well as genotyping (dbGaP appl. #17771). As regards the UKB cohort (appl. #25251), we considered 14,538 unrelated subjects with British ancestry (available in rel. January 2018). Both cohorts contained imaging data with Fractional Anisotropy (FA) measurements and genotype data available.

The summary statistics for ASD and AD were retrieved from two meta-GWAS originated from the Psychiatric Genomic Consortium (PGC) and the International Genomics of Alzheimer's Project (IGAP) [2,3]. As new phenotypes in HCP and UKB, we considered the averaged values of Tract-Based Spatial Statistics (TBBS)-projected FA measures in 48 tract masks obtained from the JHU atlas [4].

PRSice tool [1] was used to compute ASD and AD PRS for each subject of the two cohorts studied based on PGC-ASD and IGAP-AD signatures. The set of genetic variants and associated weights that entered the ASD and AD signatures was determined by PRSice.

The associations were assessed by regressing the individual white matter tract measures on the PRS. All analyses were corrected for age, sex, and four genetic principal components as covariates. False discovery rate was used to correct for multiple testing [5]. Correction was applied to the total number of statistical tests for each PRS and tract-specific TBBS-mean FA. A false discovery rate–corrected significance threshold of 5% was applied.

3 Results

Most significant associations between white matter tracts' TBBS-projected FA measurements and PRS for ASD and AD are shown in Table 1 for both UKB and HCP cohorts.

Concerning ASD, the only specific subpart of a tract that replicated its association with PRS_ASD in both cohorts was the superior corona radiata. However, by taking into account all the subparts of a broader tract, we found that the corona radiata and the cerebellar peduncle were significantly associated with PRS_ASD in both UKB and HCP (cf. Table 1).

Regarding AD, several specific subparts of tracts replicated their association with PRS_AD in both cohorts: cerebral, middle and inferior cerebellar peduncle; posterior limb and superior fronto-occipital fasciculus of internal capsule; external capsule; splenium of corpus callosum and cingulum-cingulate gyrus. However again, if we consider larger tracts constituted of these subtracts, we can see clearly, five broad families of tracts associated with PRS_AD in both cohorts: cerebellar peduncle, corona radiata, internal and external capsule, corpus callosum and cingulum.

The replication of these associations in both cohorts strengthens the hypothesis that these tracts could be important manifestation of the genetic predispositions for ASD and AD. Moreover, the replication of the associations of subtracts could indicate more accurate and specific pathways implicated in genetic predispositions for ASD or AD.

Furthermore, we can see clearly with the color code identifying groups of tracts in Table 1, that some tracts shared associations with PRS for both ASD and AD: corona radiata, cerebellar peduncle, internal and external capsule, corticospinal tract and cingulum. This could indicate that both diseases shared genetic predispositions in several tracts in common, with differences sometimes in subtracts more specific for a disease.

	UKB		HCP	
PRS_ASD	Tract name	FDR	Tract name	FDR
	Superior_corona_radiata_L+R	8.31E-03	Superior_corona_radiata_L	3.25E-02
	Posterior_corona_radiata_R	8.31E-03		
	Cerebral_peduncle_L+R	1.25E-02	Inferior_cerebellar_peduncle_L	3.25E-02
	Superior_cerebellar_peduncle_L+R	2.70E-02		
	Uncinate_fasciculus_L+R	8.31E-03		
	Superior_longitudinal_fasciculus_L+R	1.91E-02		
	Posterior_limb_of_internal_capsule_L+R	1.25E-02		
	External_capsule_L	2.78E-02		
	Corticospinal_tract_R	3.42E-02		
	Cingulum-hippocampus-L	3.42E-02		
			Fornix_column_and_body_of_fornix	4.84E-02
PRS_AD	Tract name	FDR	Tract name	FDR
	Middle_cerebellar_peduncle	1.63E-02	Middle_cerebellar_peduncle	2.28E-04
	Inferior_cerebellar_peduncle_L+R	3.39E-02	Inferior_cerebellar_peduncle_L+R	4.27E-03
	Cerebral_peduncle_L	3.39E-02	Cerebral_peduncle_L+R	1.06E-02
			Superior_cerebellar_peduncle_L+R	8.50E-03
	Posterior_corona_radiata_R	3.77E-02	Anterior_corona_radiata_L+R	9.88E-04
	Posterior_limb_of_internal_capsule_L	3.77E-02	Posterior_limb_of_internal_capsule_L+R	3.57E-03
	Superior_fronto-occipital_fasciculus-part_of_anterior_internal_capsule-R	3.77E-02	Superior_fronto-occipital_fasciculus-Part_of_anterior_internal_capsule_L	8.42E-03
	Retrolenticular_part_of_internal_Capsule_R	4.31E-02	Anterior_limb_of_internal_capsule_L+R	8.42E-03
	External_capsule_L	4.52E-02	External_capsule_L	2.23E-02
	Splenium_of_corpus_callosum	3.77E-02	Splenium_of_corpus_callosum	1.38E-02
			Genu_of_corpus_callosum	2.54E-03
			Body_of_corpus_callosum	1.38E-02
	Cingulum-cingulate_gyrus-R	4.98E-02	Cingulum_cingulate_gyrus_L	2.03E-02
	Cingulum-hippocampus_L+R	3.39E-02		
	Posterior_thalamic_radiation-include_optic_radiation-L+R	9.62E-03		
	Tapetum_L+R	1.63E-02		
	Corticospinal_tract_R	3.77E-02		

Table 1. Most significant associations between white matter tracts' TBBS-projected FA measurements and PRS for ASD and AD in UKB and HCP cohorts. Only associations passing FDR-corrected threshold of 5% are reported. Subparts of the same white matter tract are grouped by color and tracts associated to a PRS in both cohorts are aligned together for better visualization.

Triplanar and 3D representation of the most representative tracts associated with PRS_ASD and PRS_AD, corona radiata, cerebellar peduncle and internal capsule, are depicted in Figure 1. The corona radiata, consists in projections fibers radiating under the cortex from and towards the internal and external capsule [6]. The cerebellar peduncles connect the cerebellum to the brain stem [6]. The internal capsule is a thick blade of white matter located between the thalamus and the caudate nucleus on the one hand, and the lenticular nucleus on the other hand. It consists in several parts: the anterior limb, which separates the caudate nucleus of the lenticular nucleus and the posterior limb, between the thalamus and the lenticular nucleus [6].

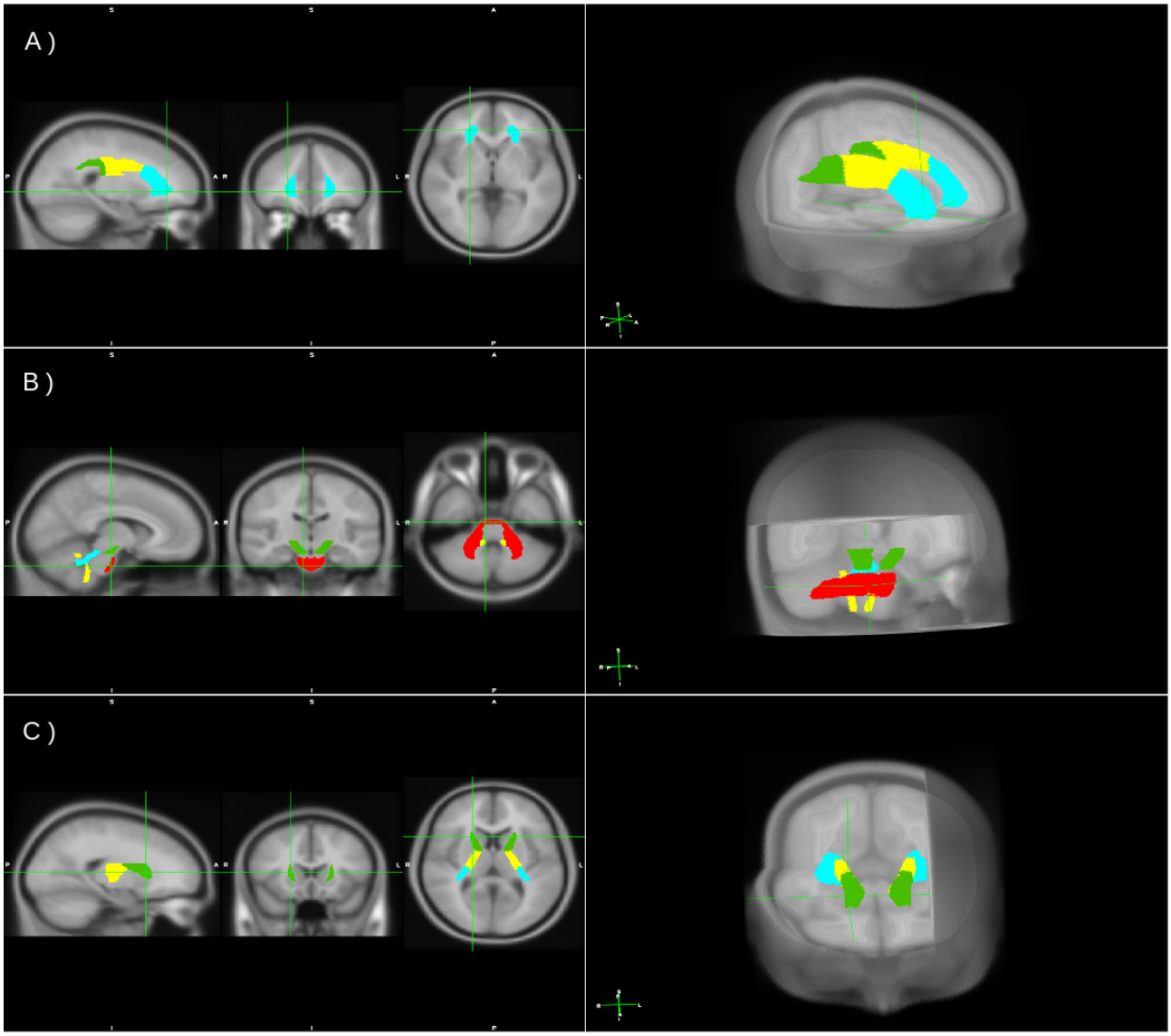

Figure 1. Triplanar and 3D representations of the most representative tracts associated with PRS_ASD and PRS_AD. A) Corona radiata. Blue: anterior ; Yellow: superior ; Green: posterior. B) Cerebellar peduncle. Green: cerebral; Yellow: inferior; Blue: superior; red: middle. C) Internal capsule. Green: anterior limb ; Yellow: posterior limb ; Blue: retrolenticular. Images obtained with FSLeyes software [7].

We summarized all the associated tracts by disease in figure 2 in the form of two glass brains exhibiting the potentially impacted tracts in ASD and AD.

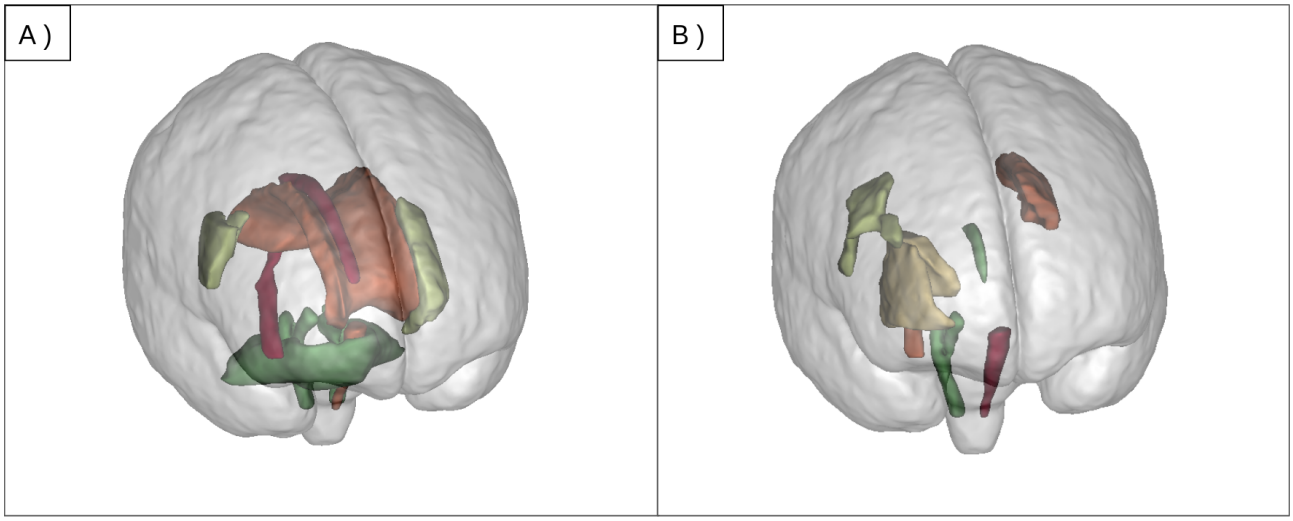

Figure 2. Glass brains exhibiting potentially impacted tracts in AD (A) versus ASD (B). Dark green: cerebellar peduncle ; Light Green: corona radiata ; Red: Fornix; Orange: Corpus callosum. White: Capsule. Images obtained with Anatomist software [8].

4 Discussion

We used polygenic risk score analysis to test potential association of the scores with diffusion-MRI derived phenotypes in two cohorts of healthy subjects. We tested association with TBSS-mean fractional anisotropy obtained in 48 white matter tracts. We found about ten regions with significant association with PRS_ASD and PRS_AD risk scores. These results suggest a shared genetic aetiology among some structures of the white matter and ASD and AD. Our results obtained on the largest imaging-genetics cohorts available to date, are in line with the methodology used by Jansen et al [9] in their neuropsychiatric study combining Polygenic Scores and White Matter Microstructure.

Concerning ASD, our results are consistent with other tractography studies carried out with ASD patients [10,11]. Gibbard et al. [10] observed similar significant FA decreased between ASD patients and controls for cortico-thalamic tracts such as corona radiata, internal capsule and superior longitudinal fasciculus; and limbic tracts such as the cingulum, fornix and uncinate fasciculus. The limbic tracts are known to be involved in social processing and a deterioration in this structures could be relevant in ASD aetiology. They suggested that cortico thalamic regions could also be involved in ASD traits such as imagination, repetitive behaviours and flexibility, which are likely to require the recruitment of several brain regions.

Moreover, Pryweller et al. [11] identified significant association with superior corona radiata and posterior limb of internal capsule and suggested their involvement in aberrant sensory behaviors seen in subjects with ASD. The superior corona radiata contains both motor and sensory fibers projecting to and from cortex. Thus, they suggested that the integrity of the fibers contained in these pathways might modulate the transmission of cortical sensory signals and subsequently impact reactivity patterns in ASD, such as hypo- or hyper-responsiveness. In addition, they suggested that the posterior limb of the internal capsule tract is associated with the function and modulation of attentional alerting according to previous studies [12,13].

Regarding AD, the middle cerebellar peduncle had the strongest association with PRS for AD. It consists in afferent fibers from the pons to the cerebellum [14]. Although cerebellum is not a primary focus of pathological change in AD, deposition of amyloid plaques and increased microglia have been reported to be found in the cerebellum of AD [15]. This association of middle cerebellar peduncle with AD is consistent with the work of Miyasaka et al. [16] who observed a significant FA decreased in the middle cerebellar peduncle in a severe AD group. Those subjects had severe cognitive impairment by AD and this result supports the hypothesis that cerebellum could play some role in cognitive function.

In addition, Huang et al. [17] identified significant differences in FA between AD patients and controls for limbic tracts: fornix, cingulum-cingulate gyrus and cingulum-hippocampus; commissural tracts: body of corpus callosum; and projection tracts: anterior corona radiata. Our results exhibited all these tracts associated with AD except for fornix.

To conclude, the associations found in these tracts could indicate a continuum of biomarkers from healthy to diseased brain related to ASD or AD. This work illustrates how polygenic risk score analysis may help in detecting the structures in which the genetic predisposition for a syndrome manifests itself in the general population.

References

[1] Jack Euesden, Cathryn M. Lewis, and Paul F. O'reilly. PRSice: polygenic risk score software. Bioinformatics, 31.9:1466-1468, 2014.

[2] Jakob Grove et al. Identification of common genetic risk variants for autism spectrum disorder. Nature genetics, 1, 2019.

[3] Jean-Charles Lambert et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nature Genetics, 45: 1452–1458, 2013.

[4] Susumu Mori et al. MRI atlas of human white matter. Elsevier, 2005.

[5] Yoav Benjamini, Yosef Hochberg, Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc Ser B, 57:289–300, 1995.

[6] Juergen K. Mai and George Paxinos, The human nervous system 3, Academic Press, 2011.

[7] Paul McCarthy, FSLeyes, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes

[8] Denis Rivière et al., Anatomist: a python framework for interactive 3D visualization of neuroimaging data, Python in Neuroscience workshop, Paris, Aug, 2011.

[9] P. R. Jansen, et al.. Polygenic Scores for Neuropsychiatric Traits and White Matter Microstructure in the Pediatric Population. Biological Psychiatry. Cognitive Neuroscience and Neuroimaging, 4(3), 243–250, 2019.

[10] Clare R. Gibbard et al. White matter microstructure correlates with autism trait severity in a combined clinical–control sample of high-functioning adults. NeuroImage: Clinical, 3:106-114, 2013.

[11] Jennifer R. Pryweller et al. White matter correlates of sensory processing in autism spectrum disorders. NeuroImage: Clinical, 6:379-387, 2014.

[12] Alicia Callejas et al. Modulations among the alerting, orienting and executive control networks. Experimental brain research, 167.1: 27-37, 2005.

[13] Jin Fan et al. Testing the behavioral interaction and integration of attentional networks. Brain and cognition, 70.2: 209-220, 2009.

[14] Jan Voogd and Tom JH Ruigrok. Cerebellum and precerebellar nuclei. The human nervous system 3: 471-545, Academic Press, 2011.

[15] Eriola Hoxha et al. The emerging role of altered cerebellar synaptic processing in Alzheimer's Disease. Frontiers in aging neuroscience, 10: 396, 2018.

[16] Toshiteru Miyasaka et al., Cerebellar White Matter Involvement in Alzheimer's Disease: Diffusion Tensor Study. Radiological Society of North America 2014 Scientific Assembly and Annual Meeting, - ,Chicago IL. http://archive.rsna.org/2014/14045714.html Accessed April 3, 2019.

[17] Hao Huang et al. Distinctive disruption patterns of white matter tracts in Alzheimer's disease with full diffusion tensor characterization. Neurobiology of aging, 33.9: 2029-2045, 2012.