



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

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Summary

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Introduction

- Numerous GWAS / meta-GWAS for complex traits / diseases (e.g. psychiatric and neurodegenerative diseases)
- Result in summary statistics publicly available
- It contains the genome-wide SNPs associated with a disease and their effect size
- Polygenic Risk Scores (PRS) can use summary statistics to evaluate an individual's propensity for a disease based on its genotype data

Polygenic Risk Score (PRS)

- PRS is a single value estimate of an individual's propensity for a disease (Euesden et al., 2014)

$$\text{PRS} = \sum (\text{individual's disease-associated SNPs} * \text{effect size})$$

- Application : PRS can be used as proxy to assess the association between the disease and a second trait (“shared aetiology” or “comorbidity”) by testing the association between the PRS for this disease and this second trait

Study plan

- 1) We computed PRS for Autism Spectrum Disorder (ASD) and Alzheimer's Disease (AD) for each subject in 2 large imaging-genetics cohorts: UKB and HCP
- 2) We used PRS_ASD and PRS_AD as proxies to assess the shared aetiology between ASD / AD and a structural connectivity phenotype
 - => We tested the association of PRS_ASD and PRS_AD with diffusion MRI measurements for 48 white matter tracts
 - => Goal : identify white matter tract biomarkers more prone to be affected by the disease

Methods: Summary statistics retrieval

- Summary statistics for ASD retrieved from ASD meta-GWAS of the Psychiatric Genomic Consortium (PGC) (Grove et al., 2019)
- Summary statistics for AD retrieved from AD meta-GWAS of the International Genomics of Alzheimer's Project (IGAP) (Lambert et al., 2013)

Methods: cohorts

Choice of independent cohorts to apply the PRS

We used the two largest imaging-genetic cohorts available to date:

- UK Biobank (UKB) = 14,538 unrelated subjects with British ancestry (Bycroft et al., 2018)
- Human Connectome Project (HCP) = 820 related subjects (extended family pedigree with twins and siblings) with European ancestry (Van Essen et al., 2013)

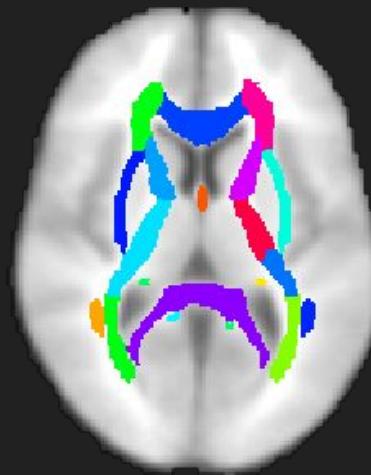
Both cohorts contained: imaging data and genotype data available.

Both cohorts contained: healthy subjects without ASD or AD

Methods: Imaging phenotype

Choice of a second trait to study the link with ASD / AD:

- Diffusion MRI derived phenotype
- Fractional Anisotropy (FA) measurements projected on a Tract-Based Spatial Statistics (TBSS) skeleton
- Skeleton split into 48 white matter tracts and FA averaged along them
- 48 tract masks obtained from the JHU white-matter atlas (Mori et al., 2005)



JHU white-matter atlas
(Mori et al., 2005)

Methods: PRS computing

- PRSice tool (Euesden et al., 2014) was used to compute PRS_ASD and PRS_AD
- for each subject of the two cohorts UKB and HCP
- based on PGC-ASD and IGAP-AD summary statistics

Methods: PRS association with imaging phenotype

- The associations were assessed with PRSice by regressing the white matter tract measures on the PRS
- Covariates: age, sex, first 4 genetic principal components
- False Discovery Rate (FDR) was used to correct for multiple testing

Results: ASD

	UKB		HCP	
	Tract name	FDR	Tract name	FDR
PRS_ASD	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

Table 1. Most significant associations between white matter tracts and PRS_ASD in UKB and HCP cohorts.

Only associations passing FDR-corrected threshold of 5% are reported.

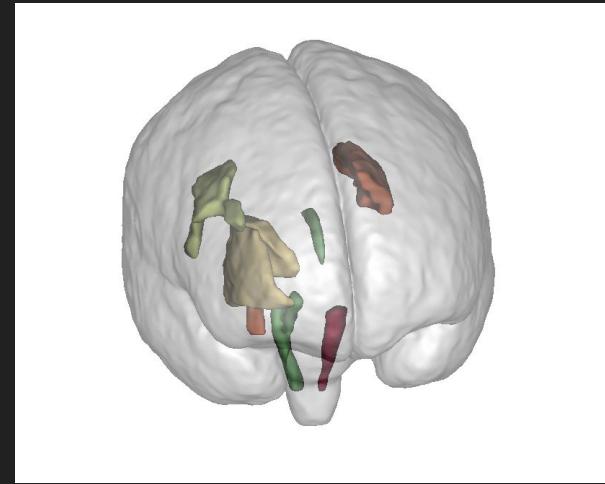


Figure 1. Glass brains showing potentially impacted tracts in ASD.

superior corona radiata L (upper orange), inferior and superior cerebellar peduncle R (lower green), uncinate fasciculus R (upper light green), external capsule and posterior limb of internal capsule R (white), corticospinal L (red), cingulum-hippocampus (lower orange), body and column of fornix (upper green).

Images obtained with Anatomist software (Rivière et al., 2011)

Results AD

	UKB		HCP	
	Tract name	FDR	Tract name	FDR
PRS_AD	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
	Posterior_corona_radiata_R	3.77E-02	Superior_cerebellar_peduncle_L+R	8.50E-03
	Posterior_limb_of_internal_capsule_L	3.77E-02	Anterior_corona_radiata_L+R	9.88E-04
	Superior_fronto-occipital_fasciculus-part_of_anterior_internal_capsule-R	3.77E-02	Posterior_limb_of_internal_capsule_L+R	3.57E-03
	Retrolenticular_part_of_internal_Capsule_R	4.31E-02	Superior_fronto-occipital_fasciculus-Part_of_anterior_internal_capsule_L	8.42E-03
	External_capsule_L	4.52E-02	Anterior_limb_of_internal_capsule_L+R	8.42E-03
	Splenium_of_corpus_callosum	3.77E-02	External_capsule_L	2.23E-02
	Cingulum-cingulate_gyrus-R	4.98E-02	Splenium_of_corpus_callosum	1.38E-02
	Cingulum-hippocampus_L+R	3.39E-02	Genu_of_corpus_callosum	2.54E-03
	Posterior_thalamic_radiation-include_optic_radiation-L+R	9.62E-03	Body_of_corpus_callosum	1.38E-02
	Tapetum_L+R	1.63E-02	Cingulum_cingulate_gyrus_L	2.03E-02
	Corticospinal tract_R	3.77E-02		

Table 2. Most significant associations between white matter tracts and PRS_AD in UKB and HCP cohorts.

Only associations passing FDR-corrected threshold of 5% are reported.

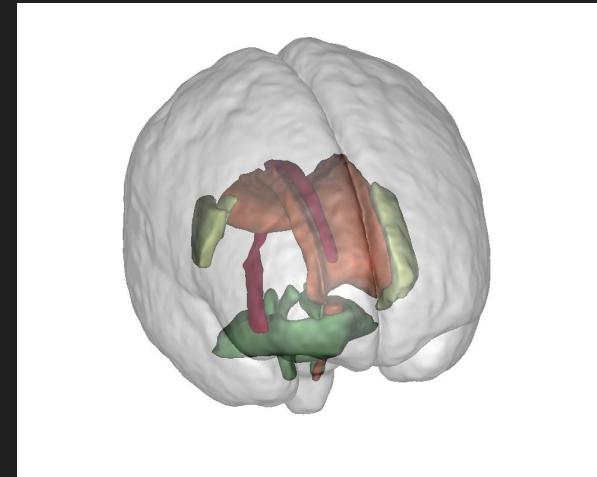


Figure 2. Glass brains showing potentially impacted tracts in AD.

cerebellar peduncle (green), anterior corona radiata L (light green), capsule L (not visible), corpus callosum (upper orange), cingulum-cingulate gyrus and cingulum-hippocampus (red), corticospinal (lower orange), posterior thalamic radiation (light green).

Images obtained with Anatomist software (Rivière et al., 2011)

Comparison ASD vs AD

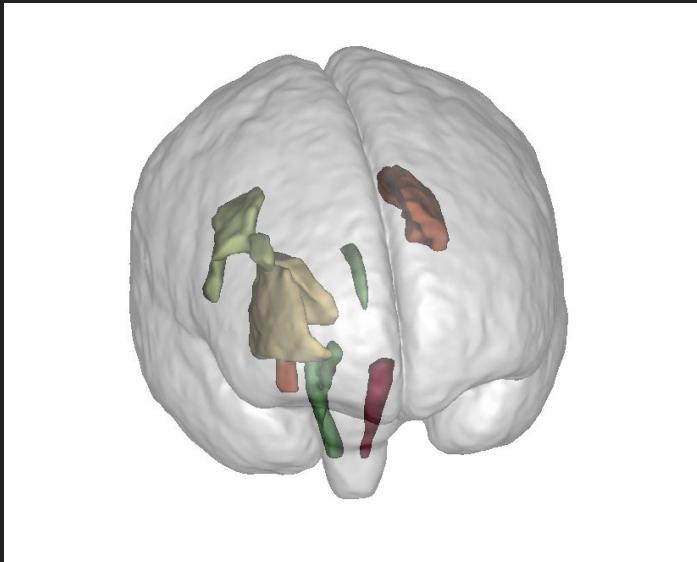


Figure 1. Glass brains ASD.

Singularities: uncinate fasciculus (upper R - light green), fornix (middle - green).

In common:

- corona radiata
- capsule
- peduncle
- cingulum

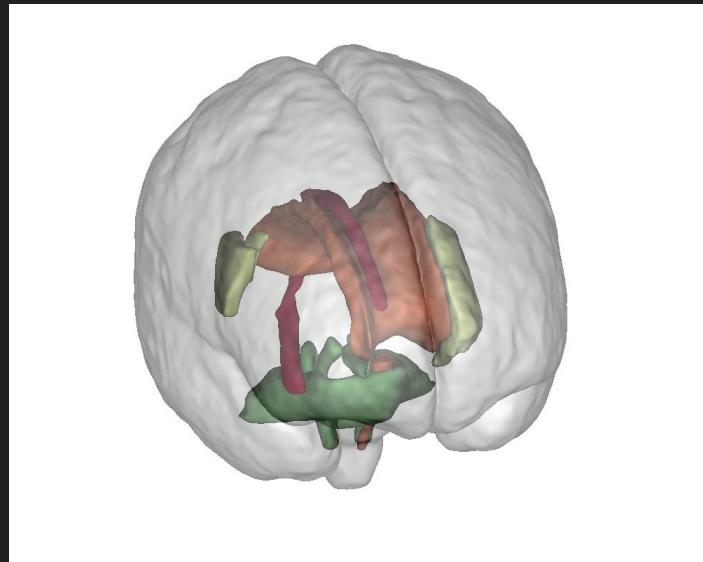


Figure 2. Glass brains AD.

Singularities: corpus callosum (middle - orange), posterior thalamic radiation (upper R - light green).

Discussion: ASD

We recovered already known associations between white matter tracts measurements and ASD:

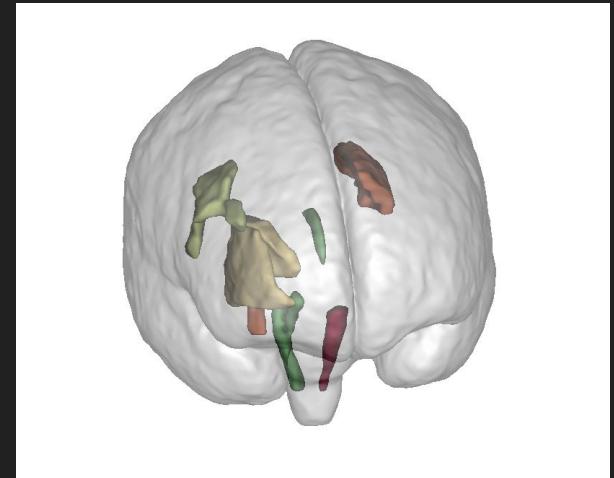
- corona radiata, internal capsule and superior longitudinal fasciculus
=> cortico-thalamic tracts involved in repetitive behaviours

(Gibbard et al., 2013)

- cingulum, fornix and uncinate fasciculus
=> limbic tracts involved in social processing (Gibbard et al., 2013)

- superior corona radiata : contains motor and sensory fibers projecting to cortex
=> could cause hypo- or hyper-responsiveness (Pryweller et al., 2014)

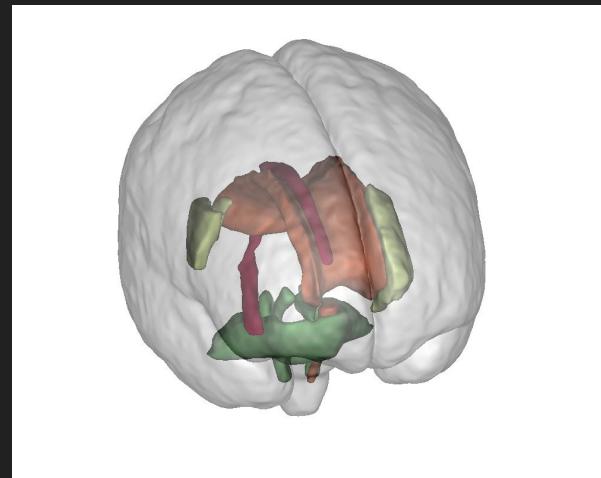
- posterior limb of internal capsule
=> involved in attentional alerting (Pryweller et al., 2014, Callejas et al., 2005, Jin Fan et al., 2009)



Discussion: AD

We recovered already known associations between white matter tracts measurements and AD:

- middle cerebellar peduncle (Miyasaka et al., 2019)
=> afferent fibers from the pons to the cerebellum
=> deposition of amyloid plaques and increased microglia reported in the cerebellum of AD (Hoxha et al., 2018)
=> cerebellum could play some role in AD
- limbic tracts: fornix, cingulum-cingulate gyrus and cingulum-hippocampus (Huang et al., 2012)
- commissural tracts: body of corpus callosum (Huang et al., 2012)
- projection tracts: anterior corona radiata (Huang et al., 2012)



Conclusion

- We have identified about ten white matter tracts significantly associated with PRS_{ASD} and PRS_{AD}
- We recovered already known associations in literature between tracts and AD/ASD
- Those tracts are involved in processes that make sense for these diseases aetiology
- This study 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

Acknowledgments

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PRSice pipeline implementation

Antoine Grigis

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