SYT1 Gene-Wide Analysis on White Matter Microstructure in Adulthood ADHD

Renata Basso Cupertino

University of Vermont

Bruna Santos da Silva

Universidade Federal do Rio Grande do Sul

Jaqueline Bohrer Schuch

Universidade Federal do Rio Grande do Sul

Cibele Edom Bandeira

Universidade Federal do Rio Grande do Sul

Maria Eduarda Tavares

Universidade Federal do Rio Grande do Sul

Pamela Ferreira da Cunha

Universidade Federal do Rio Grande do Sul

Felipe Almeida Picon

Universidade Federal do Rio Grande do Sul

Eduardo Schneider Vitola

Universidade Federal do Rio Grande do Sul

Diego Luiz Rovaris

Universidade de Sao Paulo

Eugenio Horacio Grevet

Universidade Federal do Rio Grande do Sul

Claiton Henrique Dotto Bau (✉ claiton.bau@ufrgs.br)

Federal University of Rio Grande do Sul <https://orcid.org/0000-0001-5644-3845>

Research Article

Keywords: synaptotagmin-1, attention-deficit/hyperactivity disorder, gene-wide, DTI, forceps major, inferior fronto-occipital fasciculus

Posted Date: December 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1171811/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

The Synaptotagmin-1 encoding gene (*SYT1*) is a key regulator of neurotransmitter release and is associated with cognitive and psychiatric phenotypes in GWAS, and with ADHD in single-gene studies, raising the need for dissecting possible cross-trait effects on clinical and brain phenotypes. Inferences about white matter microstructure can be made by diffusion-tensor imaging (DTI), which makes this method a promising tool in the understanding of biological changes that underpin cognitive functions and brain disorders. Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects multiple functioning domains, highly overlapping with other psychiatric disorders, and known to involve white matter abnormalities and neurotransmission dysfunction. Using a set-based analysis, the present study investigates how genetic variants within *SYT1* might affect brain white matter at a cellular level using DTI in adults with ADHD (n = 85). The combined effect of all measured variations in the gene (i.e., 468 variants) was evaluated concerning specific white matter tracts. Set-based analysis was performed in PLINK software and followed by in silico analysis of all variants included in the study. *SYT1* gene was nominally associated with white matter changes in two important tracts: forceps major and inferior fronto-occipital fasciculus. In addition, two regions within the *SYT1* have more consistent associations with different white matter tracts. These findings endorse the involvement of *SYT1* on psychiatric phenotypes and suggest that white matter tracts underlie this complex relationship.

Introduction

White matter alterations are a critical substrate in the pathophysiology of several brain disorders related to cognitive impairment, including Attention-Deficit/Hyperactivity Disorder (ADHD) (van Ewijk et al. 2014; Franck et al. 2015; Chen et al. 2016), one of the most common neurodevelopmental disorder worldwide. It is characterized by symptoms of inattention and/or hyperactivity and often accompanied by mild delays in language, motor, or social development, with individuals presenting cognitive problems on tests of attention, executive function, or memory (American Psychiatric Association 2013). Abnormalities in the white matter integrity are suggested as an early indicator of brain pathology, which is usually related to cellular scale changes in myelination and in the axon structure and maturation (Zatorre et al. 2012), leading to disturbances in the neural communication. Disrupted structural connectivity often results in abnormal functional interactions, and such alterations can be detected by diffusion-tensor imaging (DTI) studies (Cullen et al. 2010; Korgaonkar et al. 2014). Fractional anisotropy (FA) is the most common measure used in DTI studies, which is based on the water anisotropy along the axon (Beaulieu 2002), where lower FA values reflect isotropic diffusion, related to reduced white matter integrity, and it may precede tissue loss (Pfefferbaum and Sullivan 2002; Hugenschmidt et al. 2008). FA abnormalities have also been associated with axonal degeneration (Preziosa et al. 2019).

At the molecular level, neuronal dysfunction and cognitive deficits observed in psychiatric disorders are suggested to result from disturbances in proteins involved in maintenance of the synapse structure, and in the neurotransmitter release (Van Spronsen and Hoogenraad 2010; Penzes et al. 2013; Cupertino et al. 2016; Bosiacki et al. 2019). One of the key regulators of neurotransmitter release is Synaptotagmin-1,

which is abundantly expressed in the whole brain, especially in the frontal cortex. Synaptotagmin 1 is essential for the correct spatial and temporal regulation of the synaptic vesicle-mediated exocytosis, acting as a calcium sensor to induce the fusion of the presynaptic vesicle with the plasma membrane through the soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) complex binding (Südhof 2013). Besides its crucial role in neurotransmitter exocytosis, it is involved in axon branching (Greif et al. 2013), and regulation of the neuronal polarity and axon differentiation (Inoue et al. 2015).

Genome-wide association studies (GWAS) showed synaptotagmin-1 encoding gene (*SYT1*) associated with a variety of psychiatric phenotypes, including neuroticism (Luciano et al. 2018; Nagel et al. 2018b, a) and its domains of irritability and fed-up feelings (Nagel et al. 2018b, a), cognitive performance / educational attainment (Lee et al. 2018) and schizophrenia (Pardiñas et al. 2018). Considering GWAS for neuroimaging phenotypes, the *SYT1* gene was nominally associated with overall intracranial volume (Adams et al. 2016) and white matter (Zhao et al. 2019). It is noteworthy that GWAS for neuroimaging traits often have fewer significant hits than most of those for psychiatry phenotypes. This might indicate these studies have not achieve enough power.

In addition, a copy number variation study found a segment of the *SYT1* gene implicated in autism spectrum disorder (Autism Genome Project Consortium et al. 2007). Candidate gene studies showed *SYT1* variants associated with cocaine use disorder (Fernández-Castillo et al. 2012; da Silva et al. 2019), cognitive performance (Viola et al. 2019), ADHD and its related phenotypes, including susceptibility to ADHD in adults (Sánchez-Mora et al. 2013; Cupertino et al. 2017), early impairment of its symptoms (Cupertino et al. 2017), treatment response (da Silva et al. 2017) and antisocial personality disorder (Cupertino et al. 2017).

In a nutshell, overall evidence suggests that *SYT1* variants may represent a common biological factor underpinning different psychiatric phenotypes and neuroimaging features. In this sense, the present study aims to investigate how the variation in *SYT1* might affect brain white matter at a cellular level in adults with ADHD, using a set-based analysis as a data reduction approach to evaluate the effects of this gene.

Material And Methods

Sample

Participants (n = 85, mean age 46.6; 43.5% males) were recruited in the adult division of the ADHD Outpatient Clinic from Hospital de Clínicas de Porto Alegre (HCPA). ADHD diagnosis was based on DSM-5 diagnostic criteria (American Psychiatric Association 2013) and performed by experienced psychiatrists using a semi-structured interview (KSADS – E) (Grevet et al. 2005). Exclusion criteria were evidence of clinically significant neurological disease (e.g., delirium, dementia, epilepsy, head trauma) and intelligence

quotient (IQ) ≤ 70 . All participants signed an informed consent form approved by the hospital ethical committee (IRB 0000921) and in line with the principles of the Declaration of Helsinki.

Image acquisition and processing

Diffusion-weighted images were acquired using a 3T Siemens Spectra scanner with an 16-channel head coil using a single-shot echo planar imaging sequence (62 contiguous axial slices, TR/TE=11000/110ms, voxel size=2x2x2mm, slice thickness=2.0mm, FOV=240mm, one b0 image and 64 diffusion-weighted images with gradient directions $b=1400\text{s/mm}^2$). Among those 85 participants, 15 restless or claustrophobic individuals were scanned using an adapted protocol with reduced acquisition time (voxel size=2.4x2.4x2.4mm, slice thickness=2.4mm, TR/TE=11000/106ms, 32 diffusion-weighted images, other parameters remained the same). Images were corrected for motion and eddy currents and preprocessed using standard FMRIB Software Library (FSL) tools (<https://fsl.fmrib.ox.ac.uk/fsl/>), followed by visual quality control. Whole-brain FA maps for each individual were calculated using *dtifit* in FSL. Mean FA values within the TBSS skeleton were extracted for whole brain and for 11 tracts (anterior thalamic radiation - ATR, corticospinal tract - CST, dorsal cingulate gyrus - CING, ventral cingulate gyrus - HIPPCING, forceps minor, forceps major, inferior fronto-occipital fasciculus - IFOF, inferior longitudinal fasciculus - ILF, superior longitudinal fasciculus - SLF, uncinate fasciculus – UF, temporal part of SLF - SLFTEMP) according to the John Hopkins University (JHU) white-matter tractography atlas (Mori et al. 2007; Wakana et al. 2007) (<https://identifiers.org/neurovault.image:1403>). Evaluated tracts are shown in **Supplementary Figure S1**.

DNA extraction and genotyping

Blood was collected from all participants, and DNA was extracted using salting out. Samples were genotyped using Illumina Infinium PsychArray-24 v1.1. Pre-imputation quality control at individual and SNP level, principal component analyses for ancestry genetic outlier detection, and identification of related and/or duplicated individuals and gender discrepancies were performed using the Rapid Imputation and COmputational PIpeLine (RicoPili). Phasing of genotype data was performed using SHAPEIT2 algorithm, and imputation was performed with IMPUTE2 considering as reference the European ancestry panels of the 1000 Genomes Project Phase 1 version 3 (v3) (April 2012) from the genome build hg19. Post-imputation quality control was performed according to the following criteria: info score > 0.8 , minor allele frequency $> 10\%$, call rate $> 95\%$ and Hardy-Weinberg equilibrium test with $P > 1\text{e-}06$). Analyses considered a flanking region of 2kb upstream and 1kb downstream around the *SYT1* gene, resulting in 468 SNPs. Linkage disequilibrium among *SYT1* variants was calculated using the snpStats package versions 1.40.0 in R (version 4.0.3), running in RStudio (version 1.3.1073). D' and r^2 were calculated for each pair of variants to identify haplotypic blocks (**Supplementary Figure S2**).

Statistical analysis

In order to simultaneously test all measured variation in the *SYT1* gene (468 SNPs) the *set-based* test was performed under an additive genetic model in PLINK software, performing a standard single SNP analysis and selecting for the set N “independent” SNPs (linkage disequilibrium $R^2 < 0.5$, max 5 SNPs)

associated with the outcome ($p < 0.05$); the statistic for the whole set is calculated as the mean of these single SNP statistics (gene-wide analysis). Analyses were adjusted for age, gender, head motion, and the first ten principal components. Ten thousand permutations were performed, followed by False discovery rate (FDR) to correct set *p-values* per number of tracts evaluated.

In silico analysis and open databases

Prediction tools and open databases were used to investigate possible functions and previous associations of polymorphisms within the *SYT1* gene. This database search was carried out in September 2020. Genotype-Tissue Expression (GTEx - <https://gtexportal.org/home/>), RegulomeDB (<http://www.regulomedb.org>), HaploReg (<https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>), Provean (<http://provean.jcvi.org/index.php>) and GWASatlas (<https://atlas.ctglab.nl/>) were used for this purpose.

HaploReg v4.1 (Ward and Kellis 2012) is a tool for exploring annotations of the genome variants, regarding chromatin states (from DNase and histone ChIP-Seq), sequence conservation across mammals, and the effect of SNPs on regulatory motifs. Chromatin states may indicate a biologically plausible enrichment for cell type-specific enhancers. Regulatory motifs alterations are based on position weight matrices, scored on genomic sequences. RegulomeDB (Boyle et al. 2012) identifies regulatory elements, computing a probability score ranging from 0 to 1, with 1 being most likely to be a regulatory variant. Provean predicts the effect of amino acid substitution on the biological function of a protein (Choi and Chan 2015).

GTEx is a database to enable the identification of genetic variation that influence gene expression, providing data on quantitative trait locus (eQTLs). In this analysis, a *p*-value and normalized effect size (NES) of the eQTLs is attributed to each SNP. NES is a slope of the linear regression computed in a normalized space with no direct biological meaning. GWASatlas (Watanabe et al. 2019a) is a database of available GWAS summary statistics, it can provide a PheWAS for a SNP, with information regarding all phenotypes associated with this specific SNP.

Data availability

All analyses were performed by third-party and open-source publicly available software (mentioned on the manuscript). The raw data of this paper (i.e., the individual MRI scans and genotypes) cannot be publicly shared due to ethical codes of the study and preserving participants' anonymity. Population-wide brain maps, codes and summary statistics are available from the corresponding author upon a reasonable request to the corresponding author. The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files.

Results

Gene-wide analysis showed that the *SYT1* gene was nominally associated with two out of eleven evaluated tracts (Table 1): forceps major ($P_{SYT1} = 0.007$, $P_{SYT1\text{-corrected}} 0.081$), and inferior fronto-

occipital fasciculus ($P_{SYT1} = 0.026$, $P_{SYT1\text{-corrected}} = 0.143$). Moreover, all tracts tested presented significant associations with individual polymorphisms of *SYT1* gene ($P_{\text{polymorphism}} < 0.05$, **Supplementary Table S1**). Regional visualization of *SYT1* results for each outcome can be found in **Supplementary Figure S3** (designed at LocusZoom - Pruim et al., 2011).

Table 1
Gene-wide analysis of the *SYT1* gene (n = 468 variants) on Fractional Anisotropy values in adults with ADHD.

Tracts (bilateral)	N significant polymorphisms	Overall Gene Permuted P- value ^a	Overall Gene FDR corrected P-value ^b
Anterior thalamic radiation (ATR)	92	0.388	0.523
Corticospinal tract (CST)	35	0.273	0.523
Dorsal cingulate gyrus (CING)	64	0.420	0.523
Ventral cingulate gyrus (CINGHIPP)	73	0.092	0.254
Forceps major	32	0.007	0.081
Forceps minor	64	0.546	0.546
Inferior fronto-occipital fasciculus (IFOF)	108	0.026	0.143
Inferior longitudinal fasciculus (ILF)	19	0.367	0.523
Superior longitudinal fasciculus (SLF)	100	0.083	0.254
Uncinate fasciculus (UF)	12	0.544	0.546
Temporal portion of SLF (SLFTEMP)	16	0.428	0.523
FDR: False Discovery Rate. Significant P-values are represented in bold. ^a Permuted P-values (10,000 permutations). ^b Correction for the multiple phenotypes tested. Analyses adjusted for sex, age, head motion and first 10 principal components.			

Comprehensive analyses showed two regions within the *SYT1* gene appear to be more relevant considering white matter tracts (**Supplementary Figure S2**). The first region (chr12:79338164 – 79357962) includes 32 polymorphisms associated with forceps major, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus tracts, as well as 22 variants associated with the corticospinal tract and 14 with the inferior longitudinal fasciculus. Interestingly, several binding motifs and splicing quantitative trait loci (sQTL) SNPs were identified (**Supplementary Table S1**), suggesting that this region might be important to gene regulation. The second region (chr12:79781339 – 79811333) encompasses

75 variants, and most are associated with two different tracts: anterior thalamic radiation, and superior longitudinal fasciculus. Histone markers (H3K4me1, H3K27ac, H3K9ac) were detected in this region and linked to multiple polymorphisms, indicating enhancer activity and transcriptional activation. HaploReg and RegulomeDB predictions identified several binding motifs. Moreover, various SNPs were previously associated with schizophrenia and brain regions according to GWASatlas data.

Discussion

The present *SYT1* gene-wide analysis revealed nominal associations with white matter microstructure in two important tracts previously implicated in a wide variety of behaviors: the inferior fronto-occipital fasciculus and the forceps major, a part of the corpus callosum. Although other tracts were not associated in the gene-wide analysis, most of them presented several associated polymorphisms at a single SNP level. Moreover, LD pattern showed two independent regions within the *SYT1* gene encompassing many variants associated with different white matter tracts. The suggested Syt1 involvement with white matter microstructure is in agreement with its role in neurotransmitter exocytosis, axon branching (Greif et al. 2013), and regulation of the neuronal polarity and axon differentiation (Inoue et al. 2015).

Synaptotagmin 1 is also required for the release of the fibroblast growth factor 1, which is a myelination-regulator factor and is able to promote remyelination in white matter multiple sclerosis lesions (Mohan et al. 2014). The failure in this remyelination process profoundly affects axonal survival and neuronal function, and consequently cognitive functioning such as learning and memory. In addition, a lower expression of *SYT1* was observed in inflammatory processes mediated by microglia, inducing synaptic alterations (Prada et al. 2018).

Apart from the association of *SYT1* variants with psychiatry disorders and related traits, white matter has also been related to similar phenotypes. The forceps major (also known as posterior forceps of the corpus callosum) connects the occipital lobe and communicates somatosensory information between the two halves of the parietal lobe and the visual cortex at the occipital lobe (Hofer and Frahm 2006). This is particularly interesting since the corpus callosum has been associated with ADHD patients in several studies (van Ewijk et al. 2012; Lin et al. 2018; Aoki et al. 2018), being one of the most consistent findings across DTI studies (Albajara Sáenz et al. 2019). Forceps major was also associated with other psychiatric disorders, including obsessive-compulsive disorder (Watanabe et al. 2018), major depression (Shen et al. 2017; Won et al. 2017), gambling and cocaine use disorder (Yip et al. 2017), post-traumatic stress disorder (Li et al. 2016), anxiety in depressive patients (Xia et al. 2018), and mild cognitive impairment (Wen et al. 2019). Moreover, white matter abnormalities in this tract have been implicated with a wide range of cognitive behaviors, such as working memory and IQ scores (Giedd 2004; Nagy et al. 2004; Giorgio et al. 2010), control over impulses (Stoica et al. 2019), executive function (Bian et al. 2018), visual working memory (Krogsrud et al. 2018).

Another tract associated with *SYT1* in a gene-wide level was the inferior fronto-occipital fasciculus, which is the longest associative bundle, a direct pathway connecting the temporo-occipital lobe and the superior parietal lobe to the frontal lobe, integrating auditorium and visual association cortices with the prefrontal cortex (Schmahmann and Pandya 2007). This tract has been implicated with cognitive performance (Wu et al. 2016; Cocquyt et al. 2019; Kato et al. 2019), psychiatric disorders, and neurological diseases, such as early Parkinson's Disease (Li et al. 2018), subjective cognitive decline (Ohlhauser et al. 2019), high-function autism (Im et al. 2018) and autism spectrum disorder (Hattori et al. 2019), early adulthood smokers (Wang et al. 2017), depression (Wang et al. 2019), anxiety trait in healthy individuals (Lu et al. 2018). Furthermore, the inferior fronto-occipital fasciculus was identified as one of the major differences in white matter tracts between humans and macaques (Schmahmann and Pandya 2006; Martino et al. 2010; Takemura et al. 2017). In this sense, this bundle may be related to evolutionary changes underlying unique human behavioral repertoire and abilities (Thiebaut de Schotten et al. 2012; Forkel et al. 2014).

Although all variants associated in this study are intronic, several have already been pointed in GWAS. Some of the variants present in the first region of association were previously associated with Alzheimer's Disease (Lambert et al. 2013). Most polymorphisms in the second region were associated with ever smoked status (Watanabe et al. 2019), schizophrenia (Pardiñas et al. 2018) and cortical regions (Zhao et al. 2019). Some of them also presented a role as binding motifs to genes belonging to the FOX, HOX and SOX gene families, which regulates several distinct aspects of development, exerting major roles in neuronal maintenance and differentiation (Prior and Walter 1996; Krumlauf 2016; Golson and Kaestner 2016). In addition, most variants associated with forceps major and inferior fronto-occipital fasciculus are predicted to affect regulatory motifs or to act as enhancer histone markers in brain tissues (**Supplementary Table S1**).

This study must be considered in light of some strengths and limitations. The sample size of this study is relatively small for genomic analysis; however, the approach applied here has increased statistical power when compared to traditional genome-wide testing. Moreover, considering the difficulties and costs involved in the acquisition of neuroimaging data, our sample size is similar to others that have provided meaningful findings (Wu et al. 2020). Also, a specific-tract analysis as performed here restricts the findings to these structures, where a voxel-wise approach (e.g., Tract Based Spatial Statistics) would be able to identify other areas; however, such approach does not allow a gene-wide analysis. Yet, to affirm that Synaptotagmin-1 affects the white matter microstructure is beyond the scope of this paper, present results suggest the influence of the *SYT1* genetic variations on brain features that are also implicated in psychiatric disorders. Further biochemical and physiological studies can help to understand mechanism underlying this effect.

In conclusion, the variants within *SYT1* regions associated with different white matter tracts evaluated in this study appear to have important roles in the regulation of Synaptotagmin-1, which is crucial to neuronal function and white matter integrity. In particular, our findings showed a relationship between *SYT1* and microstructural changes in two substantial white matter tracts. The forceps major and the inferior fronto-occipital fasciculus tracts are both related to important cognitive functions, generally

impaired in ADHD, and other psychiatric disorders that share some of the ADHD's genetic architecture. Taken together, these results indicate that white matter abnormalities underlie the role of the *SYT1* gene in ADHD and other mental phenotypes.

Declarations

Competing interests

The author(s) declare the following potential conflict of interest with respect to the research, authorship and/or publication of the present article: Dr. EHG was on the speaker's bureau for Novartis and Shire for the last 3 years. He also received travel awards (air tickets and hotel accommodations) for participating in two psychiatric meetings from Shire and Novartis. All other authors report no financial interests or potential conflicts of interest.

Funding

This study was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (Grants 476529/2012-3, 466722/2014-1 and 424041/2016-2), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brazil (CAPES) – [finance code 001] and FIPE-HCPA 160600.

Author's contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Renata B. Cupertino, Cibele E. Bandeira, Maria Eduarda Tavares, Felipe A. Picon, and Eduardo S. Vitola. Data analyses were performed by Renata B. Cupertino, Bruna S. da Silva, Jaqueline B. Schuch, and Cibele E. Bandeira. Funding was provided by Eugenio H. Grevet and Claiton H. D. Bau. The first draft of the manuscript was written by Renata B. Cupertino and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate:

This study was performed in line with the principles of the Declaration of Helsinki. All participants signed an informed consent form approved by Ethical Committee of the Hospital de Clinicas de Porto Alegre (IRB 0000921).

Availability of data and materials:

All analyses were performed by third-party and open-source publicly available software (mentioned on the manuscript). The raw data of this paper (i.e. the individual MRI scans and genotypes) cannot be publicly shared due to ethical codes of the study and preserving participants' anonymity. Population-wide brain maps, codes and summary statistics are available upon a request to the corresponding author.

Acknowledgments:

We would like to thank all the Funding agencies, the participants included in this study who kindly accept to participate, and the whole ADHD Outpatient Program (Adult Division).

Consent to publish:

Does not apply since this manuscript does not contain any individual person's data in any form.

References

1. Adams HHH, Hibar DP, Chouraki V, et al (2016) Novel genetic loci underlying human intracranial volume identified through genome-wide association. *Nat Neurosci* 19:1569–1582. <https://doi.org/10.1038/nn.4398>
2. Albajara Sáenz A, Villemonteix T, Massat I (2019) Structural and functional neuroimaging in attention-deficit/hyperactivity disorder. *Dev Med Child Neurol* 61:399–405. <https://doi.org/https://doi.org/10.1111/dmcn.14050>
3. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. American Psychiatric Publishing, Inc., Arlington, VA, US
4. Aoki Y, Cortese S, Castellanos FX (2018) Research Review: Diffusion tensor imaging studies of attention-deficit/hyperactivity disorder: meta-analyses and reflections on head motion. *J Child Psychol Psychiatry* 59:193–202. <https://doi.org/https://doi.org/10.1111/jcpp.12778>
5. Autism Genome Project Consortium, Szatmari P, Paterson AD, et al (2007) Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet* 39:319–328. <https://doi.org/10.1038/ng1985>
6. Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system - A technical review. *NMR in Biomed* 15:435–455. <https://doi.org/10.1002/nbm.782>
7. Bian R, Zhang Y, Yang Y, et al (2018) White Matter Integrity Disruptions Correlate With Cognitive Impairments in Asthma. *J Magn Reson Imaging* 48:748–756. <https://doi.org/10.1002/jmri.25946>
8. Bosiacki M, Gąssowska-Dobrowolska M, Kojder K, et al (2019) Perineuronal Nets and Their Role in Synaptic Homeostasis. *Int J Mol Sci* 20:4108. <https://doi.org/10.3390/ijms20174108>
9. Boyle AP, Hong EL, Hariharan M, et al (2012) Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res* 22:1790–1797. <https://doi.org/10.1101/gr.137323.112>
10. Chen L, Hu X, Ouyang L, et al (2016) A systematic review and meta-analysis of tract-based spatial statistics studies regarding attention-deficit/hyperactivity disorder. *Neurosci Biobehav Rev* 68:838–847
11. Choi Y, Chan AP (2015) PROVEAN web server: A tool to predict the functional effect of amino acid substitutions and indels. *Bioinformatics* 31:2745–2747. <https://doi.org/10.1093/bioinformatics/btv195>
12. Cocquyt EM, Lanckmans E, van Mierlo P, et al (2019) The white matter architecture underlying semantic processing: A systematic review. *Neuropsychologia* 107:182.

- <https://doi.org/10.1016/j.neuropsychologia.2019.107182>
13. Cullen KR, Klimes-Dougan B, Muetzel R, et al (2010) Altered White Matter Microstructure in Adolescents With Major Depression: A Preliminary Study. *J Am Acad Child Adolesc Psychiatry* 49:. <https://doi.org/10.1097/00004583-201002000-00011>
 14. Cupertino RB, Kappel DB, Bandeira CE, et al (2016) SNARE complex in developmental psychiatry: neurotransmitter exocytosis and beyond. *J Neural Transm (Vienna)* 123:. <https://doi.org/10.1007/s00702-016-1514-9>
 15. Cupertino RB, Schuch JB, Bandeira CE, et al (2017) Replicated association of Synaptotagmin (SYT1) with ADHD and its broader influence in externalizing behaviors. *Eur Neuropsychopharmacol* 27:239–247. <https://doi.org/10.1016/j.euroneuro.2017.01.007>
 16. da Silva BS, Cupertino RB, Rovaris DL, et al (2017) Exocytosis-related genes and response to methylphenidate treatment in adults with ADHD. *Mol Psychiatry* 1–7. <https://doi.org/10.1038/mp.2017.90>
 17. da Silva BS, Cupertino RB, Schuch JB, et al (2019) The association between SYT1-rs2251214 and cocaine use disorder further supports its role in psychiatry. *Prog Neuropsychopharmacol Biol Psychiatry* 94:109642. <https://doi.org/10.1016/j.pnpbp.2019.109642>
 18. Fernández-Castillo N, Cormand B, Roncero C, et al (2012) Candidate pathway association study in cocaine dependence: The control of neurotransmitter release. *World J Biol Psychiatry* 13:126–134. <https://doi.org/10.3109/15622975.2010.551406>
 19. Forkel SJ, Thiebaut de Schotten M, Kawadler JM, et al (2014) The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography. *Cortex* 56:73–84. <https://doi.org/10.1016/j.cortex.2012.09.005>
 20. Franck W, Zwiers MP, Mennes M, et al (2015) White matter microstructure and developmental improvement of hyperactive/impulsive symptoms in attention-deficit/hyperactivity disorder. *J Child Psychol Psychiatry* 56:1289–1297. <https://doi.org/10.1111/jcpp.12379>
 21. Giedd JN (2004) Structural magnetic resonance imaging of the adolescent brain. In: *Ann N Y Acad Sci*. pp 77–85
 22. Giorgio A, Watkins KE, Chadwick M, et al (2010) Longitudinal changes in grey and white matter during adolescence. *Neuroimage* 49:94–103. <https://doi.org/10.1016/j.neuroimage.2009.08.003>
 23. Golson ML, Kaestner KH (2016) Fox transcription factors: From development to disease. *Development* 143:4558–4570. <https://doi.org/10.1242/dev.112672>
 24. Greif KF, Asabere N, Lutz GJ, Gallo G (2013) Synaptotagmin-1 promotes the formation of axonal filopodia and branches along the developing axons of forebrain neurons. *Dev Neurobiol* 73:27–44. <https://doi.org/10.1002/dneu.22033>
 25. Grevet EH, Bau CHD, Salgado CAI, et al (2005) [Interrater reliability for diagnosis in adults of attention deficit hyperactivity disorder and oppositional defiant disorder using K-SADS-E]. *Arq Neuropsiquiatr* 63(2A):307–310. <https://doi.org/10.1590/s0004-282x2005000200019>

26. Hattori A, Kamagata K, Kirino E, et al (2019) White matter alterations in adult with autism spectrum disorder evaluated using diffusion kurtosis imaging. *Neuroradiology* 61(12):1343-1353.
<https://doi.org/10.1007/s00234-019-02238-5>
27. Hofer S, Frahm J (2006) Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* 32:989–994.
<https://doi.org/10.1016/J.NEUROIMAGE.2006.05.044>
28. Hugenschmidt CE, Peiffer AM, Kraft RA, et al (2008) Relating imaging indices of white matter integrity and volume in healthy older adults. *Cereb Cortex* 18:433–442.
<https://doi.org/10.1093/cercor/bhm080>
29. Im WY, Ha JH, Kim EJ, et al (2018) Impaired white matter integrity and social cognition in high-function autism: Diffusion tensor imaging study. *Psychiatry Investig* 15:292–299.
<https://doi.org/10.30773/pi.2017.08.15>
30. Inoue Y, Kamikubo Y, Ezure H, et al (2015) Presynaptic protein Synaptotagmin1 regulates the neuronal polarity and axon differentiation in cultured hippocampal neurons. *BMC Neurosci* Dec 15;16:92. <https://doi.org/10.1186/s12868-015-0231-x>
31. Kato Y, Kagitani-Shimono K, Matsuzaki J, et al (2019) White matter tract-cognitive relationships in children with high-functioning autism spectrum disorder. *Psychiatry Investig* 16:220–233.
<https://doi.org/10.30773/pi.2019.01.16>
32. Korgaonkar MS, Fornito A, Williams LM, Grieve SM (2014) Abnormal structural networks characterize major depressive disorder: A connectome analysis. *Biol Psychiatry* 76:567–574.
<https://doi.org/10.1016/j.biopsych.2014.02.018>
33. Krogsrud SK, Fjell AM, Tamnes CK, et al (2018) Development of white matter microstructure in relation to verbal and visuospatial working memory—A longitudinal study. *PLoS ONE* 13(4):e0195540. <https://doi.org/10.1371/journal.pone.0195540>
34. Krumlauf R (2016) Hox Genes and the Hindbrain. A Study in Segments. *Curr Top Dev Bio* 116: 581–596. <https://doi.org/10.1016/bs.ctdb.2015.12.011>.
35. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *NatGenet* 45:1452–1458.
<https://doi.org/10.1038/ng.2802>
36. Lee JJ, Wedow R, Okbay A, et al (2018) Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet* 50:1112–1121. <https://doi.org/10.1038/s41588-018-0147-3>
37. Li L, Lei D, Li L, et al (2016) White Matter Abnormalities in Post-traumatic Stress Disorder Following a Specific Traumatic. *EBioMedicine* 4:176–183. <https://doi.org/10.1016/j.ebiom.2016.01.012>
38. Li XR, Ren Y De, Cao B, Huang XL (2018) Analysis of white matter characteristics with tract-based spatial statistics according to diffusion tensor imaging in early Parkinson's disease. *Neurosci Lett* 675:127–132. <https://doi.org/10.1016/j.neulet.2017.11.064>

39. Lin Q, Bu X, Wang M, et al (2018) Aberrant white matter properties of the callosal tracts implicated in girls with attention-deficit/hyperactivity disorder. *Brain Imaging Behav* 14(3): 728-735.
[https://doi.org/ 10.1007/s11682-018-0010-2](https://doi.org/10.1007/s11682-018-0010-2).
40. Lu M, Yang C, Chu T, Wu S (2018) Cerebral white matter changes in young healthy individuals with high trait anxiety: A tract-based spatial statistics study. *Front Neurol* 9:704.
<https://doi.org/10.3389/fneur.2018.00704>
41. Luciano M, Hagenaars SP, Davies G, et al (2018) Association analysis in over 329,000 individuals identifies 116 independent variants influencing neuroticism. *Nat Genet* 50:6–11.
<https://doi.org/10.1038/s41588-017-0013-8>
42. Martino J, Brogna C, Robles SG, et al (2010) Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex* 46:691–699.
<https://doi.org/10.1016/j.cortex.2009.07.015>
43. Mohan H, Friese A, Albrecht S, et al (2014) Transcript profiling of different types of multiple sclerosis lesions yields FGF1 as a promoter of remyelination. *Acta Neuropathologica Comm* 2:178.
<https://doi.org/10.1186/s40478-014-0168-9>
44. Mori S, Van Zijl P, Tamminga CA (2007) Human white matter atlas. *Am J Psychiatry* 164:1005.
<https://doi.org/10.1176/ajp.2007.164.7.1005>
45. Nagel M, Jansen PR, Stringer S, et al (2018a) Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat Genet* 2018 50:7 50:920–927. <https://doi.org/10.1038/s41588-018-0151-7>
46. Nagel M, Watanabe K, Stringer S, et al (2018b) Item-level analyses reveal genetic heterogeneity in neuroticism. *Nat Comm* 2018 9:1 9:1–10. <https://doi.org/10.1038/s41467-018-03242-8>
47. Nagy Z, Westerberg H, Klingberg T (2004) Maturation of white matter is associated with the development of cognitive functions during childhood. *J Cog Neurosci* 16:1227–1233.
<https://doi.org/10.1162/0898929041920441>
48. Ohlhauser L, Parker AF, Smart CM, Gawryluk JR (2019) White matter and its relationship with cognition in subjective cognitive decline. *Alzheimers Dement (Amst)* 11:28–35.
<https://doi.org/10.1016/j.dadm.2018.10.008>
49. Pardiñas AF, Holmans P, Pocklington AJ, et al (2018) Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet* 2018 50:3 50:381–389. <https://doi.org/10.1038/s41588-018-0059-2>
50. Penzes P, Buonanno A, Passafaro M, et al (2013) Developmental vulnerability of synapses and circuits associated with neuropsychiatric disorders. *J Neurochem* 126:165–182
51. Pfefferbaum A, Sullivan E V. (2002) Microstructural but not macrostructural disruption of white matter in women with chronic alcoholism. *Neuroimage* 15:708–718.
<https://doi.org/10.1006/nimg.2001.1018>
52. Prada I, Gabrielli M, Turola E, et al (2018) Glia-to-neuron transfer of miRNAs via extracellular vesicles: a new mechanism underlying inflammation-induced synaptic alterations. *Acta Neuropathol*

- 135:529–550. <https://doi.org/10.1007/s00401-017-1803-x>
53. Preziosa P, Kiljan S, Steenwijk MD, et al (2019) Axonal degeneration as substrate of fractional anisotropy abnormalities in multiple sclerosis cortex. *Brain* 142:1921–1937. <https://doi.org/10.1093/brain/awz143>
54. Prior HM, Walter MA (1996) Sox genes: Architects of development. *Mol Med* 2:405–412
55. Pruim RJ, Welch RP, Sanna S, et al (2011) LocusZoom: Regional visualization of genome-wide association scan results. *Bioinformatics*. pp 2336–2337
56. Sánchez-Mora C, Cormand B, Ramos-Quiroga JA, et al (2013) Evaluation of common variants in 16 genes involved in the regulation of neurotransmitter release in ADHD. *Eur Neuropsychopharmacol* 23:426–435. <https://doi.org/10.1016/j.euroneuro.2012.07.014>
57. Schmahmann JD, Pandya DN (2007) The Complex History of the Fronto-Occipital Fasciculus. *J Hist Neurosci* 16:362–377. <https://doi.org/10.1080/09647040600620468>
58. Schmahmann JD, Pandya DN (2006) *Fiber Pathways of the Brain*. Oxford University Press <https://doi.org/10.1093/acprof:oso/9780195104233.001.0001>
59. Shen X, Reus LM, Cox SR, et al (2017) Subcortical volume and white matter integrity abnormalities in major depressive disorder: Findings from UK Biobank imaging data. *Sci Rep* 7(1):5547. <https://doi.org/10.1038/s41598-017-05507-6>
60. Stoica T, Knight LK, Nazz F, et al (2019) Cortical morphometry and structural connectivity relate to executive function and estradiol level in healthy adolescents. *Brain Behav* 9(12):e01413. <https://doi.org/10.1002/brb3.1413>
61. Südhof TC (2013) Neurotransmitter release: The last millisecond in the life of a synaptic vesicle. *Neuron* 80:675–690. <https://doi.org/10.1016/j.neuron.2013.10.022>
62. Takemura H, Pestilli F, Weiner KS, et al (2017) Occipital White Matter Tracts in Human and Macaque. *Cerebr Cortex* 27:3346–3359. <https://doi.org/10.1093/cercor/bhx070>
63. Thiebaut de Schotten M, Dell'Acqua F, Valabregue R, Catani M (2012) Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex* 48:82–96. <https://doi.org/10.1016/j.cortex.2011.10.001>
64. van Ewijk H, Heslenfeld DJ, Zwiers MP, et al (2014) Different mechanisms of white matter abnormalities in attention-deficit/hyperactivity disorder: a diffusion tensor imaging study. *J Am Acad Child Adolesc Psychiatry* 53:790–9.e3. <https://doi.org/10.1016/j.jaac.2014.05.001>
65. van Ewijk H, Heslenfeld DJ, Zwiers MP, et al (2012) Diffusion tensor imaging in attention deficit/hyperactivity disorder: A systematic review and meta-analysis. *Neurosci Biobehav Rev* 36:1093–1106. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2012.01.003>
66. Van Spronsen M, Hoogenraad CC (2010) Synapse pathology in psychiatric and neurologic disease. *Curr Neurol Neurosci Rep* 10:207–214. <https://doi.org/10.1007/s11910-010-0104-8>
67. Viola TW, Schuch JB, Rovaris DL, et al (2019) Association between cognitive performance and SYT1-rs2251214 among women with cocaine use disorder. *J Neural Transm* 126(12):1707-1711.

<https://doi.org/10.1007/s00702-019-02086-w>

68. Wakana S, Caprihan A, Panzenboeck MM, et al (2007) Reproducibility of quantitative tractography methods applied to cerebral white matter. *Neuroimage* 36:630–644.
<https://doi.org/10.1016/j.neuroimage.2007.02.049>
69. Wang S, Zuo L, Jiang T, et al (2017) Abnormal white matter microstructure among early adulthood smokers: a tract-based spatial statistics study. *Neurol Res* 39:1094–1102.
<https://doi.org/10.1080/01616412.2017.1379277>
70. Wang Z, Yuan Y, You J, Zhang Z (2019) Disrupted structural brain connectome underlying the cognitive deficits in remitted late-onset depression. *Brain Imaging Behav*.
<https://doi.org/10.1007/s11682-019-00091-x>
71. Ward LD, Kellis M (2012) HaploReg: A resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. *Nucleic Acids Res* 40:.
<https://doi.org/10.1093/nar/gkr917>
72. Watanabe A, Nakamae T, Sakai Y, et al (2018) The detection of white matter alterations in obsessive–compulsive disorder revealed by TRActs constrained by underlying anatomy (TRACULA). *Neuropsychiatr Dis Treat* 14:1635–1643. <https://doi.org/10.2147/NDT.S164058>
73. Watanabe K, Stringer S, Frei O, et al (2019) A global overview of pleiotropy and genetic architecture in complex traits. *Nat Genet* 2019 51:9 51:1339–1348. <https://doi.org/10.1038/s41588-019-0481-0>
74. Wen Q, Mustafi SM, Li J, et al (2019) White matter alterations in early-stage Alzheimer's disease: A tract-specific study. *Alzheimers Dement (Amst)* 11:576–587.
<https://doi.org/10.1016/j.dadm.2019.06.003>
75. Won E, Han KM, Kang J, et al (2017) Vesicular monoamine transporter 1 gene polymorphism and white matter integrity in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 77:138–145. <https://doi.org/10.1016/j.pnpbp.2017.02.028>
76. Wu Y, Sun D, Wang Y, Wang Y (2016) Subcomponents and connectivity of the inferior fronto-occipital fasciculus revealed by diffusion spectrum imaging fiber tracking. *Front Neuroanat* 10:88.
<https://doi.org/10.3389/fnana.2016.00088>
77. Wu Z-M, Wang P, Yang L, et al (2020) Altered brain white matter microstructural asymmetry in children with ADHD. *Psychiatry Res* 285:112817.
<https://doi.org/https://doi.org/10.1016/j.psychres.2020.112817>
78. Xia W, Zhou R, Zhao G, et al (2018) Abnormal white matter integrity in Chinese young adults with first-episode medication-free anxious depression: A possible neurological biomarker of subtype major depressive disorder. *Neuropsychiatric Dis Treat* 14:2017–2026
79. Yip SW, Morie KP, Xu J, et al (2017) Shared Microstructural Features of Behavioral and Substance Addictions Revealed in Areas of Crossing Fibers. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2(2):188–195. <https://doi.org/10.1016/j.bpsc.2016.03.001>
80. Zatorre RJ, Fields RD, Johansen-Berg H (2012) Plasticity in gray and white: Neuroimaging changes in brain structure during learning. *Nat Neurosci* 15:528–536

81. Zhao B, Luo T, Li T, et al (2019) Genome-wide association analysis of 19,629 individuals identifies variants influencing regional brain volumes and refines their genetic co-architecture with cognitive and mental health traits. Nat Genet 2019 51:11 51:1637–1644. <https://doi.org/10.1038/s41588-019-0516-6>

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CupertinoSupplementaryTable.xlsx](#)
- [CupertinoSupplementaryFigures.docx](#)