

SAMRC InfoSpace

ENIGMA-DTI: Translating reproducible white matter deficits into personalized vulnerability metrics in cross-diagnostic psychiatric research

Item Type	Article
Authors	Kochunov, P.;Hong, L.E.;Dennis, E.L.;Morey, R.A.;Tate, D.F.;Wilde, E.A.;Logue, M.;Kelly, S.;Donohoe, G.;Favre, P.;Houenou, J.;Ching, C.R.K.;Holleran, L.;Andreassen, O.A.;van Velzen, L.S.;Schmaal, L.;Villalón-Reina, J.E.;Bearden, C.E.;Piras, F.;Spalletta, G.;van den Heuvel, O.A.;Veltman, D.J.;Stein, D.J.;Ryan, M.C.;Tan, Y.;van Erp, T.G.M.;Turner, J.A.;Haddad, L.;Nir, T.M.;Glahn, D.C.;Thompson, P.M.;Jahanshad, N.
Citation	Kochunov P, Hong LE, Dennis EL, Morey RA, Tate DF, Wilde EA, Logue M, Kelly S, Donohoe G, Favre P, Houenou J, Ching CRK, Holleran L, Andreassen OA, van Velzen LS, Schmaal L, Villalón-Reina JE, Bearden CE, Piras F, Spalletta G, van den Heuvel OA, Veltman DJ, Stein DJ, Ryan MC, Tan Y, van Erp TGM, Turner JA, Haddad L, Nir TM, Glahn DC, Thompson PM, Jahanshad N. ENIGMA-DTI: Translating reproducible white matter deficits into personalized vulnerability metrics in cross-diagnostic psychiatric research. Hum Brain Mapp
Publisher	Wiley
Journal	Hman Brain Mapping
Rights	Attribution 3.0 United States
Download date	2026-03-06 23:35:01
Item License	http://creativecommons.org/licenses/by/3.0/us/
Link to Item	https://infospace.mrc.ac.za/handle/11288/595318

**EDITORIAL**

ENIGMA-DTI: Translating reproducible white matter deficits into personalized vulnerability metrics in cross-diagnostic psychiatric research

Abstract

The ENIGMA-DTI (diffusion tensor imaging) workgroup supports analyses that examine the effects of psychiatric, neurological, and developmental disorders on the white matter pathways of the human brain, as well as the effects of normal variation and its genetic associations. The seven ENIGMA disorder-oriented working groups used the ENIGMA-DTI workflow to derive patterns of deficits using coherent and coordinated analyses that model the disease effects across cohorts worldwide. This yielded the largest studies detailing patterns of white matter deficits in schizophrenia spectrum disorder (SSD), bipolar disorder (BD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), traumatic brain injury (TBI), and 22q11 deletion syndrome. These deficit patterns are informative of the underlying neurobiology and reproducible in independent cohorts. We reviewed these findings, demonstrated their reproducibility in independent cohorts, and compared the deficit patterns across illnesses. We discussed translating ENIGMA-defined deficit patterns on the level of individual subjects using a metric called the regional vulnerability index (RVI), a correlation of an individual's brain metrics with the expected pattern for a disorder. We discussed the similarity in white matter deficit patterns among SSD, BD, MDD, and OCD and provided a rationale for using this index in cross-diagnostic neuropsychiatric research. We also discussed the difference in deficit patterns between idiopathic schizophrenia and 22q11 deletion syndrome, which is used as a developmental and genetic model of schizophrenia. Together, these findings highlight the importance of collaborative large-scale research to provide robust and

reproducible effects that offer insights into individual vulnerability and cross-diagnosis features.

KEYWORDS

big data, cross-disorder, DTI, ENIGMA, RVI, white matter deficit patterns

1 | INTRODUCTION

The Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium was conceived in 2009 with the goal of performing large-scale neuroimaging genetic studies and has since grown into a collaboration of more than 1,400 scientists worldwide (Thompson et al., 2013). The ENIGMA diffusion imaging working group was organized in 2009 to develop analytic workflows that analyze the effects of genes, environment, and neuropsychiatric disorders on white matter microarchitecture. The initial focus was on the multi-site analysis of fractional anisotropy (FA) images, as this is the most commonly studied scalar parameter extracted from diffusion tensor imaging (DTI) (Basser, Mattiello, & LeBihan, 1994; Pierpaoli & Basser, 1996). The absolute FA values are sensitive to fiber coherence and organization, myelination levels, and axonal integrity and have been widely used as an index of white matter health (Thomason & Thompson, 2011). FA has emerged as a sensitive index of normal white matter maturation and aging (Penke, Munoz Maniega, Houlihan, et al., 2010; Penke, Munoz Maniega, Murray, et al., 2010). Prior to the ENIGMA studies, microstructural abnormalities were reported in many neuropsychiatric illnesses and brain disorders including schizophrenia spectrum disorder (SSD) (Alba-Ferrara & de Erausquin, 2013; Friedman et al., 2008; Mandl et al., 2013; Nazeri et al., 2013), bipolar disorder (BD) (Barysheva, Jahanshad, Foland-Ross, Altshuler, & Thompson, 2013; Sprooten et al., 2011), major depressive disorder (MDD) (Carballedo et al., 2012) and others. To date, the ENIGMA-DTI

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. *Human Brain Mapping* published by Wiley Periodicals, Inc.

protocols have been used in the largest studies ranking effect sizes for case-control differences in six common neuropsychiatric disorders and a genetic microdeletion syndrome (Table 1). We review the workflow used to derive these findings, and how their high reproducibility provides a basis for individual-level measurements of microstructural signatures, thereby enabling neuropsychiatric research across diagnostic boundaries (Jahanshad et al., 2013).

2 | ENIGMA-DTI WORKFLOW

The ENIGMA-DTI workflow provided a generalizable analysis approach to extract phenotypes from DTI data collected by imaging groups around the world (Jahanshad et al., 2013). This workflow is based on tract-based spatial statistics (TBSS) (Smith et al., 2006), that uses a skeleton of major white matter tracts as the basis for determining statistical differences in regional FA values. The ENIGMA-DTI protocol adapts the TBSS approach for performing ROI-based multisite research by providing a custom protocol that includes QA/QC steps, a custom ENIGMA-DTI minimal deformation warping target along with the skeleton of major white matter tracts, and steps to extract tract-average FA values (Jahanshad et al., 2013). Diffusion measures extracted using the ENIGMA-DTI workflow showed excellent reproducibility in both test-retest (McGuire et al., 2017) and longitudinal data (Acheson et al., 2017).

The inaugural aim of the workflow was to perform multisite heritability analyses of these quantitative DTI-based phenotypes. We demonstrated that tractwise diffusion measures extracted using this workflow were consistently heritable ($h^2 = 0.42-0.75$)—regardless of the data collection protocol and study designs that included twins and siblings, extended families and pedigree-based cohorts (Jahanshad et al., 2013; Kochunov, Fu, et al., 2016). The regional heritability patterns in data collected using different DTI protocols were likewise strongly correlated with each other ($r \sim 0.6-0.9$) (Kochunov, Fu, et al., 2016; Kochunov et al., 2015; Kochunov, Jahanshad, et al., 2014; Kochunov, Patel, et al., 2019). The high reproducibility and consistent heritability of ENIGMA-DTI measures across diverse study designs and data collection protocols provided a strong rationale for disorder-oriented ENIGMA working groups to use this workflow to map deficit

patterns in studies of several major neuropsychiatric illnesses (Table 1).

3 | ENIGMA-DTI FINDINGS IN NEUROPSYCHIATRIC DISORDERS

To date, the ENIGMA-DTI workflow was used to elucidate regional patient-control differences in brain microstructure in SSD (Kelly et al., 2018), MDD (van Velzen et al., 2019), BD (Favre et al., 2019), obsessive compulsive disorder (OCD) (Piras et al., 2019), traumatic brain injury (TBI) (Dennis et al., 2018), posttraumatic stress disorder (PTSD) (Dennis et al., 2019), and 22q11 deletion syndrome (Villalón-Reina et al., 2019) (Table 1). The results are reported as Cohen's d -value effect sizes for the average FA values and for 24 regional tractwise measurements. The average FA was calculated for the entire white matter skeleton and their effect sizes are informative of the whole-brain effect sizes. The average FA values include the values for regional measurements that constitute about 20% of the total skeletons. The effect sizes were derived using the largest samples of the respective disorders available to date and consisted of hundreds to thousands of patients and controls. The use of the ENIGMA-DTI workflow across sites and disorders led to harmonized analyses of data and the reporting of effect sizes (Table 2). The triad of the most debilitating major psychiatric illnesses: SSD, BD, and MDD were characterized by highly significant reductions in the average FA values in patients compared with controls (Table 2). The largest effect size for the average FA values was observed for SSD (Cohen's $d = -0.42$, $p = 4.10^{-24}$). The patients with BD and MDD showed significant and similar negative effect sizes on the average FA values (Cohen's $d = -0.26$, $p \leq 10^{-3}$) (Table 2). Patients with SSD, BD, and MDD also showed a pattern of significant regional reductions in FA values. The comparison of regional effect sizes across the disorders provided a unique opportunity to summarize the impact of these illnesses across diagnostic categories (discussed in Section 4.2). Other illnesses did not show significant patient-control differences for the average FA values. Patients with OCD showed a modest number of regions, including the sagittal stratum (SS) and posterior thalamic radiation (PTR), where cases on average, had lower FA than controls (Table 2).

TABLE 1 The number of subjects and cohorts that were used to derive disorder specific patterns for patient control differences

Disorder	N-subjects (patients/controls)	N-cohorts	Citation
SSD	N = 4,322 (1963/2359)	29	(Kelly et al., 2018)
BD	N = 3,033 (1,482/1551)	26	(Favre et al., 2019)
MDD	N = 2,907 (1,305/1602)	20	(van Velzen et al., 2019)
22q11DS	N = 594 (334 /260)	10	(Villalón-Reina et al., 2019)
PTSD	N = 3,049 (1,446/1,603)	28	(Dennis et al., 2019)
OCD	N = 1,345 (700/645)	19	(Piras et al., 2019)
TBI	N = 705 (437/268)	5	(Dennis et al., 2018)

Abbreviations: BD, bipolar disorder; ENIGMA, Enhancing Neuro Imaging Genetics through Meta-Analysis; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SSD, schizophrenia spectrum disorder; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

TABLE 2 Meta-analytical effect sizes (Cohen's *d*-values) (with group-wise significance in parentheses) of the patients versus control differences in disorders studied by ENIGMA disorder-oriented workgroups. The sample information for each disorder is provided in Table 1

Region	SSD	BD	MDD	22q11DS	PTSD	OCD	TBI
Average FA	-0.42 (4.10 ⁻²⁴)	-0.26 (6.10 ⁻⁴)	-0.26 (1.10 ⁻³)	0.09 (0.3)	-0.02 (0.7)	-0.20 (0.07)	0.12 (0.2)
Anterior corona radiata (ACR)	-0.40 (9.10 ¹⁹)	-0.24 (1.10 ⁻⁶)	-0.25 (1.10 ⁻³)	0.23 (0.1)	-0.01 (0.9)	-0.12 (0.2)	0.04 (0.7)
Anterior limb of internal capsule (ALIC)	-0.37 (2.10 ⁻¹⁵)	-0.15 (4.10 ⁻³)	-0.23 (4.10 ⁻³)	0.64 (1.10 ⁻¹²)	-0.04 (0.3)	-0.06 (0.6)	0.04 (0.7)
Body of corpus callosum (BCC)	-0.39 (2.10 ⁻¹⁸)	-0.43 (2.10 ⁻¹⁶)	-0.24 (2.10 ⁻³)	0.37 (3.10 ⁻⁵)	-0.04 (0.30)	-0.11 (0.30)	0.03 (0.7)
Corpus callosum (CC)	-0.40 (8.10 ⁻¹⁹)	-0.46 (5.10 ⁻¹⁷)	-0.25 (2.10 ⁻³)	0.54 (1.10 ⁻⁹)	-0.05 (0.2)	-0.16 (0.1)	0.002 (0.9)
Cingulum (cingulate gyrus part) CGC	-0.27 (3.10 ⁻⁹)	-0.39 (6.10 ⁻¹¹)	-0.17 (2.10 ⁻³)	0.20 (0.04)	-0.03 (0.4)	-0.06 (0.4)	-0.01 (0.9)
Perihippocampal cingulum tract (CGH)	-0.11 (0.01)	-0.07 (0.14)	-0.07 (0.14)	-0.45 (1.10 ⁻⁴)	0.02 (0.7)	-0.07 (0.3)	0.07 (0.4)
Corona radiata (CR)	-0.33 (3.10 ⁻¹⁷)	-0.20 (4.10 ⁻⁴)	-0.25 (2.10 ⁻³)	0.38 (1.10 ⁻⁵)	-0.02 (0.5)	-0.13 (0.3)	0.09 (0.3)
Cortico-spinal tract (CST)	-0.04 (0.24)	0.00 (1.00)	-0.10 (0.10)	0.05 (0.7)	0.03 (0.5)	0.06 (0.3)	-0.14 (0.2)
External capsule (EC)	-0.21 (1.10 ⁻⁷)	-0.23 (4.10 ⁻⁷)	-0.16 (0.02)	-0.47 (1.10 ⁻⁴)	0.03 (0.4)	-0.12 (0.2)	0.20 (0.02)
Fornix (FX)	-0.31 (7.10 ⁻¹²)	-0.29 (8.10 ⁻⁸)	-0.08 (0.09)	-0.74 (1.10 ⁻¹³)	-0.02 (0.7)	-0.11 (0.2)	0.08 (0.4)
Fornix/Stria terminalis (FXST)	-0.32 (8.10 ⁻¹⁴)	-0.16 (7.10 ⁻⁵)	-0.18 (3.10 ⁻³)	-0.30 (0.01)	0.00 (1.0)	-0.08 (0.4)	-0.04 (0.7)
Genu of corpus callosum (GCC)	-0.37 (1.10 ⁻¹⁶)	-0.37 (2.10 ⁻⁶)	-0.25 (1.10 ⁻³)	0.58 (4.10 ⁻⁹)	-0.01 (0.8)	-0.17 (0.04)	-0.01 (0.9)
Internal capsule (IC)	-0.18 (2.10 ⁻⁵)	-0.07 (0.2)	-0.23 (0.01)	0.68 (1.10 ⁻¹³)	0.00 (0.9)	-0.02 (0.9)	0.03 (0.7)
Uncinate fasciculus (UNC)	-0.11 (0.004)	-0.19 (2.10 ⁻⁶)	-0.12 (0.01)	0.03 (0.7)	0.02 (0.6)	-0.04 (0.6)	0.12 (0.2)
Posterior corona radiata (PCR)	-0.25 (2.10 ⁻¹²)	-0.15 (3.10 ⁻³)	-0.20 (4.10 ⁻³)	0.52 (6.10 ⁻⁹)	-0.04 (0.3)	-0.16 (0.02)	0.18 (0.03)
Posterior limb of internal capsule (PLIC)	0.04 (0.37)	0.04 (0.5)	-0.15 (0.08)	0.81 (2.10 ⁻¹⁵)	0.03 (0.5)	0.04 (0.6)	0.01 (0.9)
Posterior thalamic radiation (PTR)	-0.31 (1.10 ⁻¹⁸)	-0.30 (3.10 ⁻¹²)	-0.14 (0.12)	-0.01 (0.9)	-0.03 (0.5)	-0.26 (1.10 ⁻³)	0.12 (0.3)
Retrolenticular limb of the internal capsule (RLIC)	-0.13 (0.002)	-0.05 (0.40)	-0.15 (0.05)	0.20 (0.07)	0.00 (1.00)	-0.03 (0.8)	0.04 (0.6)
Splenium of corpus callosum (SCC)	-0.22 (4.10 ⁻⁶)	-0.34 (2.10 ⁻¹⁰)	-0.13 (0.04)	0.44 (2.10 ⁻⁴)	-0.08 (0.10)	-0.12 (0.2)	0.02 (0.9)
Superior corona radiata (SCR)	-0.15 (7.10 ⁻⁶)	-0.09 (0.13)	-0.20 (0.02)	0.26 (3.10 ⁻³)	-0.02 (0.6)	-0.07 (0.4)	0.12 (0.2)
Superior fronto-occipital fasciculus (SFO)	-0.29 (4.10 ⁻⁸)	-0.15 (4.10 ⁻³)	-0.23 (4.10 ⁻³)	-0.12 (0.5)	-0.10 (0.01)	-0.08 (0.3)	0.06 (0.50)
Superior longitudinal fasciculus (SLF)	-0.22 (6.10 ⁻⁸)	-0.23 (5.10 ⁻⁶)	-0.17 (0.04)	-0.32 (2.10 ⁻⁴)	0.03 (0.5)	-0.12 (0.3)	0.26 (0.003)
Sagittal stratum (SS)	-0.30 (5.10 ⁻¹⁴)	-0.20 (8.10 ⁻⁵)	-0.23 (4.10 ⁻³)	0.08 (0.5)	-0.02 (0.6)	-0.21 (0.001)	0.09 (0.4)
Tapetum (TAP)	-0.16 (9.10 ⁻⁷)	-0.25 (2.10 ⁻⁶)	-0.12 (0.17)	0.86 (6.10 ⁻²¹)	-0.11 (0.01)	-0.18 (0.01)	0.14 (0.09)

Abbreviations: BD, bipolar disorder; ENIGMA, Enhancing Neuro Imaging Genetics through Meta-Analysis; FA, fractional anisotropy; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SSD, schizophrenia spectrum disorder; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

Subjects with PTSD showed no difference in either average (Cohen's $d = -0.02$, $p = .7$) or regional FA values (Table 2). Subjects with the 22q11 deletion syndrome showed no significant difference in average FA values from controls (Cohen's $d = 0.09$, $p = .3$), yet there were large regional effect sizes in both directions. On average, cases had higher FA values compared to controls in the callosal and cortico-thalamic tracts and lower FA in the fornix-stria terminalis (FX-ST), superior longitudinal fasciculus (SLF), and the external/extreme capsules (EC). 22q11 deletion syndrome is a chromosomal microdeletion syndrome that greatly elevates risk for psychosis and schizophrenia. A finding of higher FA values in frontal areas in 22q11 deletion subjects stands in contrast with generally negative effects on FA observed in the three major neuropsychiatric disorders. However, it is consistent with post-mortem histological examinations that showed higher cumulative cellular membrane circumference of cerebral white matter axons in 22q11 deletion patients (Villalón-Reina et al., 2019). Subjects with TBI (primarily mild TBI) likewise showed nonsignificant effects in the average FA (Cohen's $d = 0.12$, $p = .20$) and chiefly positive but nonsignificant regional effect sizes (higher FA values) when compared with controls (Table 2). This finding was interpreted as a possible marker of recovery by the original study (Dennis et al., 2018). Together, these findings provide the first opportunity to evaluate the cross-disorder similarity, especially if these findings are reproducible in the independent samples.

4 | REPRODUCIBILITY OF ENIGMA FINDINGS IN NEUROPSYCHIATRIC DISORDERS

Research findings in neuropsychiatric illnesses have historically suffered from a substantial variability and heterogeneity both within and across disorders including genetics, environmental risk factors, mean age of onset, symptom presentations, treatment response, and long-term prognosis. The sources of heterogeneity have long remained elusive to clinicians and scientists and have contributed to a surprisingly poor reproducibility of neuroanatomical, functional, and genetic findings in neuropsychiatric illnesses. Meta-analysis has always offered a principled approach to screen studies for false positive findings by overcoming the “chasing of significance” observed in some discovery studies (Ioannidis, 2014). The big data analyses performed by ENIGMA differ from the traditional meta-analytic studies that derive the mean effect from group-level comparisons based on *previously published* effect sizes and often fall prey to the heterogeneity of the underlying methods used in the original studies. Instead, ENIGMA analyses are more akin to the “multisite-study analytic” approaches that directly coordinate the analysis of many data sets, by a group of collaborating scientists using the methods vetted for multisite research. However, ENIGMA does not enforce an a priori selection of image acquisition protocols and behavioral or diagnostic assessments. Instead, ENIGMA pays considerable attention at each participating site to ensure the quality, integrity, and homogeneity of the underlying data, validity of the outcomes, and reproducibility of the deficit patterns.

A study by the ENIGMA-schizophrenia workgroup on subcortical deficits was the first validation of large-scale cooperative analyses of neuroimaging data in a severe mental illness. It used standardized methods to assess a sample of 2,028 patients and 2,540 controls from 15 centers worldwide (van Erp et al., 2015). This was the first study to show that the effect size for the smaller hippocampus in SSD patients was greater than that for the well-known enlargement of the lateral ventricles, refocusing attention on the neurological basis of this disorder. It also provided the first opportunity to test the premise that Big Data neuroimaging approaches could improve the reproducibility of findings in a disorder known for its heterogeneity. In a recent editorial, we observed that the effect sizes for patient-control group differences for volumes of subcortical structures reported by the ENIGMA-schizophrenia group were in remarkable correlation ($r^2 > 0.9$) with two studies performed since then in largely independent cohorts (Alnaes et al., 2019; Kochunov, Thompson, & Hong, 2019; Okada et al., 2016).

The ENIGMA-schizophrenia group followed up with the study of white matter alterations based on a sample of 1,963 patients and 2,359 healthy controls from 29 independent international cohorts (Kelly et al., 2018; Holleran et al., 2020). This study was the first to report a regional localization of deficits in this illness as the regional pattern of effect sizes. The associative white matter tracts that connect the frontal, parietal, temporal, and limbic areas such as the anterior *corona radiata* (ACR) and the body and *genu* of the corpus callosum (GCC), showed significantly lower FA values in individuals with schizophrenia compared with controls. In contrast, cerebral pathways that carry sensorimotor fibers, such as the corticospinal tract and posterior limb of the internal capsule, showed no detectable patient-control group differences (Table 2). Importantly, patients diagnosed with schizophrenia also had significantly lower integrity of the fornix (FX)—the primary tract connecting the hippocampus with the frontal brain regions, consistent with the anatomical specificity observed for the subcortical volumetric deficits.

The regional pattern of white matter deficits reported by the ENIGMA illness-focused working groups has since been replicated by several independent studies, including a recent meta-analysis study from the Japanese Cognitive Genetics Collaborative Research Organization (COCORO) consortium. The Social Processes Initiative in the Neurobiology of Schizophrenia (SPINS) study showed that regression of site-specific sources of methodological variance—such as day-to-day variations in scanner magnetic field gradients, RF coils, and electronics performance measured using a diffusion phantom—significantly improved the agreement between white matter deficit patterns in the SPINS sample and the ENIGMA-schizophrenia pattern; correlations increased from 0.55 to 0.81 (Kochunov, Dickie Erin, et al., 2018). Kochunov and colleagues showed that the ENIGMA-schizophrenia pattern was very highly correlated ($r = 0.92$) with the measured deficit pattern in another cohort and partly explained the two chief cognitive deficits in SSD: processing speed and working memory (Kochunov et al., 2017). A report on findings from the Beijing Connectome Project (BCP) found a high correlation ($r = 0.86$) between regional effect sizes observed in a sample of Han Chinese and the

The regional vulnerability index (RVI) was developed as a simple correlational approach to quantify the agreement between an individual's brain and the expected pattern for the disorder. In contrast to PRS, the RVI approach is based on effect sizes derived from ethnically diverse samples and therefore RVI values are translatable across ethnicities (Kochunov, Huang, et al., 2019). RVI is a correlation coefficient between the normalized regional measures in an individual, such as tractwise FA or cortical gray matter thickness values, and the pattern of regional effect sizes reported by ENIGMA. A normalization process is used before computing the index, which includes a linear regression to remove effects of covariates, such as age and sex, from the individual's data, followed by z-transforming the residuals using the average and SD calculated from the healthy controls. For each subject, this produces a vector of regional measurements that captures the deviation from the normative values for each brain region and therefore mimics the contrast captured by the Cohen's *d*-values reported by ENIGMA. Higher RVI values (with a maximum of 1.0) indicate a better correlation with the expected disorder pattern. We hypothesized that higher similarity to the expected pattern is indicative of individual vulnerability to a disorder (Kochunov, Huang, et al., 2019).

We evaluated the RVI calculated for white matter DTI as a marker of treatment resistance in SSD (Kochunov, Huang, et al., 2019). The link between treatment resistance and cerebral white matter in SSD was suggested by previous white matter volume reduction findings (Molina et al., 2005) and reduced FA values (Holleran et al., 2014; Vanes, Mouchlianitis, Wood, & Shergill, 2018). In our study, we observed that RVI in treatment resistant patients was significantly higher than in patients who responded to treatment. Yet, no individual white matter region could consistently separate the treatment-resistant and treatment-responsive patients. This suggested that ENIGMA-schizophrenia pattern in white matter may capture the deficits in this illness that do not improve with treatment. In Kochunov and colleagues' manuscript (published in this issue, Kochunov et al., 2020) we present the findings of white matter, cortical, and subcortical RVI in SSD. We show that the "agreement" with the respective SSD patterns can be used as a novel biomarker that is independent of the absolute differences in regional traits. Domain-specific RVI values were significantly correlated with cognition and negative symptoms, even in the absence of significant correlation in the individual traits from that neuroimaging domain. It is not immediately clear why RVI captures individual variance in cognitive deficits and symptoms severity, but individual regional measures do not. Higher RVI-SSD values likely reflect the contrast between the high vulnerability of associative and the lower vulnerability of motor and sensory brain regions to SSD (Kochunov, Ganjgahi, et al., 2016; Weinberger, 1996; Weinberger & Lipska, 1995). We hypothesize that by considering findings across the whole brain, RVI accentuates the regional effects specific to SSD. Therefore, higher RVI values are identified in the individuals with more severe patterns of neurodevelopmental damage, who, in turn, are more vulnerable to developing cognitive deficits and negative symptoms.

In Kochunov et al. (2020), presented in this issue, we show that RVI can be calculated as a multimodal index by considering cortical

thickness, subcortical gray matter volumes, and white matter microstructure measurements. Combining phenotypes across diverse neuroimaging modalities to derive a meaningful index of vulnerability is challenging, but the ENIGMA-schizophrenia findings provided a common denominator to combine these data. We first showed that RVI derived from cortical gray matter thickness, subcortical gray matter volume, and white matter integrity can inform patient-control differences and provide insight into the timeline for establishing these deficits in SSD. Elevated cortical RVI was readily detectable in the early diagnosis group (≤ 5 years since diagnosis) and remained stable with illness duration. This suggests that cortical deficits may develop before the onset of illness and do not change with illness duration. In contrast, white matter RVI was significantly elevated between early and chronic patients, suggesting ongoing illness progression. However, the multimodal RVI showed both the highest effect sizes among all measurements for all groups and was higher in chronic patients. While these findings are preliminary and are based on cross-sectional analyses, they demonstrate the potential for translating ENIGMA patterns to the individual level. We expect that novel analytic approaches, including machine learning, will take advantage of the ENIGMA datasets to derive more comprehensive measures that translate statistics from a large group to make predictions about an individual.

4.2 | ENIGMA-DTI: Facilitating cross-diagnostic analyses

The patterns of patient-control deficits derived using the ENIGMA-DTI workflow by neuropsychiatric disorder-oriented workgroups provide a "bottom-up" approach to evaluate the "integrative" versus "diagnostic silos" heuristics in neuropsychiatric research (Bzdok & Meyer-Lindenberg, 2017; McEwen, 2017). The integrative heuristic argues that risk factors, including genetics, stress, and others, are shared across major neuropsychiatric illnesses, while the diagnostic silos heuristic argues for separation of etiopathological factors while accepting potential co-morbidity of these illnesses. Big data psychiatric genetics research provides evidence for the integrative nature of mental illness by showing strong genetic correlation ($\rho_G = 0.5-0.7$) among the risk loci for a range of common neuropsychiatric disorders and a significant overlap in PRS across SSD, BD, MDD, and OCD (Brainstorm et al., 2018; Cross-Disorder Group of the Psychiatric Genomics, 2013; Docherty, Moscati, & Fanous, 2016). The combined efforts of the ENIGMA working groups provide us with the opportunity to examine the overlap in deficit patterns across disorders and to compare them to deficit patterns in chiefly genetic disorders (22q11 deletion syndrome) and/or with chiefly acquired (TBI) conditions.

The patterns of the effect sizes of the patient-control differences showed strong correlations in regional effects sizes between SSD and BD ($r = 0.72$), SSD and MDD ($r = 0.68$), and SSD and OCD ($r = 0.66$) (Figure 2). The regional effect sizes were also strongly correlated between BD and OCD ($r = 0.64$) but not between BD and MDD ($r = 0.28$); nor MDD and OCD ($r = 0.29$) (Figures 2 and 3). The SSD, BD, and MDD had a striking similarity in the negative effects these

illnesses have on the association and commissural tracts: both anterior (ACR, BCC, and GCC) and posterior (*sagittal stratum* [SS] and *posterior corona radiata* [PCR]) tracts. A notable difference was the integrity of the FX and FX/ST tracts that showed significant deficits in SSD and BD but not in MDD (Figure 3, Table 2). This suggests some anatomical specificity and partially replicates the findings of shared genetic risk factors among SSD, BD, and MDD (Brainstorm et al., 2018; Docherty et al., 2016). Strong correlations in regional effect sizes between SSD and BD ($r = 0.75$) and SSD and MDD ($r = 0.82$) were later replicated in COCORO data, however, the MDD and BD patients also showed a strong correlation in that cohort ($r = 0.73$) (Koshiyama et al., 2019). The deficit pattern of PTSD showed moderate correlation with the

deficit pattern of BD ($r = 0.43$), OCD ($r = 0.43$), and SSD ($r = 0.39$) and a very weak correlation with MDD ($r = 0.22$). This further supports anatomical specificity of the white matter deficits and partially replicates genetic correlation patterns among these illnesses (Brainstorm et al., 2018). We observed no significant correlation between disorders with a strong genetic component (SSD, BD, MDD, PTSD, OCD, and 22q11) and TBI—which is presumed to have mainly causes of acquired injury and environment, though individual genetics likely affects the recovery and preexisting psychiatric disorders are associated with a worse outcome after TBI (Gerring et al., 1998). However, we observed a moderate negative correlation between TBI and OCD ($r = 0.40$) but this finding is difficult to interpret.

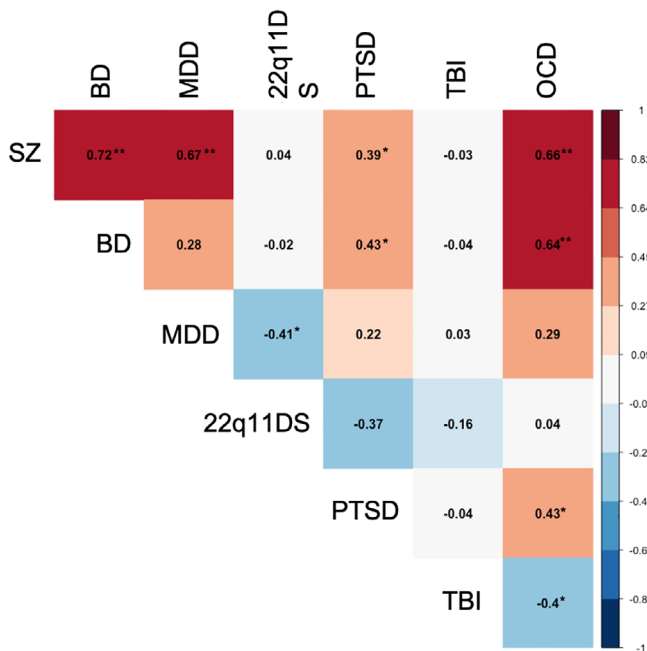


FIGURE 2 The correlation in regional deficit patterns among common neuropsychiatric disorders. **Indicates strong correlation coefficients. *Indicates moderate correlation coefficients

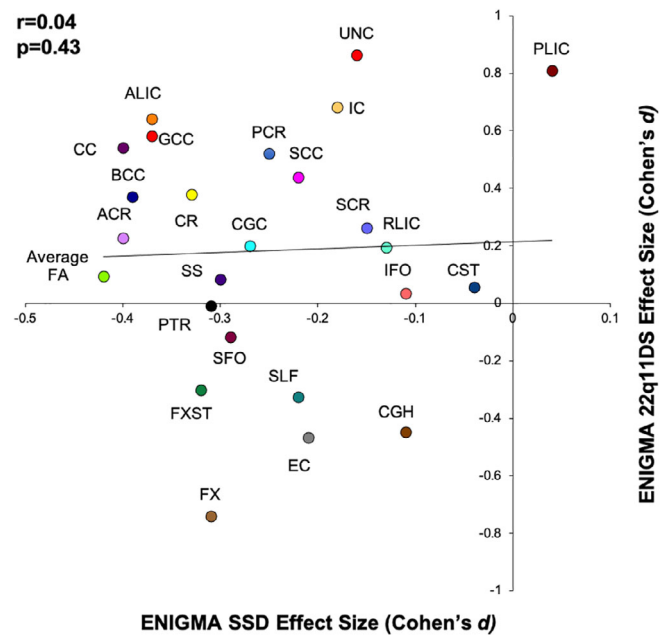


FIGURE 4 The scatter plot of regional effect sizes for 22q11DS versus SSD. Notable is high negative effect size in the Fornix (FX) 22q11DS that overlaps with negative effects of this tract in SSD. SSD, schizophrenia spectrum disorder

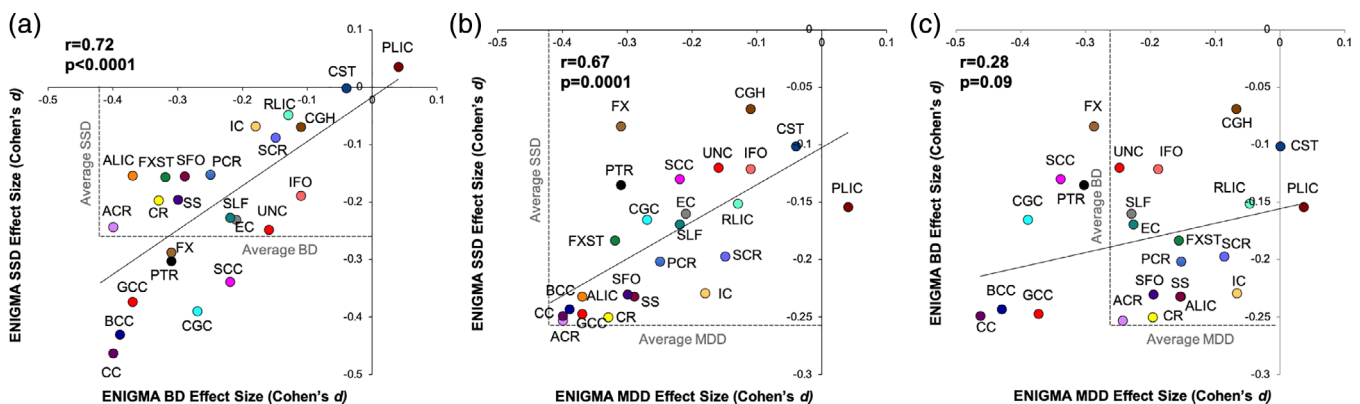


FIGURE 3 The scatter plot of regional effect sizes for (a) BD versus SSD; (b) MDD versus SSD, and (c) MDD versus BD. BD, bipolar disorder; MDD, major depressive disorder; SSD, schizophrenia spectrum disorder

We observed no correlation ($r = 0.04$) between the 22q11 deletion pattern of regional effect sizes and that of SSD (Figure 4). 22q11 deletion is used as a developmental and genetic animal model for SSD (Mancini et al., 2019; Sumitomo et al., 2018) because people born with this deletion are 20–30 times more likely to develop psychosis. In striking similarity with SSD, the onset of psychosis is preceded by development of cognitive deficits, chiefly in the verbal learning and working memory domains (Vorstman et al., 2015). While subjects with the 22q11 deletion showed higher FA values in frontal areas, both SSD and 22q11 showed significantly lower integrity of the FX and FX/ST tracts (Figure 4), which is supported by findings of lower hippocampal volumes in both conditions compared to controls. This difference in regional deficits is also mirrored by the pattern of cognitive deficits between the two conditions. The deficits in processing speed are pervasive in SSD and are linked to lower integrity of associative white matter tracts (Kochunov et al., 2010; Kochunov et al., 2017), but these deficits are minored in 22q11 deletion syndrome. Conversely, both

disorders showed significant deficits in verbal learning and working memory domains (Chawner et al., 2017; Vorstman et al., 2015).

To summarize the regional deficit data, we performed a hierarchical clustering analysis and measured the Euclidean distance among clusters (Figure 5, Table 3). Ward's minimum variance method was used to cluster the illness-specific patterns based on the half-square Euclidean distance among the deficit vectors. The disorder patterns were separated into three clusters based on their proximity. MDD, SSD, and BD were clustered together with the average distance between them of 0.56 ± 0.07 . PTSD and OCD likewise were clustered together with TBI with an average distance between them equal to 0.73 ± 0.28 . The pattern for 22q11 deletion syndrome was given its own cluster based on large distances from the MDD, SSD, and BD (distance = 2.9 ± 0.09) and PTSD, OCT, and TBI (distance = 2.36 ± 0.14).

4.3 | Limitations

This summary of ENIGMA cross-disorder analyses demonstrates significant limitations of the biological interpretations that can be derived from DTI data within and across disorders. We observed that patient-control differences can be both negative and positive indicating that neuropsychiatric conditions are associated with both lower and higher FA values in affected individuals. This signifies the general limitation of the DTI approach to quantify diffusion behavior of water (Basser & Pierpaoli, 1996). FA is a convenient statistical parameter produced by fitting a tensor that assumes a nonanisotropic Gaussian diffusion process and does not carry explicit biological information. While FA is often interpreted as an index sensitive to the degree of axonal myelination (Song et al., 2003; Song et al., 2005), it is neither a direct nor a specific measurement (Beaulieu, 2002). There are physical limitations to the assumptions of a multivariate Gaussian model used by DTI to approximate the diffusion in complex biological tissues. Chief among them is that this assumption is only successful at modest diffusion weighting (b -values up to ~ 1000 s/mm²). At higher diffusion weighting, the diffusion decay cannot be approximated by a mono-exponential fit that suggests a complex, multicompartamental nature of this signal (Assaf & Cohen, 1998; Clark, Hedehus, & Moseley, 2002; Kochunov, Chiappelli, & Hong, 2013; Kochunov, Chiappelli, et al., 2014; Wu, Field, Duncan, et al., 2011; Wu, Field, Whalen, &

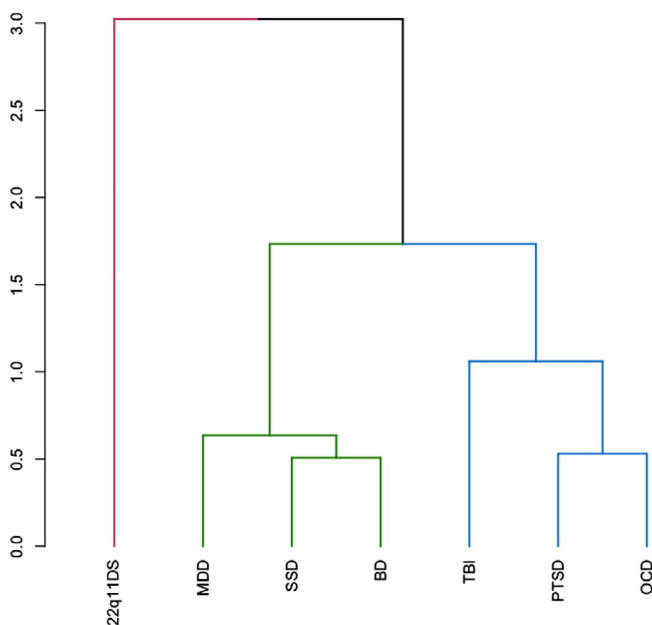


FIGURE 5 Hierarchical clustering of white matter deficit patterns across neuropsychiatric illnesses ascertained by ENIGMA. ENIGMA, Enhancing Neuro Imaging Genetics through Meta-Analysis

TABLE 3 Euclidean distance among illness-specific patterns of white matter deficits identified by the hierarchical clustering analysis

	SSD	BD	MDD	22q11DS	PTSD	TBI
BP	0.5063376					
MDD	0.5643102	0.6361531				
X22q	3.0234198	2.9166163	2.8504258			
PTSD	1.2727376	1.1126883	0.8718744	2.355787		
TBI	1.7329883	1.5730065	1.333859	2.2347175	0.6215351	
OCD	0.8618856	0.7279523	0.567146	2.513722	0.5301395	1.059763

Abbreviations: BD, bipolar disorder; ENIGMA, Enhancing Neuro Imaging Genetics through Meta-Analysis; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SSD, schizophrenia spectrum disorder; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

Alexander, 2011). These non-Gaussian diffusion components (Novikov Dmitry, Kiselev Valerij, & Jespersen Sune, 2017; Novikov, Fieremans, Jensen, & Helpert, 2011) may both carry important information relevant to a disorder (Kochunov, Rowland, et al., 2016) as well as affect the fit of DTI model due to incomplete quantification of the diffusion process (Kochunov, Chiappelli, et al., 2014).

5 | CONCLUSION

The ENIGMA-DTI workflow was developed for imaging genetic analysis and validated by demonstrating uniform and reproducible heritability patterns across regional phenotypes. It was used across multiple brain disorders by ENIGMA workgroups and other studies for its ability to run the same analysis protocol worldwide, thus allowing multiple regional phenotypes to be aggregated and to deduce salient, consistent, and robust deficit patterns across illnesses. The regional deficits patterns published by ENIGMA in SSD and BD were already replicated in independent cohorts across the world, with the MDD pattern showing partial replication. ENIGMA deficit patterns can also be used to measure the agreement between an individual's brain scans and the aggregated patterns for each illness, offering a similarity metric to the canonical signatures observed in each disorder. Data across neuroimaging modalities can be combined into a multimodal index of individual vulnerability to various disorders. Such metrics may represent potential biomarkers for pharmacological studies of agents that aim to shift an individual away from the established pattern that is characteristic of a given disease. ENIGMA is equipped to run standardized analysis pipelines across disorders. Therefore, the similarity in deficit patterns across the major neuropsychiatric conditions can be readily assessed. The overlap and uniqueness in disorder-specific white matter deficit patterns were consistent with the genetic correlation of risk loci for common neuropsychiatric disorders.

ACKNOWLEDGMENTS

Support was received from the National Institutes of Health grants: R01MH111671, R01MH112180, R01MH116948, S10OD023696, 5T32MH073526, R01EB015611, U01MH108148, and NIMH R01085953 (CEB), R21 MH116473 (CEB), and R01MH117601. Core funding for ENIGMA was provided by the NIH Big Data to Knowledge (BD2K) program under consortium grant U54 EB020403 (PI: Thompson). Additional support was provided by grants to the ENIGMA World Aging Center (R56 AG058854; PI: Thompson), the ENIGMA Sex Differences Initiative (R01 MH116147; PI: Thompson), the ENIGMA-PGC PTSD Working Group (R01 MH111671; PI: Morey), the ENIGMA Epilepsy Working Group (R01 NS107739; to McDonald), a Kavli Foundation Neuroscience without Borders seed grant (to Jahanshad and Thompson), an NIH instrumentation grant (S10 OD023696 to Kochunov), and ENIGMA-COINSTAC: Advanced Worldwide Transdiagnostic Analysis of Valence System Brain Circuits (1R01MH121246-01, to Turner, Calhoun, and van Erp). Support was also provided by the Italian Ministry of Health, grant RC 15-16-17-18-19/A, Fondation pour la recherche médicale


“Bioinformatics for Biology 2014” grant. These funding sources provided financial support to enable design and conduct of the study and collection, management, and analysis of the data. None of the funding agencies had a role in the interpretation of the data. None had a role in the preparation, review, or approval of the manuscript. None had a role in the decision to submit the manuscript for publication. N.J. is supported by R01 AG059874 and R01 MH117601 (to N.J. and L.S.). C.R.K.C. is supported by ENIGMA's NIH Big Data to Knowledge (BD2K) initiative U54 EB020403, T32 Postdoctoral Scholar Fellowship Trainee Grant 5251831121, NIA T32AG058507. O.A.A. is supported by Research Council of Norway (223273, 248778, 248980, 249711), South-East Norway Health Authority (2019108), and the Kristian Gerhard Jebsen Stiftelsen (SKGJ-MED-008). C.E.B. is supported by NIH/NIMH grant R01 MH085953, NIH/NIMH grant R01 MH100900, ENIGMA's NIH Big Data to Knowledge (BD2K) initiative U54 EB020403, and SFARI Explorer Award. G.D. is supported by funding from the European Research Council (ERC677467), Science Foundation Ireland (16ERCS3787), and the Health Research Board (CDA-2018-001). T.G.M.v.E. is supported by ENIGMA's NIH Big Data to Knowledge (BD2K) initiative U54 EB020403, ENIGMA Sex Differences R01MH116147, and ENIGMA-COINSTAC: Advanced Worldwide Transdiagnostic Analysis of Valence System Brain Circuits R01MH121246. L.S. is supported by a NHMRC Career Development Fellowship (1140764) and R01 MH117601 (to N.J. and L.S.). M.W.L. is supported by VA BLR&D I01BX003477 (PI: Logue), R01-MH111671 (PI: Morey). E.L.D. is supported by K99NS096116. D.F.T. is supported by Chronic Effects of Neurotrauma Consortium. E.A.W. is supported by the Department of Defense, Chronic Effects of Neurotrauma Consortium (CENC) Award W81XWH-13-2-0095, 5 I01 RX002174. D.J.S. is supported by the South African Medical Research Council. F.P. is supported from the Santa Lucia Foundation in Rome, Italy are funded by the Italian Ministry of Health grants RC12-13-14-15-16-17-18-19/A. J.E.V.-R. is supported by ENIGMA's NIH Big Data to Knowledge (BD2K) initiative U54 EB020403. O.A.v. d.H. is supported by the Dutch Research Council (VIDI grant 91717306).

CONFLICT OF INTEREST

P.M.T. and N.J. are MPLs of a research related grant from Biogen, Inc., for research unrelated to the contents of this manuscript. C.R.K.C. has received partial research support from Biogen, Inc. (Boston, USA) for work unrelated to the topic of this manuscript. O.A.A. is a consultant to HealthLytix, Speakers honorarium from Lundbeck. In the past 3 years, D.J.S. has received research grants and/or consultancy honoraria from Lundbeck and Sun. L.E.H. has received or plans to receive research funding or consulting fees on research projects from Mitsubishi, Your Energy Systems LLC, Neuralstem, Taisho, Heptares, Pfizer, Sound Pharma, Takeda, and Regeneron. All other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data Sharing: The data reviewed by this editorial are available from the manuscripts that published it.

Peter Kochunov¹ 
 L. Elliot Hong¹
 Emily L. Dennis^{2,3,4,5}
 Rajendra A. Morey⁶
 David F. Tate^{4,5}
 Elisabeth A. Wilde^{4,5}
 Mark Logue^{7,8,9,10}
 Sinead Kelly^{3,11}
 Gary Donohoe¹²
 Pauline Favre^{13,14}
 Josselin Houenou^{13,14,15,16}
 Christopher R. K. Ching³
 Laurena Holleran¹²
 Ole A. Andreassen^{17,18}
 Laura S. van Velzen^{19,20}
 Lianne Schmaal^{19,20}
 Julio E. Villalón-Reina³
 Carrie E. Bearden^{21,22}
 Fabrizio Piras²³
 Gianfranco Spalletta^{23,24} 
 Odile A. van den Heuvel²⁵
 Dick J. Veltman²⁵
 Dan J. Stein²⁶
 Meghann C. Ryan¹
 Yunlong Tan²⁷
 Theo G. M. van Erp^{28,29}
 Jessica A. Turner³⁰
 Liz Haddad³
 Talia M. Nir³
 David C. Glahn^{31,32}
 Paul M. Thompson³
 Neda Jahanshad³

⁹Boston University School of Medicine, Biomedical Genetics, Boston, Massachusetts

¹⁰Boston University School of Public Health, Department of Biostatistics, Boston, Massachusetts

¹¹Harvard Medical School, Boston, Massachusetts

¹²Centre for Neuroimaging and Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, National University of Ireland Galway, Galway, Ireland

¹³Neurospin, CEA, Université Paris-Saclay, Gif-sur-Yvette, France

¹⁴INSERM Unit U955, team "Translational Neuro-Psychiatry", Créteil, France

¹⁵Psychiatry Department, Assistance Publique-Hôpitaux de Paris (AP-HP), CHU Mondor, Créteil, France

¹⁶Faculté de Médecine, Université Paris Est Créteil, Créteil, France

¹⁷Norwegian Centre for Mental Disorders Research (NORMENT), Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

¹⁸Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Oslo, Norway

¹⁹Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia

²⁰Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia

²¹Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California at Los Angeles, Los Angeles, California

²²Department of Psychology, University of California at Los Angeles, Los Angeles, California

²³Laboratory of Neuropsychiatry, Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation, Rome, Italy

²⁴Division of Neuropsychiatry, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas

²⁵Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Psychiatry, Department of Anatomy & Neurosciences, Amsterdam Neuroscience, Amsterdam, The Netherlands

²⁶Department of Psychiatry & Neuroscience Institute, University of Cape Town, SA MRC Unit on Risk & Resilience in Mental Disorders, Cape Town, South Africa

²⁷Beijing Huilongguan Hospital, Peking University Huilongguan Clinical Medical School, Beijing, China

²⁸Clinical Translational Neuroscience Laboratory, Department of Psychiatry, University of California Irvine, Irvine, California

²⁹Center for the Neurobiology of Learning and Memory, University of California Irvine, Irvine, California

³⁰Department of Psychology and Neuroscience Institute, Georgia State University, Atlanta, Georgia

³¹Department of Psychiatry, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts

³²Olin Neuropsychiatric Research Center, Hartford Hospital, Hartford, Connecticut

¹Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland

²Psychiatry Neuroimaging Laboratory, Brigham & Women's Hospital, Boston, Massachusetts

³Imaging Genetics Center, USC Mark and Mary Stevens Neuroimaging & Informatics Institute, Keck School of Medicine of USC, Marina del Rey, California

⁴Department of Neurology, University of Utah School of Medicine, Salt Lake City, Utah

⁵George E. Wahlen VA, Salt Lake City, Utah

⁶Brain Imaging and Analysis Center, Duke University, Durham, North Carolina

⁷VA Boston Healthcare System, National Center for PTSD, Boston, Massachusetts

⁸Boston University School of Medicine, Department of Psychiatry, Boston, Massachusetts

Correspondence

Peter Kochunov, Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland, School of Medicine, Baltimore, MD.

Email: pkochunov@som.umaryland.edu

ORCID

Peter Kochunov  <https://orcid.org/0000-0003-3656-4281>

Gianfranco Spalletta  <https://orcid.org/0000-0002-7432-4249>

REFERENCES

- Acheson, A., Wijtenburg, S., Rowland, L., Winkler, A., Mathias, C. W., Hong, L., ... Dougherty, D. D. (2017). Reproducibility of tract-based white matter microstructural measures using the ENIGMA-DTI protocol. *Genes, Brain, and Behavior*, 7(2), 1–10. <https://doi.org/10.1002/brb1003.1615>
- Alba-Ferrara, L. M., & de Erausquin, G. A. (2013). What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. *Frontiers in Integrative Neuroscience*, 7, 9. <https://doi.org/10.3389/fnint.2013.00009>
- Alnaes, D., Kaufmann, T., van der Meer, D., Córdova-Palomera, A., Rokicki, J., Moberget, T., ... Karolinska Schizophrenia Project Consortium. (2019). Brain heterogeneity in schizophrenia and its association with polygenic risk. *JAMA Psychiatry*, 76, 739–748. <https://doi.org/10.1001/jamapsychiatry.2019.0257>
- Assaf, Y., & Cohen, Y. (1998). Non-mono-exponential attenuation of water and N-acetyl aspartate signals due to diffusion in brain tissue. *Journal of Magnetic Resonance*, 131(1), 69–85. <https://doi.org/10.1006/jmre.1997.1313>
- Barysheva, M., Jahanshad, N., Foland-Ross, L., Altschuler, L. L., & Thompson, P. M. (2013). White matter microstructural abnormalities in bipolar disorder: A whole brain diffusion tensor imaging study. *Neuroimage. Clinical*, 2, 558–568. <https://doi.org/10.1016/j.nicl.2013.03.016>
- Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66(1), 259–267. [https://doi.org/10.1016/S0006-3495\(94\)80775-1](https://doi.org/10.1016/S0006-3495(94)80775-1)
- Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance. Series B*, 111(3), 209–219.
- Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system—A technical review. *NMR in Biomedicine*, 15(7–8), 435–455. <https://doi.org/10.1002/nbm.782>
- Brainstorm, C., Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., ... Murray, R. (2018). Analysis of shared heritability in common disorders of the brain. *Science (New York, N.Y.)*, 360(6395), eaap8757. <https://doi.org/10.1126/science.aap8757>
- Bzdok, D., & Meyer-Lindenberg, A. (2017). Machine learning for precision psychiatry: Opportunities and challenges. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 3(3), 223–230. <https://doi.org/10.1016/j.bpsc.2017.11.007>
- Carballedo, A., Amico, F., Ugwu, I., Fagan, A. J., Fahey, C., Morris, D., ... Frodl, T. (2012). Reduced fractional anisotropy in the uncinate fasciculus in patients with major depression carrying the met-allele of the Val66Met brain-derived neurotrophic factor genotype. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 159B(5), 537–548. <https://doi.org/10.1002/ajmg.b.32060>
- Chawner, S., Doherty, J. L., Moss, H., Niarchou, M., Walters, J. T. R., Owen, M. J., & van den Bree, M. B. M. (2017). Childhood cognitive development in 22q11.2 deletion syndrome: Case-control study. *The British Journal of Psychiatry*, 211(4), 223–230. <https://doi.org/10.1192/bjp.bp.116.195651>
- Choi, S. W., Heng Mak, T. S., & O'Reilly, P. F. (2018). A guide to performing polygenic risk score analyses. *bioRxiv*, 416545. <https://doi.org/10.1101/416545>
- Clark, C. A., Hedehus, M., & Moseley, M. E. (2002). In vivo mapping of the fast and slow diffusion tensors in human brain. *Magnetic Resonance in Medicine*, 47(4), 623–628. <https://doi.org/10.1002/mrm.10118>
- Colodro-Conde, L., Couvy-Duchesne, B., Whitfield, J. B., Streit, F., Gordon, S., Kemper, K. E., ... Martin, N. G. (2018). Association between population density and genetic risk for schizophrenia. *JAMA Psychiatry*, 75(9), 901–910.
- Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *Lancet (London, England)*, 381(9875), 1371–1379. [https://doi.org/10.1016/S0140-6736\(12\)62129-1](https://doi.org/10.1016/S0140-6736(12)62129-1)
- Dennis, E., Disner, S. G., Fani, N., Salminen, L. E., Logue, M., Clarke, E. K., ... Morey, R. A. (2019). Altered White Matter Microstructural Organization in Post-Traumatic Stress Disorder across 3,047 adults: Results from the PGC-ENIGMA PTSD consortium. *Mol Psychiatry*. <https://doi.org/10.1038/s41380-019-0631-x>
- Dennis, E., Wilde, E. A., Newsome, M. R., Scheibel, R. S., Troyanskaya, M., Velez, C., ... Tate, D. F. (2018). Enigma military brain injury: A coordinated meta-analysis of diffusion MRI from multiple cohorts. *Proceedings. IEEE International Symposium on Biomedical Imaging*, 2018, 1386–1389. <https://doi.org/10.1109/ISBI.2018.8363830>
- Docherty, A. R., Moscati, A. A., & Fanous, A. H. (2016). Cross-disorder psychiatric genomics. *Current Behavioral Neuroscience Reports*, 3(3), 256–263. <https://doi.org/10.1007/s40473-016-0084-3>
- Favre, P., Pauling, M., Stout, J., Hozer, F., Sarrazin, S., Abe, C., ... ENIGMA Bipolar Disorder Working Group. (2019). Widespread white matter microstructural abnormalities in bipolar disorder: Evidence from mega- and meta-analyses across 3033 individuals. *Neuropsychopharmacology*, 44(13), 2285–2293. <https://doi.org/10.1038/s41386-019-0485-6>
- Friedman, J. I., Tang, C., Carpenter, D., Buchsbaum, M., Schmeidler, J., Flanagan, L., ... Davis, K. L. (2008). Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. *The American Journal of Psychiatry*, 165(8), 1024–1032. <https://doi.org/10.1176/appi.ajp.2008.07101640>
- Gerring, J. P., Brady, K. D., Chen, A., Vasa, R., Grados, M., Bandeen-Roche, K. J., ... Denckla, M. B. (1998). Premorbid prevalence of ADHD and development of secondary ADHD after closed head injury. *Journal of the American Academy of Child & Adolescent Psychiatry*, 37(6), 647–654. <https://doi.org/10.1097/00004583-199806000-00015>
- Holleran, L., Ahmed, M., Anderson-Schmidt, H., McFarland, J., Emsell, L., Leemans, A., ... Cannon, D. M. (2014). Altered interhemispheric and temporal lobe White matter microstructural Organization in Severe Chronic Schizophrenia. *Neuropsychopharmacology*, 39(4), 944–954. <https://doi.org/10.1038/npp.2013.294>
- Holleran, L., Kelly, S., Alloza, C., Agartz, I., Andreassen, O., Arango, C., ... Donohoe, G., ENIGMA Schizophrenia Working Group (2020). The relationship between white matter microstructure and general cognitive ability in patients with schizophrenia and healthy participants in the ENIGMA consortium. *The American Journal of Psychiatry*. <https://doi.org/10.1176/appi.ajp.2019.19030225>
- Ioannidis, J. P. A. (2014). How to make more published research true. *PLoS Medicine*, 11(10), e1001747. <https://doi.org/10.1371/journal.pmed.1001747>
- Jahanshad, N., Kochunov, P., Sprooten, E., Mandl, R. C., Nichols, T. E., Almassy, L., ... Glahn, D. C. (2013). Multi-site genetic analysis of diffusion images and voxelwise heritability analysis: A pilot project of the ENIGMA-DTI working group. *Neuroimage*, 81:455–469. <https://doi.org/10.1016/j.neuroimage.2013.04.061>

- Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., ... Donohoe, G. (2018). Widespread white matter microstructural differences in schizophrenia across 4322 individuals: Results from the ENIGMA schizophrenia DTI working group. *Molecular Psychiatry*, 23(5), 1261–1269. <https://doi.org/10.1038/mp.2017.170>
- Kochunov, P., Chiappelli, J., & Hong, L. E. (2013). Permeability-diffusivity modeling vs. fractional anisotropy on white matter integrity assessment and application in schizophrenia. *NeuroImage. Clinical*, 3, 18–26. <https://doi.org/10.1016/j.nicl.2013.06.019>
- Kochunov, P., Chiappelli, J., Wright, S. N., Rowland, L. M., Patel, B., Wijtenburg, S. A., ... Hong, L. E. (2014). Multimodal white matter imaging to investigate reduced fractional anisotropy and its age-related decline in schizophrenia. *Psychiatry Research*, 223(2), 148–156. <https://doi.org/10.1016/j.psychres.2014.05.004>
- Kochunov, P., Coyle, T., Lancaster, J., Robin, D. A., Hardies, J., Kochunov, V., ... Fox, P. T. (2010). Processing speed is correlated with cerebral health markers in the frontal lobes as quantified by neuroimaging. *NeuroImage*, 49(2), 1190–1199. <https://doi.org/10.1016/j.neuroimage.2009.09.052>
- Kochunov, P., Coyle, T., Rowland, L., Jahanshad, N., Thompson, P., Kelly, S., ... Elliot Hong, L. (2017). White matter and core cognitive deficits in schizophrenia. *JAMA Psychiatry*, 74, 958–966.
- Kochunov, P., Dickie Erin, W., Viviano Joseph, D., Turner, J., Kingsley Peter, B., Jahanshad, N., ... Voineskos Aristotle, N. (2018). Integration of routine QA data into mega-analysis may improve quality and sensitivity of multisite diffusion tensor imaging studies. *Human Brain Mapping*, 39(2), 1015–1023. <https://doi.org/10.1002/hbm.23900>
- Kochunov, P., Fan, F., Ryan, M. C., Hatch, K. S., Tan, S., Jahanshad, N., ... Hong, L. E. (in review). Translating ENIGMA Schizophrenia findings using the Regional Vulnerability Index: Association with Cognition, Symptoms and Disease Trajectory. *Human Brain Mapping*.
- Kochunov, P., Fu, M., Nugent, K., Wright, S. N., Du, X., Muellerklein, F., ... Hong, L. E. (2016). Heritability of complex white matter diffusion traits assessed in a population isolate. *Human Brain Mapping*, 37(2), 525–535. <https://doi.org/10.1002/hbm.23047>
- Kochunov, P., Ganjgahi, H., Winkler, A., Kelly, S., Shukla, D. K., Du, X., ... Hong, L. E. (2016). Heterochronicity of white matter development and aging explains regional patient control differences in schizophrenia. *Human Brain Mapping*, 37, 4673–4688. <https://doi.org/10.1002/hbm.23336>
- Kochunov, P., Huang, J., Chen, S., Li, Y., Tan, S., Fan, F., ... Hong, L. E. (2019). White matter in schizophrenia treatment resistance. *The American Journal of Psychiatry*, 176, 829–838.
- Kochunov, P., Jahanshad, N., Marcus, D., Winkler, A., Sprooten, E., Nichols, T. E., ... Van Essen, D. C. (2015). Heritability of fractional anisotropy in human white matter: A comparison of human connectome project and ENIGMA-DTI data. *NeuroImage*, 111, 300–311. <https://doi.org/10.1016/j.neuroimage.2015.02.050>
- Kochunov, P., Jahanshad, N., Sprooten, E., Nichols, T. E., Mandl, R. C., Almasy, L., ... Glahn, D. C. (2014). Multi-site study of additive genetic effects on fractional anisotropy of cerebral white matter: Comparing meta and mega-analytical approaches for data pooling. *NeuroImage*, 95C, 136–150. <https://doi.org/10.1016/j.neuroimage.2014.03.033>
- Kochunov, P., Rowland, L. M., Fieremans, E., Veraart, J., Jahanshad, N., Eskandar, G., ... Hong, L. E. (2016). Diffusion-weighted imaging uncovers likely sources of processing-speed deficits in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, 113(47), 13504–13509.
- Kochunov, P., Patel, B., Ganjgahi, H., Donohue, B., Ryan, M., Hong, E. L., ... Nichols, T. E. (2019). Homogenizing estimates of heritability among SOLAR-eclipse, OpenMx, APACE, and FPHI software packages in neuroimaging data. *Frontiers in Neuroinformatics*, 13(16), 1–16. <https://doi.org/10.3389/fninf.2019.00016>
- Kochunov, P., Thompson, P. M., & Hong, L. E. (2019). Toward high reproducibility and accountable heterogeneity in schizophrenia research toward high reproducibility and accountable heterogeneity in schizophrenia research editorial. *JAMA Psychiatry*, 76, 680–681. <https://doi.org/10.1001/jamapsychiatry.2019.0208>
- Koshiyama, D., Fukunaga, M., Okada, N., Morita, K., Nemoto, K., Usui, K., ... COCORO. (2019). White matter microstructural alterations across four major psychiatric disorders: Mega-analysis study in 2937 individuals. *Molecular Psychiatry*. <https://doi.org/10.1038/s41380-019-0553-7>
- Mancini, V., Sandini, C., Padula, M. C., Zoller, D., Schneider, M., Schaer, M., & Eliez, S. (2019). Positive psychotic symptoms are associated with divergent developmental trajectories of hippocampal volume during late adolescence in patients with 22q11DS. *Molecular Psychiatry*. <https://doi.org/10.1038/s41380-019-0443-z>
- Mandl, R. C., Rais, M., van Baal, G. C., van Haren, N. E., Cahn, W., Kahn, R. S., & Hulshoff Pol, H. E. (2013). Altered white matter connectivity in never-medicated patients with schizophrenia. *Human Brain Mapping*, 34(9), 2353–2365. <https://doi.org/10.1002/hbm.22075>
- McEwen, B. S. (2017). Integrative medicine: Breaking down silos of knowledge and practice an epigenetic approach. *Metabolism—Clinical and Experimental*, 69, S21–S29. <https://doi.org/10.1016/j.metabol.2017.01.018>
- McGuire, S. A., Wijtenburg, S. A., Sherman, P. M., Rowland, L. M., Ryan, M., Sladky, J. H., & Kochunov, P. V. (2017). Reproducibility of quantitative structural and physiological MRI measurements. *Brain and Behavior*, 7(9), e00759. <https://doi.org/10.1002/brb3.759>
- Molina, V., Reig, S., Sanz, J., Palomo, T. s., Benito, C., Sánchez, J., ... Desco, M. (2005). Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. *Schizophrenia Research*, 80(1), 61–71. <https://doi.org/10.1016/j.schres.2005.07.031>
- Nazeri, A., Chakravarty, M. M., Felsky, D., Lobaugh, N. J., Rajji, T. K., Mulsant, B. H., & Voineskos, A. N. (2013). Alterations of superficial white matter in schizophrenia and relationship to cognitive performance. *Neuropsychopharmacology*, 38(10), 1954–1962. <https://doi.org/10.1038/npp.2013.93>
- Novikov Dmitry, S., Kiselev Valerij, G., & Jespersen Sune, N. (2017). On modeling. *Magnetic Resonance in Medicine*, 79(6), 3172–3193. <https://doi.org/10.1002/mrm.27101>
- Novikov, D. S., Fieremans, E., Jensen, J. H., & Helpert, J. A. (2011). Random walk with barriers. *Nature Physics*, 7(6), 508–514. <https://doi.org/10.1038/nphys1936>
- Okada, N., Fukunaga, M., Yamashita, F., Koshiyama, D., Yamamori, H., Ohi, K., ... Hashimoto, R. (2016). Abnormal asymmetries in subcortical brain volume in schizophrenia. *Molecular Psychiatry*, 21(10), 1460–1466. <https://doi.org/10.1038/mp.2015.209>
- Penke, L., Munoz Maniega, S., Houlihan, L. M., Murray, C., Gow, A. J., Clayden, J. D., ... Deary, I. J. (2010). White matter integrity in the splenium of the corpus callosum is related to successful cognitive aging and partly mediates the protective effect of an ancestral polymorphism in ADRB2. *Behavior Genetics*, 40(2), 146–156. <https://doi.org/10.1007/s10519-009-9318-4>
- Penke, L., Munoz Maniega, S., Murray, C., Gow, A. J., Hernandez, M. C., Clayden, J. D., ... Deary, I. J. (2010). A general factor of brain white matter integrity predicts information processing speed in healthy older people. *The Journal of Neuroscience*, 30(22), 7569–7574. <https://doi.org/10.1523/JNEUROSCI.1553-10.2010>
- Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magnetic Resonance in Medicine*, 36(6), 893–906. <https://doi.org/10.1002/mrm.1910360612>
- Piras, F., Piras, F., Abe, Y., Agarwal, S. M., Anticevic, A., Ameis, S., ... Spalletta, G. (2019). White matter microstructure and its relation to clinical features of obsessive-compulsive disorder: Findings from the ENIGMA OCD working group. *bioRxiv*, 855916. <https://doi.org/10.1101/855916>

- Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., ... Behrens, T. E. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31(4), 1487–1505.
- Song, S. K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage*, 20(3), 1714–1722.
- Song, S. K., Yoshino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage*, 26(1), 132–140. <https://doi.org/10.1016/j.neuroimage.2005.01.028>
- Sprooten, E., Sussmann, J. E., Clugston, A., Peel, A., McKirdy, J., Moorhead, T. W., ... McIntosh, A. M. (2011). White matter integrity in individuals at high genetic risk of bipolar disorder. *Biological Psychiatry*, 70(4), 350–356. <https://doi.org/10.1016/j.biopsych.2011.01.021>
- Sumitomo, A., Horike, K., Hirai, K., Butcher, N., Boot, E., Sakurai, T., ... Tomoda, T. (2018). A mouse model of 22q11.2 deletions: Molecular and behavioral signatures of Parkinson's disease and schizophrenia. *Science Advances*, 4(8), eaar6637. <https://doi.org/10.1126/sciadv.aar6637>
- Thomason, M. E., & Thompson, P. M. (2011). Diffusion imaging, white matter, and psychopathology. *Annual Review of Clinical Psychology*, 7, 63–85. <https://doi.org/10.1146/annurev-clinpsy-032210-104507>
- Thompson, P. M., Stein, J. L., Medland, S. E., Hibar, D. P., Vasquez, A. A., Renteria, M. E., ... Drevets, W. (2013). The ENIGMA consortium: Large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging and Behavior*, 8, 153–182. <https://doi.org/10.1007/s11682-013-9269-5>
- van Erp, T. G. M., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., ... Turner, J. A. (2015). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry*, 21(4), 547–553. <https://doi.org/10.1038/mp.2015.63>
- van Velzen, L. S., Kelly, S., Isaev, D., Aleman, A., Aftanas, L. I., Bauer, J., ... Schmaal, L. (2019). White matter disturbances in major depressive disorder: A coordinated analysis across 20 international cohorts in the ENIGMA MDD working group. *Molecular Psychiatry*. <https://doi.org/10.1038/s41380-019-0477-2>
- Vanes, L. D., Mouchlianitis, E., Wood, T. C., & Shergill, S. S. (2018). White matter changes in treatment refractory schizophrenia: Does cognitive control and myelination matter? *NeuroImage Clinical*, 18, 186–191. <https://doi.org/10.1016/j.nicl.2018.01.010>
- Villalón-Reina, J. E., Martínez, K., Qu, X., Ching, C. R. K., Nir, T. M., Kothapalli, D., ... Bearden, C. E. (2019). Altered white matter microstructure in 22q11.2 deletion syndrome: A multisite diffusion tensor imaging study. *Molecular Psychiatry*. <https://doi.org/10.1038/s41380-019-0450-0>
- Vorstman, J. A., Breetvelt, E. J., Duijff, S. N., Eliez, S., Schneider, M., Jalbrzikowski, M., ... International 22q11.2 Brain Behavior Syndrome Consortium. (2015). Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. *JAMA Psychiatry*, 72(4), 377–385. <https://doi.org/10.1001/jamapsychiatry.2014.2671>
- Weinberger, D. R. (1996). On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia. *Neuropsychopharmacology*, 14(3 Suppl), 1S–11S. [https://doi.org/10.1016/0893-133X\(95\)00199-N](https://doi.org/10.1016/0893-133X(95)00199-N)
- Weinberger, D. R., & Lipska, B. K. (1995). Cortical maldevelopment, antipsychotic drugs, and schizophrenia: A search for common ground. *Schizophrenia Research*, 16(2), 87–110.
- Wu, Y. C., Field, A. S., Duncan, I. D., Samsonov, A. A., Kondo, Y., Tudorascu, D., & Alexander, A. L. (2011). High b-value and diffusion tensor imaging in a canine model of dysmyelination and brain maturation. *NeuroImage*, 58(3), 829–837. <https://doi.org/10.1016/j.neuroimage.2011.06.067>
- Wu, Y. C., Field, A. S., Whalen, P. J., & Alexander, A. L. (2011). Age- and gender-related changes in the normal human brain using hybrid diffusion imaging (HYDI). *NeuroImage*, 54(3), 1840–1853. <https://doi.org/10.1016/j.neuroimage.2010.09.067>