Structural brain imaging studies offer clues about the effects of the shared genetic etiology among neuropsychiatric disorders

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Received: 29 May 2020 / Revised: 7 December 2020 / Accepted: 11 December 2020 / Published online: 17 January 2021

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Abstract
Genomewide association studies have found significant genetic correlations among many neuropsychiatric disorders. In contrast, we know much less about the degree to which structural brain alterations are similar among disorders and, if so, the degree to which such similarities have a genetic etiology. From the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium, we acquired standardized mean differences (SMDs) in regional brain volume and cortical thickness between cases and controls. We had data on 41 brain regions for: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BD), epilepsy, major depressive disorder (MDD), obsessive compulsive disorder (OCD), and schizophrenia (SCZ). These data had been derived from 24,360 patients and 37,425 controls. The SMDs were significantly correlated between SCZ and BD, OCD, MDD, and ASD. MDD was positively correlated with BD and OCD. BD was positively correlated with OCD and negatively correlated with ADHD. These pairwise correlations among disorders were correlated with the corresponding pairwise correlations among disorders derived from genomewide association studies ($r = 0.494$). Our results show substantial similarities in sMRI phenotypes among neuropsychiatric disorders and suggest that these similarities are accounted for, in part, by corresponding similarities in common genetic variant architectures.

Introduction

Neuropsychiatric disorders have substantial heritability, as shown by many studies of twins and families [1]. Genomewide association studies (GWAS) have shown that common genetic variants account for some of this heritability, and that some of this heritability is shared across neuropsychiatric disorders [2–5]. The genetic overlap across disorders may partly explain why these disorders tend to co-occur with one another in both clinical and community samples [6].

Subcortical brain volumes and cortical thickness/surface area dynamically change from early development through adulthood and old age. A study of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Plasticity Working Group reported that changes in structural magnetic resonance imaging (sMRI) phenotypes have heritabilities ranging from 5% for pallidum to 42% for cerebellar gray matter [7]. Heritability estimates of change rates were age-related and generally higher in adults than in children, probably due to an increasing influence of genetic factors with age [7]. However, it appears that later in adulthood heritability decreases most likely due to cumulative effect of environmental influences over the lifespan [8]. ENIGMA sMRI studies of different psychiatric and neurological disorders further characterized MRI-derived phenotypes that can be used to assess heritability (reviewed in [9]).

ENIGMA has also reported significant case vs. control differences in sMRI phenotypes for: attention-deficit/hyperactivity disorder (ADHD) [10, 11], autism spectrum disorder (ASD) [12], bipolar disorder (BD) [13, 14],

Supplementary information The online version of this article (https://doi.org/10.1038/s41380-020-01002-z) contains supplementary material, which is available to authorized users.

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common epilepsy syndromes \cite{15}, major depressive disorder (MDD) \cite{16,17}, obsessive compulsive disorder (OCD) \cite{18,19}, and schizophrenia (SCZ) \cite{20,21}. Here we estimate the degree of similarity in sMRI phenotypes among these disorders and evaluate whether these similarities are influenced by corresponding similarities in common genetic variant architectures.

### Methods

#### Collection of structural neuroimaging summary statistics

Summary statistics from ENIGMA structural neuroimaging studies were collected from 12 multisite analyses published by the ENIGMA Consortium for the following neuropsychiatric disorders: ADHD \cite{10,11}, ASD \cite{12}, BD \cite{13,14}, epilepsy \cite{15}, MDD \cite{16,17}, OCD \cite{18,19}, and SCZ \cite{20,21}. Prior to computing the summary statistics, the regional brain volumes had been segmented with a common ENIGMA protocol using FreeSurfer software. Each site performed these segmentations on their raw data. In addition, quality control protocols provided by ENIGMA were run at each site. Details are at: [http://enigma.ini.usc.edu/protocols/imaging-protocols](http://enigma.ini.usc.edu/protocols/imaging-protocols).

The ADHD and ASD samples comprised both youth and adults. The other samples comprised adults only. The ethnicity of the patients was not available for all participants. The “epilepsy” cohort comprised temporal lobe epilepsy, genetic generalized epilepsy, and extra temporal epilepsy. We analyzed 7 subcortical and 34 cortical regions (total of 41 brain regions; the mean of left and right structures) that were included in the above specified ENIGMA studies. We extracted the covariate-adjusted Cohen’s $d$ standardized mean differences (SMDs) denoting the case versus unaffected comparison subject differences in subcortical volume and cortical thickness/surface area measures. The covariates used in these studies adjusted SMDs for several covariates as indicated in Supplementary Table 1.

#### Collection of GWAS results among neuropsychiatric disorders

Publicly available summary statistics from GWAS were downloaded from the Psychiatric Genomics Consortium (PCG) website [https://www.med.unc.edu/pgc/results-and-downloads/](https://www.med.unc.edu/pgc/results-and-downloads/) with the exception of GWAS results for MDD coming from an online resource hosted by the University of Edinburgh [https://doi.org/10.7488/ds/2458](https://doi.org/10.7488/ds/2458) and of GWAS results for epilepsy coming from the online Epilepsy Genetic Association Database (epiGAD) [http://www.epigad.org/gwas_ilae2018_16loci.html](http://www.epigad.org/gwas_ilae2018_16loci.html). Presented in Supplementary Table 2 are the numbers of affected cases and unaffected control participants included in each GWAS. Note, the full meta-analysis GWAS of MDD that included data from 23andMe was not available for public release, thus we used the meta-analysis that combined results from the PGC cohorts and UK Biobank.

#### Genetic and sMRI phenotype correlations among neuropsychiatric disorders

Linkage disequilibrium (LD)-score regression, a popular approach designed to analyze summary statistics from GWAS, was used to quantify the amount of shared genetic heritability, or genetic correlation ($r_g$), existing between pairs of neuropsychiatric disorders, considering HapMap3 LD-scores \cite{22}. For these analyses, the largest and latest GWAS available for each neuropsychiatric disorder was selected and filtered to exclude markers with INFO $<0.90$ or within the MHC region (hg19:chr6:25–35 Mb) (Supplementary Table 1). GWAS summary statistics were merged with the HapMap3 reference panel (hg37 build), wherein variants with a MAF $\geq5\%$ in the HapMap3 dataset were retained, prior to computing (co)heritability estimates.

To derive an estimate of the degree to which sMRI phenotypes were similar among disorders, we computed pairwise Spearman’s rank correlation between the Cohen’s $d$ SMDs for each pair of disorders. We then used Pearson’s correlation to estimate, whether the genetic correlations for each disorder covaried with the sMRI phenotype correlations. We used a traditional permutation framework to generate a null distribution of sMRI phenotype correlations by randomly shuffling Cohen’s $d$ values 10,000 times for each pair of disorders, then recalculating sMRI correlations from the shuffled sets. From the null distributions, we derived an empirical permutation $p$ value for each sMRI phenotype correlation. However, a reliable $p$ value could not be calculated due to nonindependence between pairwise caused by sample overlap between imaging studies. Adjustments for sample overlap would be possible with individual-level data, but the present study only had access to summary statistics. In a leave-one-out analysis, we iteratively excluded one pair of disorder correlations from the set and recalculated Spearman’s correlation coefficients to determine whether correlations were driven by any pair of disorders. Binomial sign tests were used to determine whether the number of disorders showing the same direction of effect in the sMRI phenotypes was greater than expected by chance (null probability of 50\%). Per brain region, we performed Cochran’s $Q$ test implemented in the R package metafor (v.2.1–0) to determine whether variability among Cohen’s $d$ values was greater than expected by chance. All statistical analyses were performed with R version 3.5.2.
(R Core Team, 2018). We adjusted for repeated correlation tests using the Bonferroni procedure. Correlations showing a Bonferroni-adjusted \( p < 0.05 \) were considered significant (threshold \( p = 0.00227 \)).

### Results

Sample demographics for the twelve studies by the ENIGMA Consortium on structural brain abnormalities in neuropsychiatric disorders are presented in Table 1.

**Case–control differences in subcortical volume and cortical surface area and thickness within neuropsychiatric disorders**

Figure 1 presents an anatomical graph of the standardized effect sizes (Cohen’s \( d \)) measuring alterations in subcortical volume, cortical surface area and cortical thickness for 41 brain regions within seven neuropsychiatric disorders—ADHD, ASD, OCD, epilepsy, MDD, BD, and SCZ. These have been reported on prior publications. The variation in color from blue to red illustrates the phenomenon of SBRV, with some regions showing significant reductions (blue) in volume/thickness/surface areas and others not being affected. As indicated by the blueness of the cells, the most prominent reductions were seen for SCZ (mean Cohen’s \( d \) across all regions = −0.22, SE = 0.014), epilepsy (mean Cohen’s \( d = −0.12, SE = 0.017 \) and BD (mean Cohen’s \( d = −0.097, SE = 0.011 \)). The smallest changes were observed for MDD (mean Cohen’s \( d = −0.018, SE = 0.006 \). All regions except for the caudate and putamen exhibited significant differences in the magnitude of Cohen’s \( d \) across disorders (Cochran’s \( Q \) \( p \) values = 0.012–2.8 × 10\(^{-32}\)). Eighteen sMRI phenotypes exhibited homogeneity with respect to sign of Cohen’s \( d \) across each of the neuropsychiatric disorders evaluated (binomial sign test \( p \) values < 0.05): cortical thicknesses for caudal middle frontal gyrus, entorhinal cortex, fusiform gyrus, inferior temporal gyrus, insula, lateral orbitofrontal cortex, lingual gyrus, middle temporal gyrus, paracentral lobule, parahippocampal gyrus, pars opercularis of inferior temporal gyrus, precentral gyrus, precuneus, rostral anterior cingulate cortex, and supramarginal gyrus; subcortical volume for the hippocampus; and surface area for middle temporal gyrus, pars triangularis of inferior temporal gyrus, and pericalcarine cortex. For sMRI phenotypes for 39 regions of interest varying degrees of heterogeneity were noted in terms of discrepancy of signs of Cohen’s \( d \). For example, individuals with ASD showed a slightly thicker cortex in the rostral region.

| Disorder | MRI measure     | Cases (\( n \)) | Controls (\( n \)) | Total \( n \) | Sites | Weighted mean age (cases) | Weighted mean age (controls) | References |
|----------|-----------------|-----------------|-------------------|-------------|-------|---------------------------|----------------------------|------------|
| ADHD     | Cortical thickness | 2246            | 1934              | 4180        | 36    | 19.2                      | 18.1                      | [2, 28]    |
|          | Surface area    | 2246            | 1934              | 4180        | 36    | 18.1                      |                           |            |
|          | Subcortical volume | 1713            | 1529              | 3242        | 23    | 18.6                      |                           |            |
| ASD      | Cortical thickness | 1571            | 1651              | 3222        | 49    | 15.4                      |                           | [18]       |
|          | Surface area    |                 |                   |             |       |                           |                           |            |
|          | Subcortical volume |               |                   |             |       |                           |                           |            |
| BD       | Cortical thickness | 1837            | 2582              | 4419        | 28    | 38.4\(^a\)                | 35.6\(^a\)               | [19, 30]   |
|          | Surface area    | 1820            | 2582              | 4402        | 28    | 38.4\(^a\)                | 35.6\(^a\)               |            |
|          | Subcortical volume | 1710            | 2594              | 4304        | 20    | 40.1\(^a\)                | 36.5\(^a\)               |            |
| Epilepsy | Cortical thickness | 2149            | 1727              | 3876        | 24    | 34.4                      | 33.3                     | [7]        |
|          | Surface area    |                 |                   |             |       |                           |                           |            |
|          | Subcortical volume |               |                   |             |       |                           |                           |            |
| MDD      | Cortical thickness | 1911            | 7663              | 9574        | 20    | 44.8\(^a\)                | 54.6\(^a\)               | [6, 22]    |
|          | Surface area    | 1902            | 7658              | 9560        | 20    | 44.8\(^a\)                | 54.6\(^a\)               |            |
|          | Subcortical volume | 1728            | 7199              | 8927        | 15    | 43.3\(^a\)                | 56\(^a\)                 |            |
| OCD      | Cortical thickness | 1498            | 1435              | 2933        | 27    | 32.1                      | 30.5                     | [26, 41]   |
|          | Surface area    | 1497            | 1433              | 2930        | 27    | 32.1                      | 30.5                     |            |
|          | Subcortical volume | 1495            | 1472              | 2967        | 25    | 32.0                      | 30.6                     |            |
| SCZ      | Cortical thickness | 4474            | 5098              | 9572        | 39    | 32.3\(^a\)                | 34.5\(^a\)               | [27, 34]   |
|          | Surface area    | 4434            | 5073              | 9507        | 39    | 32.3\(^a\)                | 34.5\(^a\)               |            |
|          | Subcortical volume | 2028            | 2540              | 4568        | 15    | 34.0\(^a\)                | 31.0\(^a\)               |            |

\(^a\)Weighted mean not provided in paper; computed from descriptive statistics.
middle frontal gyrus, individuals with ADHD showed no difference, and all other disorders showed a thinner cortex in this region compared to controls.

sMRI phenotype correlations among neuropsychiatric disorders

For each pair of disorders, we computed the Pearson correlation between their sMRI phenotypes listed in Fig. 1. These are listed in Table 2 (and visualized in Fig. 2), sorted by the magnitude of the correlation. The $p$ values reported in Table 2 are potentially downwardly biased due to inability to properly adjust for spatial coherence of nearby brain regions. Traditional permutation $p$ values are provided as a column in Table 2, which attempts to correct for potential biases due to spatial coherence. However, we were restricted from using a spatial permutation framework to generate a null distribution of correlations, because we are jointly analyzing two cortical maps (cortical thickness and surface area) that are fully overlapped. The highest positive correlation was between SCZ and BD ($r = 0.81$, df = 73, $p < 1.3 \times 10^{-18}$, Bonferroni $p = 2.38 \times 10^{-17}$). There were a few additional nominally significant negative correlations, which did not survive multiple testing correction: MDD and epilepsy ($r = -0.37$, $p = 0.02$), MDD and ADHD ($r = -0.33$, $p = 0.004$), SCZ and ADHD ($r = -0.32$, $p = 0.005$), ADHD and epilepsy ($r = -0.36$, $p = 0.02$), and a positive correlation between MDD and ASD ($r = 0.26$, $p = 0.02$).

Correlation of shared genetic heritability with brain structural correlation

Figure 3 shows the pairwise correlations of sMRI phenotypes and genetic overlap across each pair of neuropsychiatric disorders. The LD-score cross-disorder genetic correlations are positively correlated with the sMRI phenotype cross-disorder correlations (Spearman’s $\rho = 0.44$, $p = 0.049$). Leave-one-out sensitivity analyses confirmed that the direction of the correlation was positive and remained moderate in magnitude despite removal of individual pairs of disorders from the correlation test (range of Spearman’s $\rho = 0.35$–0.58), except for removing SCZ/BD (Spearman’s $p = 0.35$). SCZ and BD showed the highest degree of concordance with respect to genetic and sMRI phenotype correlations.

Discussion

Our analysis of summary statistics from the ENIGMA ADHD, ASD, BD, MDD, OCD, SCZ, and epilepsy Working Groups and the predominantly PGC case–control GWAS identified two novel findings. First, we found substantial correlations for some disorders in the pattern of sMRI case–control differences across subcortical and cortical regions in line with recently published study of [23]. Second, these cross-disorder
correlations in SBRV could partly be explained by the genetic correlations reported for these disorders from GWAS [3].

The cross-disorder correlations in SBRV are intriguing because, like cross-disorder genetic correlations, they suggest that these disorders, to varying degrees, share aspects...
of their etiology and pathophysiology. Any interpretation of
the cross-disorder sMRI correlations must keep in mind
that, for all disorders, the case–control differences in sMRI
measures are small (Fig. 1). The largest Cohen’s d values
are only −0.5 for SCZ [20, 21], −0.4 for epilepsy [15],
−0.3 for BD [13, 14], −0.2 for ADHD [10, 11] and ASDs
[12], and −0.1 for MDD [16, 17] and OCD [18, 19]. These
small case–control differences are consistent with results
from GWAS and environmental risk studies, which speaks
to the fact that the effects of common risk factors are, with
some rare exceptions, individually small. Although it is
conceivable that these small risks could accumulate to
create a more dramatic pathophysiology in the brain, the
ENIGMA data show that this is not the case for sMRI
measures. Consistent with this finding, interindividual dif-
fferences in neuroimaging account for only a small amount
of the variance in symptom expression or behavioral mea-
sures of symptomatic or behavioral variance [24].

The most prominent case–control differences in cortical
thickness/surface area and subcortical volumes were
observed for SCZ [20, 21] and BD [13, 14]. These disorders
also had the highest sMRI phenotype correlations and both
also showed strong sMRI phenotype correlations with
MDD [16, 17] and OCD [18, 19]. As Fig. 2 shows, these
disorders clustered together in the three-dimensional con-
figuration required to capture cross-disorder sMRI phenot-
type similarity. The high sMRI correlation between SCZ
and BD is consistent with prior reports of sMRI similarities
between the two disorders [25]. Moreover, a large body of
literature reports substantial etiologic overlap between the
two disorders [26–30]. Because of such data, the SCZ and
BD have been described as sharing a continuum of etiology
leading to psychotic [31], neurophysiological [31] and
neurocognitive [32] symptoms. The ENPACT study [33]
showed shared fronto–temporo–occipital gray matter
volume deficits in the right hemisphere of two disorders. A
systematic review of associations between functional MRI
activity and polygenic risk for SCZ and BD [26] reported
that genetic load for these disorders affects task-related
recruitment of predominantly frontal lobe brain regions.

Many studies have reported that OCD can be a comorbid
diagnosis with SCZ or that patients with SCZ can have OCD
symptoms [34–41]. Presented findings of a significant over-
lap in sMRI phenotypes along with the known SCZ/OCD
genetic correlations suggests that more work should examine
shared pathophysiologic features between these disorders and
should assess the degree to which confounds, such as med-
ication status or chronicity, might explain these results.

The sMRI phenotype correlations mirror, to some extent,
the cross-disorder correlations from GWAS. Figure 3 shows
a modest, yet distinct, linear correlation between the sMRI
phenotype and genetic correlations. In the upper right-hand
section of the plot, we see disorders having high genetic and
high sMRI correlations. These are SCZ/BD, SZ/MDD, BD/
MDD, OCD/BD, and OCD/MDD. The inclusion of MDD
in this group is notable given that it is part of the bipolar
diagnosis and often occurs comorbid with other disorders.
MDD also has a high genetic correlation with ADHD but a
negative sMRI correlation, which makes that pair an outlier
in Fig. 3.

In the lower left region of Fig. 3, we see disorders with
low genetic and low sMRI correlations. These involve
correlations of epilepsy, and correlations of ADHD with all
disorders except ASDs and MDD, although the latter is
somewhat of an outlier. ASDs tend to have both modest
genetic correlations and modest sMRI correlations with
most other disorders and, hence, populates the middle range
of the figure. Like the sMRI correlations among disorders,
all genetic correlations with epilepsy are low, which is
consistent with the low genetic correlation between neuro-
logical and psychiatric disorders as reported by [2].

The finding that SBRV correlations are correlated with
genetic correlations suggests that future studies of SBRV
should consider genetic sources of etiology. Yet, because
only about 24% of the variance in the SBRV correlations can
be accounted for by the genetic correlations, environmental
sources of etiology and disease-specific genetic contributions
must also be considered. These include shared confounders,
such as chronicity and medication exposure, along with
shared etiologic events such as birth complications or expo-
sure to toxins in utero. Our prior studies of SBRV in ADHD
implicated the regulation of genes in apoptosis, autophagy
and neurodevelopment pathways in ADHD [42, 43]. Neu-
rodevelopmental pathways had also been implicated in the
cross-disorder analysis of the PCG [3], which suggests that
cross-disorder similarities in these pathways may account for
cross-disorder similarities in SBRV.

Although we used data derived from very large samples
(ENIGMA, iPSYCH, and the PGC), several limitations
moderate the strength of our conclusions. We inherit all the
limitations of the constituent studies, but are further limited
because we analyzed summary statistics, not the original
data, which would require the sharing of individual subject
level data, an ongoing effort among the ENIGMA disorder
working groups. Thus, we cannot determine whether the
possible use of controls shared among studies affected our
results. It is also possible that some research participants
were included in the genetic and sMRI data sets for the
same disorder. The p value obtained by our Spearman’s
correlation test of cross-disorder sMRI and genetic corre-
lations may be inaccurate due to spatial autocorrelation
among sMRI Cohen’s d estimates, which can downwardly
bias standard errors and lead to deflated p values. Con-
sidering we are not able to completely address with auto-
correlation among brain regions using summary statistics
alone, the p value from our primary analysis (presented in
Fig. 3) should be interpreted with caution. Another problem is that we could not address effects of medications or chronicity on brain structure. Furthermore, for some of the disorders, we could use youth and adult data, whereas for others only adult effect data were used. Because findings can differ substantially depending on the age range of the samples included (e.g., [10, 11, 18, 19]), this might have influenced our findings. For these reasons, analyses of participant level data will be needed to address these issues to draw stronger and more detailed conclusions. We also did not have any longitudinal data available, which limits the ability to test hypotheses about shared and unique developmental trajectories among disorders.

Despite these limitations, we have documented cross-disorder correlations in SBRV as assessed by sMRI. These cross-disorder SBRV correlations are positively associated with the disorders’ corresponding cross-disorder genetic correlations. This finding is a novel contribution worthy of further study that contributes to novel body of literature focused on cross-level correspondence of genetic and neuroimaging presentations of different psychiatric disorders [44–49]. Our work supports conclusions from previous GWAS studies suggesting a partially shared etiology and pathophysiology among many disorders [2, 50]. Disorders like SCZ and BD or ADHD and ASD, which are distinct in the diagnostic nomenclature, show significant overlap in etiology and pathophysiology. Further studies are needed to discern why brain regions are selectively affected by the risk factors that cause sMRI abnormalities [42, 43] and why these effects are correlated across disorders. Such studies may give insights into new treatment targets.

**Data availability**

**URLs for GWAS SCZ from ckqny.sch2snpres.gz** (https://www.med.unc.edu/pgc/results-and-downloads), ASD from iPSYCH-PGC-ASD_Nov2017.gz (https://www.med.unc.edu/pgc/results-and-downloads), OCD from PGC_OCD_D_Aug2017-20171122T182645Z-001.zip > ocd_aug2017.gz (https://www.med.unc.edu/pgc/results-and-downloads), ADHD from adhd_ul2017.gz (https://www.med.unc.edu/pgc/results-and-downloads), BD from daner_PGC_BIP32b_mds7a_0416a.gz (https://www.med.unc.edu/pgc/results-and-downloads), Epilepsy from all_epilepsy_METAL.gz (http://www.epigad.org/gwas_ilae2018_16loci.html), and MDD from PGC_UKB_depression_genome-wide.txt (https://doi.org/10.7488/ds/2458).

**Code availability**

Custom R scripts used to generate results in this study can be made available upon request.

**Acknowledgements** SVF is supported by the European Union’s Seventh Framework Program for research, technological development and demonstration under grant agreement no. 602805, the European Union’s Horizon 2020 research and innovation program under grant agreements nos. 667302 and 728018 and NIMH grants 5R01MH101519 and U01 MH109536-01. Research Council of Norway (#223273). BF is supported by a personal Vici grant from the Netherlands Organization for Scientific Research (NWO, grant number 91813669) and by a grant from the European Union’s Horizon 2020 program for the CoCa project (grant agreement no 667302). ENIGMA work is supported by NIH grants U54 EB020403 (PI: PT), R01 MH116147 (PI: PT) and R01MH117601 (MPIs: NJ and LS). MH is supported by a personal Ven grant from the Netherlands Organization for Scientific Research (NWO, grant number 91619115). CMD is supported by NIH grants R01 NS065838 and R21 NS107739. PR is a recipient of a pre-doctoral fellowship from the Agència de Gestió d’Ajuts Universitaris i de Recerca (AGAUR), Generalitat de Catalunya, Spain (2016FI_B_00899). LS is supported by a NHMRC Career Development Fellowship (1140764). SMS is supported by Epilepsy Society, UK, and the work was partly undertaken at UCLH/UCL, which received a proportion of funding from the UK Department of Health’s NIHR Biomedical Research Centers funding scheme.). TGMVE is supported by NIH grants U54 EB020403 (PI: PT, R01 MH116147 (PE: PT), R01MH117601 (MPIs: NJ and LS), and R01MH121246 (MPIs: Turner, TGMVE, and Calhoun).

**Compliance with ethical standards**

**Conflict of interest** OA has received speaker’s honorarium from Lundbeck and is a consultant to HealthLytx. In the past year, SVF received income, potential income, travel expenses continuing education support, and/or research support from Tris, Otsuka, Arbor, Ironshore, Shire, Akili Interactive Labs, Enzymotec, Sunovion, Supernus and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium–hydrogen exchange inhibitors in the treatment of ADHD. He also receives royalties from books published by Guilford Press: Straight Talk about Your Child’s Mental Health, Oxford University Press: Schizophrenia: The Facts and Elsevier: ADHD: Non-Pharmacologic Interventions. He is Program Director of www.adhdinadults.com. BF received educational speaking fees from Medice. All other authors declare no conflict of interest.

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